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First substoichiometric version of the catalytic enantioselective addition of an alkyllithium to an aldehyde†

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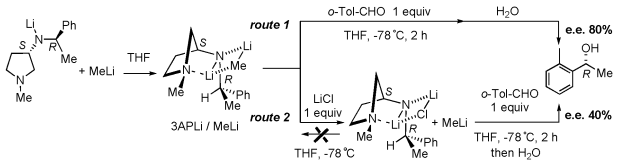
A substoichiometric enantioselective version of the extremely fast nucleophilic addition of Alk-Li to RCHO is made possible thanks to a thorough analysis of the aggregation phenomena involved in the reaction: calculated quantities of LiCl must be added to the medium at the right time to keep the catalytic cycle running.

The beneficial effect of lithium halides on ees is well documented in enantioselective protonation,[1] deprotonation[2] and 1,4-nucleophilic addition reactions.[3] In contrast, only a detrimental influence of these salts on the enantioselective 1,2-addition of alkyllithiums onto aldehydes has been reported to date.[4,5] The exact role played by LiX often remains presumptive,[6] relying on *ad hoc* models built from the results.[3] Even if modern spectroscopic techniques can shed useful light on the structures of the mixed aggregates resulting from the empirical addition of LiX to a solution containing one or more lithiated partner(s),[7] the reactions involving highly polar organometallic compounds run generally very fast, and thus, only a "static" description of these solution structures (that is before or after addition of the substrate) can be proposed. Note however the spectacular results obtained in the field by rapid injection NMR spectroscopy, which open promising perspectives to overcome this difficulty.[8] We conjectured that, without resorting to such sophisticated equipment, we could take advantage of the detailed knowledge of the composition of the medium to avoid the formation of undesired complexes that could jeopardize the induction phenomenon. This requires complete knowledge of the structure of the aggregates all along the reaction course and their eventual control by addition of the appropriate salt at the proper time. The results we report below show that this approach works and allows: (i) improvement of the ees of a catalytic stoichiometric 1,2-nucleophilic addition; (ii) refinement of the model reaction into its substoichiometric version, which has not been described previously.



Scheme 1 Nucleophilic addition of 3APLi/MeLi onto *ortho*-tolualdehyde, without (route 1) or with (route 2) LiCl.

We showed earlier that, when a 3-aminopyrrolidine lithium amide (3APLi) is used as a chiral dipolar ligand for an alkyllithium (RLi), a well-organized 1 : 1 3APLi/RLi mixed aggregate forms in THF, and enantioselective nucleophilic additions of these alkyllithiums onto aromatic aldehydes (Scheme 1) are possible.[5,9] We assumed the aggregate to be responsible for the ~80% ee measured on the final alcohol.[7] Considering then the role of lithium halides in the induction, this reaction proved to be particularly sensitive to LiCl or LiBr poisoning since the enantiomeric excesses dropped upon addition of such a salt to the 3APLi/MeLi aggregate.[5] The competitive affinities between the lithium amide, the methyllithium and lithium chloride examined by multinuclear NMR spectroscopy and DFT calculations led to the conclusion that, in THF-d_8, MeLi is displaced from the 3APLi/MeLi complex and irreversibly replaced by LiCl. The chiral inductor being trapped in an inactive complex, only "naked" MeLi is thus left to react with the aldehyde.

However, if the situation depicted above was that simple, the induction should have plummeted, while a reproducible 40% ee is measured. Such a puzzling observation led us to deepen our investigation on the mechanism of this multi-partner reaction. Keeping in mind that the overall system involves *four* highly polar entities, namely the three lithiated species introduced at the onset of the reaction *plus* the lithium alkoxide progressively produced in the medium, a series of

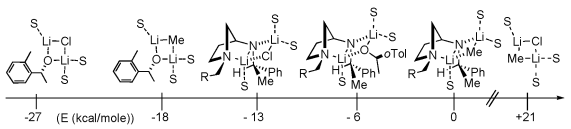


Fig. 1 Relative DFT stabilities of the six 1 : 1 mixed aggregates combining 3APLi, MeLi, LiCl and ArCH(CH_3)OLi.

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† Electronic supplementary information (ESI) available: Typical procedure for the addition of methyllithium on *o*-tolualdehyde and NMR data for the alkoxide/lithium chloride mixed aggregate. See DOI: 10.1039/c1cc13513a

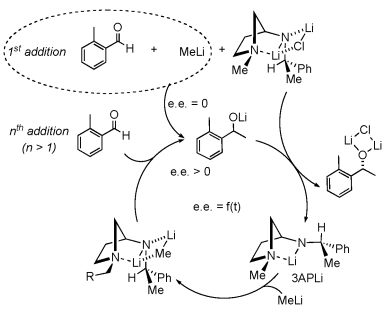
Table 1 Influence of the experimental protocol on the induction of reaction in Scheme 3.

Entry	*x* equiv. 3APLi	*y* equiv. LiCl	ee%[a,b]
1	1	0	80
2	0.33	0	65
3	0.1	0	45
4	1	1	86
5	1	0.33	82
6	0.33	0.33	80
7	0.1	0.33	40
8	0.1 "salt free" MeLi[c]	0.33	70

[a] Measured on a Betadex 120 GC column chromatograph. [b] Alcohol *R* as the major enantiomer. [c] Solution of commercial methyllithium LiCl freed by addition of $PhCH(CH_3)OLi$ (see the text).

DFT computations[10] have been undertaken, which compare the relative stabilities of the six 1 : 1 mixed aggregates possibly appearing between these four partners (Fig. 1). The dramatic role played by solvation in aggregation phenomena is taken into account by incorporating three explicit molecules of THF (noted S) into the super-molecule.[11] The energy scale is calibrated on the 3APLi/MeLi aggregate (E = 0.0 kcal mol^{-1}).

The simple MeLi/LiCl heterodimer is by far the least stable aggregate possible, a result in line with our recent NMR data on this species.[12] By contrast, all other aggregates are found to be more stable than the reference heterodimer 3APLi/MeLi. If previous results showed that the 3APLi/LiX (X = Cl, Br) affinity is larger than the 3APLi/MeLi one by *ca.* −13 kcal mol^{-1},[5] these new calculations point the finger to the 3APLi/R*OLi couple, for which the cohesion energy exceeds the 3APLi–MeLi one by −6 kcal mol^{-1}.[13] These data suggest that a stoichiometric amount of the chiral ligand is necessary to reach significant ees (see entries 1–3 in Table 1): the 3APLi is gradually sequestered by the alkoxide accumulating in the solution. On the other hand, the DFT results indicate that an even more stable complex (by −18 kcal mol^{-1}) forms between the alkoxide and the alkyllithium. It yields a R*OLi/MeLi aggregate likely to compete with the 3APLi/MeLi inductive complex.[14] We checked that the former also converts *o*-Tol-CHO into 1-*o*-Tol-ethanol, albeit as a racemic mixture. Note that such a result can explain the limitation of the induction at ~80% ee. Last, but not least, the DFT data highlight a remarkably strong relative affinity between R*OLi and LiCl (−27 kcal mol^{-1}), a result of high importance for the following.

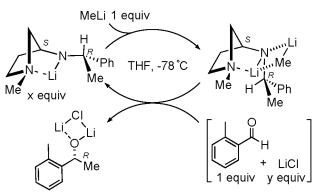


Scheme 2 Sub-stoichiometric catalytic version of the enantioselective hydroxyalkylation adding progressively calculated amounts of LiCl to the medium.

Let us first consider, at the molecular scale, the progress of the reaction conducted in the presence of 1 equiv. LiCl directly added onto the 3APLi/MeLi mixed aggregate (Scheme 2, route 2). The data in Fig. 1 suggest that at t = 0, the medium consists of a mixture of free MeLi and 3APLi/LiCl inert mixed aggregate. Thus, when the aldehyde is introduced, the addition is bound to generate racemic alkoxide, at least at its very early stage. This latter accumulates and extracts, little by little, the lithium chloride out of the 3APLi/LiCl dormant complex. Chiral lithium amide is thus progressively released in the medium and its concentration is expected to increase at a rate similar to the reaction rate. The freed 3APLi can then aggregate with unreacted MeLi, affording the 3APLi/MeLi entity able to react enantioselectively with the forthcoming aldehyde. According to this analysis, the chiral nucleophile builds up during the reaction and the enantiomeric excess should increase gradually as the reaction proceeds (ee = $f(t)$) to reach a final 40% average value. Note that such a thermodynamic scenario relies on the assumption that all the exchanges between partners of the complexes are fast, thus that there is no high kinetic barrier governing the exchanges.

Now, the major advantage that can be taken of the higher stability of the alkoxide/LiCl mixed aggregate is the possibility to run the above model reaction using sub-stoichiometric amounts of chiral 3APLi ligands. Following the procedure depicted in route 1 of Scheme 1, the asymmetric induction drops progressively when the amount of the 3APLi ligand is decreased from 1 to 0.1 eq. (Table 1, entries 1–3). The theoretical data suggest that a sub-stoichiometric version can be set up in the presence of LiCl *provided this salt does not interfere with the two active partners* (3APLi and MeLi). This was achieved by adding LiCl to the THF solution of the aldehyde *before* it is introduced onto the preformed 3APLi–MeLi aggregate (Scheme 3, ESI† section).

In fact, following this new protocol, when 1 equiv. LiCl is used, the induction phenomenon is improved as shown by the 86% ee (entry 4). An NMR study conducted in parallel to determine the structure in solution of the alkoxide/lithium chloride mixed aggregate led to the conclusion that it organizes as a 3 : 1 *o*-tolCH(CH_3)OLi/LiCl cubic tetramer (ESI† section). We thus run the above reaction in the presence of only a third equivalent of lithium halide. In this case, an 82% ee is measured (entry 5). From these latter conditions, reducing the amount of the 3APLi chiral inductor to 0.33 equiv. proved to be successful since an 80% ee is measured (entry 6). Further reducing the amount of the chiral ligand to 0.1 equiv. triggered a severe drop of the enantiomeric excess (ee = 40%, entry 7). This disappointing result can be directly related to the ~10 mol% LiCl contaminating the commercial solutions of



Scheme 3 Evolutionary inductive process during the nucleophilic addition of MeLi onto *o*-TolCHO in the presence of 1 equiv. 3APLi/MeLi and 1 equiv. LiCl.

methyllithium in diethylether. The DFT data suggest that this pollutant is likely to seize most of the 10 mol% 3APLi in solution. To thwart this problem, the "native" LiCl in MeLi was first titrated by silvermetry,[12] then trapped by three equivalents of (*S*)-PhCH(CH_3)OLi. The resulting "cleansed" MeLi solution was used to repeat the experiment with 0.1 equivalent of the chiral ligand and this time, a rewarding 70% ee was measured (entry 8). This reproducible value remains below the 80% measured when 0.33 equiv. of a ligand is used, probably because the fine-tuning and handling of low amounts of water and air-sensitive aggregates is delicate at the 1–5 mmol bench scale.

In conclusion, the data presented in this communication show that LiCl can be an ally in the enantioselective nucleophilic 1,2-addition of organolithium reactants to aldehydes. In its absence, our DFT values suggest that the chiral lithium amide used here as a chiral "ligand" is selectively trapped by the alkoxide produced by the reaction, progressively hampering its enantioselectivity. The same calculations hint at a higher affinity between ROLi and LiCl, and explain that this salt can act as a scavenger provided it is added at the proper time to keep the lithium alkoxide apart from the catalytic cycle. These matches helped us to improve a catalytic stoichiometric enantioselective nucleophilic 1,2-addition of an alkyllithium onto an aldehyde and even transform it into the *first sub-stoichiometric version* with marginal alteration of the ee. Obviously, the levels of asymmetric induction now remain to be optimized and this work is extended to other electrophiles and organolithium reactants or additives to check if the phenomenon observed here can be general. However, we think that the actual procedure provides hints to fine-tune other enantioselective processes. Otherwise, it is worth underlining that reaching 70% ee with extremely reactive reactants using no more than 10% of a cheap catalyst is groundbreaking in this field.[15]

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