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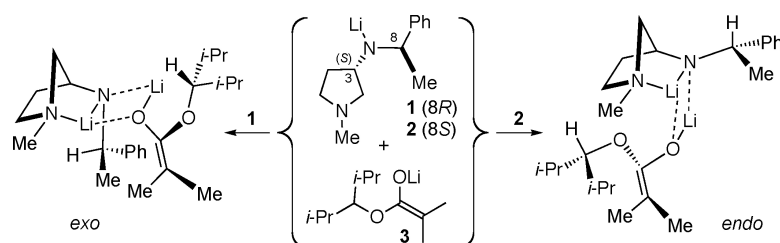
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Enantioselective Conjugate Addition of a Lithium Ester Enolate Catalyzed by Chiral Lithium Amides: A Possible Intermediate Characterized

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ABSTRACT
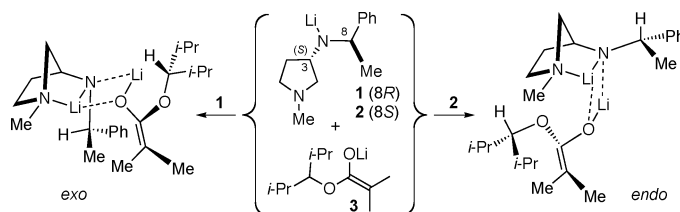
Two 1:1 noncovalent mixed aggregates between a lithium enolate and two diastereomeric lithium amides have been identified spectroscopically in THF. The NMR data, as well as DFT theoretical calculations, shine some light on a puzzling reversal of induction, observed when switching from one diastereomer of the amide to the other in the enantioselective Michael addition of the lithium enolate to an unsaturated ester.

Asymmetric catalysis has emerged as one of the most important tools in enantioselective synthesis. This field has reached a point where screening of chiral ligands is often the limiting step in terms of time invested and creativity. Even when the mechanisms involved are relatively well-known, the stereochemical outcome is often seen as the product of a "black-box" mechanism relying on a blind structural investigation. A more rational approach is based on the characterization of putative intermediates at reach of theoretical and analytical means. Organometallic chemistry provides excellent platform to showcase the combination of synthesis, NMR spectroscopy, and DFT calculations to elucidate mechanisms.[1] This paper presents such an analysis applied to the useful, but poorly understood, catalytic enantioselective conjugate addition of lithium enolates.

We showed recently that the chiral 3-aminopyrrolidine lithium amides (3APLi **1** and **2**) mediate the enantioselective Michael additions of lithium ester enolate **3** on (*E*)-*tert*-butyl crotonate (Scheme 1).[2] The resulting diester **4** exhibited ee's up to 74–76%; interestingly, the direction of the induction was revealed to be sensitive to both the configuration of the C^8 stereogenic center of the amide or the solvent (THF vs toluene).
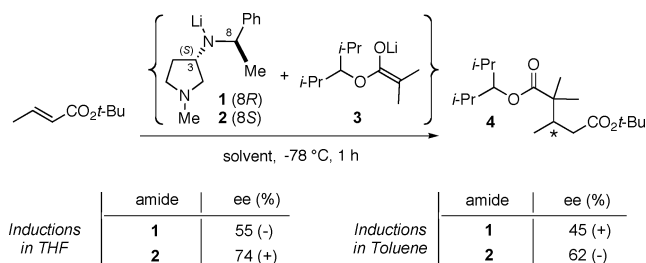
[†] University of Rouen.

[‡] Kyoto University.

(1) For a review, see: Gielen, M., Willem, R., Wrackmeyer, B., Eds. *Advanced Applications of NMR to Organometallic Chemistry*; Wiley: New York, 1996. (a) Corruble, A.; Davoust, D.; Desjardins, S.; Fressigné, C.; Giessner-Prettre, C.; Harrison-Marchand, A.; Houte, H.; Lasne, M.-C.; Maddaluno, J.; Oulyadi, H.; Valnot, J.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 15267–15279. (b) See also among recent references: Pregosin, P. S.; Kumar, P. G. A.; Fernandez, I. *Chem. Rev.* **2005**, *105*, 2977–2998. (c) Singh, K. J.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 13753–13760. (d) Tang, J. A.; Ellis, B. D.; Warren, T. H.; Hanna, J. V.; Macdonald, C. L. B.; Schurko, R. W. *J. Am. Chem. Soc.* **2007**, *129*, 13049–13065. (e) Liu, J.; Li, D.; Sun, C.; Williard, P. G. *J. Org. Chem.* **2008**, *73*, 4045–4052.

(2) Duguet, N.; Harrison-Marchand, A.; Maddaluno, J.; Tomioka, K. *Org. Lett.* **2006**, *8*, 5745–5748.

	amide	ee (%)		amide	ee (%)
Inductions in THF	**1**	55 (-)	*Inductions in Toluene*	**1**	45 (+)
	2	74 (+)		**2**	62 (-)

To investigate this further, we embarked on a study of the intermediates formed when the 3APLi's **1** or **2** and the lithium ester enolate **3** are combined. The formation of a noncovalent mixed aggregate between **3** and 3APLi could be anticipated on the basis of the literature data: several [6]Li and ^{15}N NMR investigations made on achiral systems, in particular by Collum and colleagues, showed the formation of mixed aggregates. Thus, LDA and the lithium enolate of pinacolone[3] (Figure 1, left) or LDA and a lithium ester
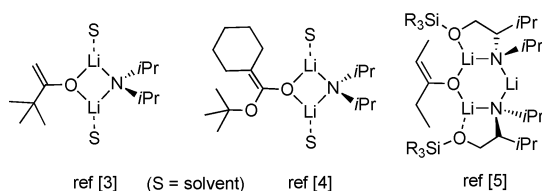

Figure 1. Mixed aggregates of lithium amide and lithium enolate described in the literature.

enolate formed in situ[4] (Figure 1, middle) both yielded well-organized 1:1 complexes in THF. However, in toluene, Williard and co-workers described a 2:1 chiral Li-amide/Li-enolate (derived from 3-pentanone) trimer on the basis of [6]Li NMR spectra (Figure 1, right) supported by an X-ray diffraction.[5] These rare results are significant since getting a detailed picture of key intermediates arising *in solution* still remains a challenge for asymmetric synthesis.

Our own experimental results also suggested that a mixed aggregate between the lithium amide and the lithium enolate could form.[2] We thus tried to characterize such complexes *in solution* at the onset of the reaction. The reagents were prepared, first in THF, following a procedure similar to that

(3) (a) Galiano-Roth, A. S.; Kim, Y. J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053–5055. (b) Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575–9585. (c) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9198–9202.

(4) (a) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2452–2458. (b) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2459–2463.

(5) (a) Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7829–7830. (b) Li, D.; Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 11726–11736.

previously described.[2] The lithium amides **1** and **2** were preformed at −20 °C, directly in a NMR tube, by adding 1 equiv of Me[6]Li[6] in THF-d_8 ($c = 0.25$ M) to a solution of amine in the same solvent. After 30 min at this temperature, 1 equiv of the ester precursor of the enolate **3** was introduced in solution, still in THF-d_8. After 30 min at −20 °C, the enolate was assumed to be formed and the amine regenerated. This latter was redeprotonated by 1 equiv of the same solution of Me[6]Li. This procedure ensured no free amine remained in the medium. The species were left at −20 °C for another 30 min, and then the sample was cooled to −78 °C before analyses.

The split of proton pairs H_a^4 and H_a^5 from the ^{1}H NMR spectra[7] of the two amines suggests that the amides adopt an aza-norbornyl folding (see Figure 2 for amide **1**, and the Supporting Information for **2**).[1b,c,8] The split of protons H_e^6 of the enolate (by ~0.2 ppm) indicates that this partner strongly interacts with the amide.

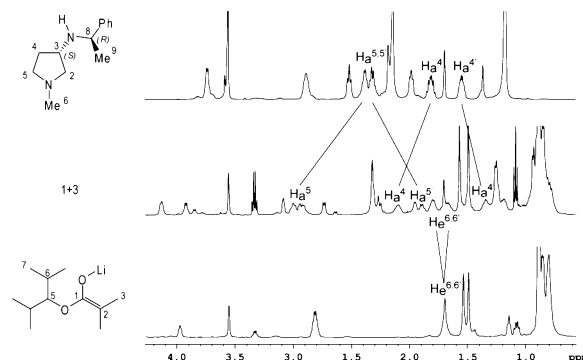**Figure 2.** [1]H spectra (−78 °C, THF-d_8) of **1** + **3**.

The hypothesis of an association between **3** and the amide **1** or **2** was strengthened by [6]Li NMR analyses (parts a and b of Figure 3, respectively). Both spectra exhibit two major
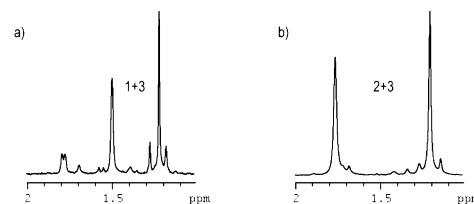

Figure 3. [6]Li spectra of (a) **1** + **3** (−55 °C) and (b) **2** + **3** (−78 °C) in THF-d_8.

singlets (1.13 + 1.44 ppm for **1/3**,[9] 1.20 + 1.77 ppm for **2/3**) with similar integrations.[10] The analogies between these

(6) Paté, F.; Oulyadi, H.; Harrison-Marchand, A.; Maddaluno, J. *Organometallics* **2008**, *27*, 3564–3569.

(7) H_a and H_e correspond to protons on the amides and on the enolate, respectively.

spectra and those recorded for the 3APLi/AlkLi[1a] (3APLi = **1** or **2**, Alk = Me or *n*-Bu) or the 3APLi/LiCl[8] complexes strongly suggest the formation of 1:1 mixed aggregates.

The ^{6}Li spectra of **1** + **3** mixture were registered at −55 °C because, at −78 °C, a broad singlet at 1.12 ppm is observed, which corresponds to the overlapping of the two lithium signals (Supporting Information). Varying the temperature from −95 to −55 °C showed that one of the ^{6}Li peaks remains at 1.12 ppm while the other is shifted downfield from 0.9 ppm at −95 °C to 1.6 ppm at −55 °C. Both Li signals for the **1** + **3** couple are distinct at −55 °C, and all additional NMR experiments were run at this temperature. In contrast, the **2** + **3** mixture is insensitive to temperature; therefore, all spectra were registered at −78 °C.

The aggregation could be confirmed by ^{1}H DOSY experiments.[5b,11] This bidimensional diffusion-ordered NMR technique plots a regular ^{1}H NMR spectrum vs the diffusion coefficients. It differentiates species into solution on the basis of their hydrodynamic radius that is directly correlated to their size, according to the Stokes−Einstein equation.[12] Williard and co-workers have recently shown that DOSY applies very well to organolithium aggregates.[13]

In our case, the spectrum in Figure 4 shows the formation of a single species out of the lithium enolate and the lithium amide (Figure 4). A distinct diffusion coefficient (blue spectrum) is measured for the mixture, different from those of the isolated partners (red and black). These recordings were done at −20 °C to get sufficient diffusion.
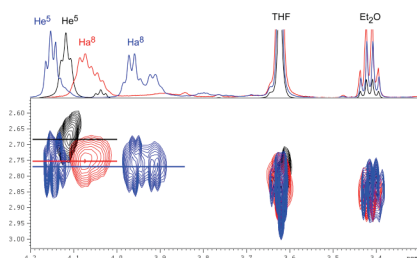

Figure 4. Superposition of selected portions of the ^{1}H DOSY spectra of **1** (red), **3** (black), and **1** + **3** (blue) at −20 °C in THF-d_8.

The structure of the newly formed complexes was determined by bidimensional experiments. The ^{1}H,^{1}H NOE-

SY spectrum of the **1** + **3** complex (Figure 5) shows H_e^5/H_a^2, H_e^5/H_a^6, H_e^3/H_a^9, and H_e^3/H_a^{Ar} cross-peaks. These data indicate that the alkoxy group of the enolate ($CH_e^5iPr_2$) faces the CH_a^2 methylene bridge of the amide, while the ethylidenic part ($C_e^1{=}C_e^2$) is near the C_a^8 chiral chain.
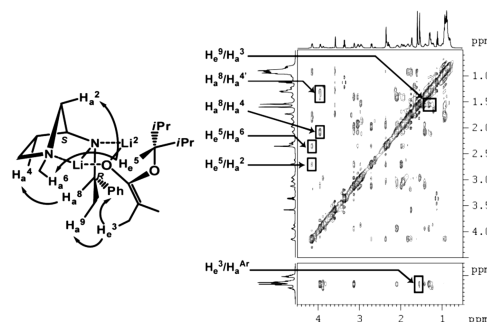

Figure 5. ^{1}H,^{1}H NOESY spectrum of **1** + **3** (THF-d_8, −55 °C).

In the ^{6}Li,^{1}H HOESY spectrum (Figure 6), only one of the two lithium cations gives cross-peaks with both the enolate and the amide protons. The larger half-height signal width associated with this lithium ion suggests that it corresponds to the most solvated one (Li^2). The strong correlation observed between Li^2 and H_a^2 implies that the complex adopts an *exo* topology,[1a,8] an observation confirmed by the NOESY correlations between H_a^8 and H_a^4.
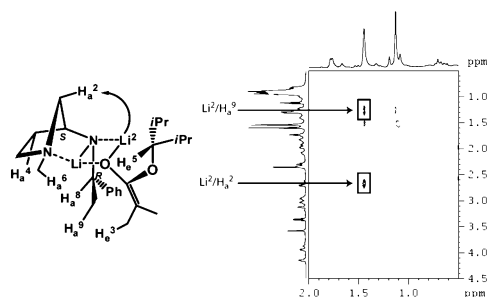

Figure 6. ^{6}Li,^{1}H HOESY spectrum of **1** + **3** (THF-d_8, −55 °C).

A similar protocol was followed for **2** + **3**. The NOESY and HOESY (Supporting Information) evince an *endo* topology for this second complex[1a,8] (Figure 7) in which the alkoxy group of the enolate (CH_e^5-*i*-Pr$_2$) faces the ethylenic bridge ($CH_a^4{-}CH_a^5$) of the amide. The absence of correlation between the ethylidenic part of **3** and the amide indicates that this appendage points to the outer part of the complex.

In addition to these experiments, DFT calculations were undertaken on models of **1** + **3** and **2** + **3** in THF. The computational method retained (B3P86, 6-31G** as implemented in the Jaguar software[14]) was in line with our previous works in the field.[7] A simplified model was adopted

(8) Paté, F.; Duguet, N.; Oulyadi, H.; Harrison-Marchand, A.; Fressigné, C.; Valnot, J.-Y.; Lasne, M.-C.; Maddaluno, J. *J. Org. Chem.* **2007**, *72*, 6982−6991.

(9) Values of chemical shifts at −55 °C. Several ^{6}Li spectra have been registered for the **1/3** mixture at different temperatures, and the results are discussed in this paper.

(10) ^{6}Li chemical shifts are given with respect to an external reference of 0.3 M ^{6}LiCl in MeOH-d_4 (δ 0.0).

(11) The DOSY is a remarkable tool for the analysis of aggregates into solution. For recent examples, see refs 1d, 5b, and: Li, D.; Sun, C.; Liu, J.; Hopson, R.; Li, W.; Williard, P. G. *J. Org. Chem.* **2008**, *73*, 2373−2381.

(12) $D = (k_B T)/(6\pi\eta r)$, where D is the diffusion coefficient, k_B is the Boltzman constant, T is the temperature, η is the viscosity of the solution, and r is the radius of the molecular sphere.

(13) Li, D.; Keresztes, I.; Hopson, R.; Williard, P. G. *Acc. Chem. Res.* **2009**, *42*, 270−280.

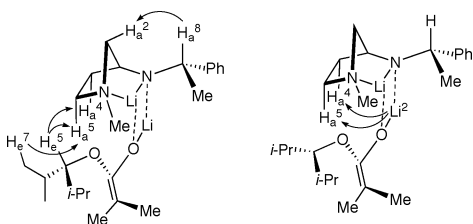(14) Jaguar 5.5, release 11, Schrödinger, LLC., Portland, OR, 2003.

Figure 7. NOE (left) and HOE (right) correlations of *endo* **2** + **3**.

whereby the 2,4-dimethylpentan-3-oxy appendage of the enolate **3** was replaced by an isopropoxy. With the solvent playing a pivotal role on the stability of these species, two explicit THF molecules were added on the lithium cations to model the solvation first shell. The optimization of 1:1 arrangements of **1** + **3** and **2** + **3** inspired from those obtained with mixed aggregates of amide **1** or **2** and MeLi was undertaken. It led to four local minima based on a tight O−Li−N−Li parallelogram and presenting either an *endo* or an *exo* topology. For the sake of space saving, only one of those is displayed in Figure 8 (see the Supporting Information for the others).
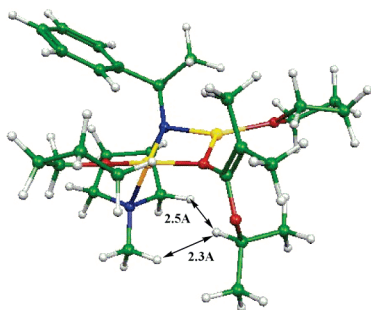

Figure 8. Optimized conformer A of *exo* **1** + **3** complex.

Conformers A and B (see the Supporting Information) of the *endo* **2** + **3** complex are similar in energy ($\delta E \approx 0.3$ kcal·mol^{-1}). Their geometries differ mainly by the orientation of the enolate chain. For the *exo* **1** + **3** complex, the same duality is calculated, the two conformers A′ and B′ being separated by ~1 kcal·mol^{-1}. Overall, the theoretical results are in fine agreement with the NOE data, even if the main conformer of the **1** + **3** aggregate, as determined by NMR, is the less stable one (but by 0.3 kcal·mol^{-1}, a very small value to be related to the sensitivity of complex **1** + **3** to temperature), while the **2** + **3** aggregate corresponds to the more stable situation (distances in Figure 8 and spectra in Figure 5).

Extending the experimental study to toluene-d_8 proved problematic. First, methyllithium is insoluble in toluene, and ^{6}Li n-butyllithium was employed to deprotonate the amines. The monodimensional ^{1}H spectra displayed broad signals that

we were unable to decipher. In contrast, the ^{6}Li elements brought information that proved somewhat helpful (see the Supporting Information). The ^{6}Li spectrum of **2** alone in toluene-d_8 recorded at different temperatures suggests that several species are in equilibrium, one of those dominating at 253 K. Next, we mixed **2** with enolate **3** in the 2:1−1:1 range at 195 K in the same solvent, and three new major singlets (at 1.35, 1.92, and 2.40 ppm) were observed.[15] Unfortunately, no convincing information could be obtained from the extra bidimensional spectra that were run.[16] Some THF-d_8 was added to the solution to check that these troubles were not due to partial hydrolysis of the sample. After introduction of 2 equiv of this solvent, signals similar to those in pure THF could be observed.

It is somewhat difficult to go further in this analysis. The large number of degrees of liberty associated with the approach and the docking of the *tert*-butyl crotonate on the **1** + **3** or **2** + **3** complex characterized in THF makes their formal description difficult. It is nevertheless worth noting that the orientation of the nucleophilic double bond of the enolate can flip relatively easily in **1** + **3** (which gives average ee's), while it is more rigid in **2** + **3** (which provides ee's up to 74%). The Curtin−Hammett principle indicates that the study of reactant structures cannot put any specific mechanism in evidence. However, the 1:1 mixed aggregates formed in THF between lithium enolate **3** and chiral lithium amides **1** or **2** at low temperature can reasonably be related to the chemical results, since diester **4** is obtained preferentially as its (−) enantiomer when the *exo* complex is formed, while the *endo* complex leads principally to the (+) enantiomer. Unfortunately, a similar parallel between the structures into toluene and the inductions obtained in this solvent could not be done. The possible formation of an enolate/lithium amide 1:2 trimer in this hydrocarbon can only be evoked at this time by analogy with recent results in the literature.[1d,5,11,17] A different experimental approach will have to be developed to circumvent the problems encountered at this stage.

Supporting Information Available: Materials and spectra for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The accuracy of the ratio is limited by the entangled ^{1}H signals in the spectra used to evaluate the conversion of the protonated species in toluene.

(16) The analogy between this NMR profile and that published by Williard et al. (ref 11) suggests that we could also be dealing here with a heterogeneous trimer associating two amides **2** to one enolate **3**. If the complexes in toluene are trimers instead of dimers, the condensation process is likely to be different, explaining the reversal of the induction.

(17) Hilmersson, G.; Malmros, B. *Chem. Eur. J.* **2001**, *7*, 337–341.