

Enantioselective Conjugate Addition of a Lithium Ester Enolate Catalyzed by Chiral Lithium Amides

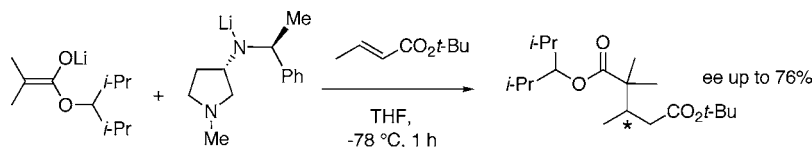
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ABSTRACT



Mixed aggregates of chiral lithium amide and lithium ester enolate have been employed in the enantioselective conjugate addition on α,β -unsaturated esters. Michael adducts were obtained in ee's up to 76% combining a lithium enolate and a chiral 3-aminopyrrolidine lithium amide. The sense of the induction was found to be determined by both the relative configuration of the stereogenic centers borne by the amide and the solvent in which the reaction was conducted.

The stereoselective formation of carbon–carbon bonds by conjugate addition of carbon nucleophiles to α,β -unsaturated systems has been studied intensively over the past few years.¹ Among the useful nucleophiles used in this process, lithium enolates derived from ketones or esters, which have found countless applications in aldolisation reactions,² remain relatively underemployed.^{3,4} Most reported examples are limited to the addition of stabilized enolates such as those derived from malonates, cyanoacetates, and acetoacetates.⁵

Indeed, the reactions with simple, unstabilized enolates are often complicated by side reactions, which include proton transfers, undesired condensations between reacting species, and concomitant 1,2-additions.

Nevertheless, a few diastereo-⁶ and enantioselective⁷ versions of the conjugate addition were successfully developed. In the latter case, the lithium enolates have been closely associated to chiral diethers,^{7c} amines,^{7a–c} lithium alkoxides,^{7e} or lithium amides.^{7a} Thus, Tomioka's group has been studying the influence of chiral diethers (such as **2**, Scheme 1), on the 1,4-addition of lithium ester enolates onto cyclic

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(1) For reviews on the asymmetric Michael addition, see for instance: (a) Sibi, P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196. (c) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894. (d) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688–1690.

(2) Valnot, J.-Y.; Maddaluno, J. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley and Sons Ltd.: Chichester, U.K., 2006; Vol. 2, pp 525–646.

(3) (a) Yamaguchi, M.; Tsukamoto, M.; Hirao, I. *Chem. Lett.* **1984**, 375–376. (b) Yamaguchi, M.; Tsukamoto, M.; Hirao, I. *Tetrahedron Lett.* **1985**, *26*, 1723–1726.

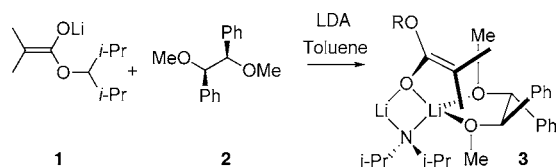
(4) Yamataka, H.; Yamada, K.; Tomioka, K. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley and Sons Ltd.: Chichester, U.K., 2004; Vol. 1, pp 901–939.

(5) RajanBabu, T. V. *J. Org. Chem.* **1984**, *49*, 2083–2089.

(6) (a) Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025–5028. (b) Bernardi, A.; Marchionni, C.; Novo, B.; Karamfilova, K.; Potenza, D.; Scolastico, C.; Roversi, P. *Tetrahedron* **1996**, *52*, 3497–3508. (c) Davies, S. G.; Diez, D.; Dominguez, S. H.; Garrido, N. M.; Kruchinin, D.; Price, P. D.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 1284–1301.

(7) (a) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271–1290. (b) Yasuda, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 6343–6346. (c) Iguchi, M.; Doi, H.; Hata, S.; Tomioka, K. *Chem. Pharm. Bull.* **2004**, *52*, 125–129. (d) Tomioka, K. *Yakugaku Zasshi* **2004**, *124*, 43–53. (e) Kumamoto, T.; Aoki, S.; Nakajima, M.; Koga, K. *Tetrahedron: Asymmetry* **1994**, *5*, 1431–1432.

Scheme 1. Putative Ternary Complex Formed between a Chiral Diether, LDA, and a Lithium Enolate^{7c}

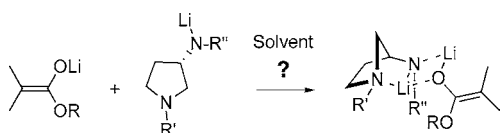


and acyclic enones.^{7c} Interestingly, the best ee (74%) was obtained when adding one equiv of LDA to the stoichiometric mixture of enolate and chiral ligand (1:1:1). More generally, the reaction of putative ternary complexes (such as **3**, Scheme 1) was found to give adducts in higher ee's than the corresponding binary complexes working without the assistance of a lithium amide.^{8,9}

The formation of mixed aggregates of ketone or ester enolates and chiral or achiral lithium amides has also been evidenced, both in the solid state¹⁰ and in solution.^{8,11} These entities have been proposed to be decisive actors controlling the kinetics, the regioselectivity and the enantioselectivity of the reaction in which they are involved.

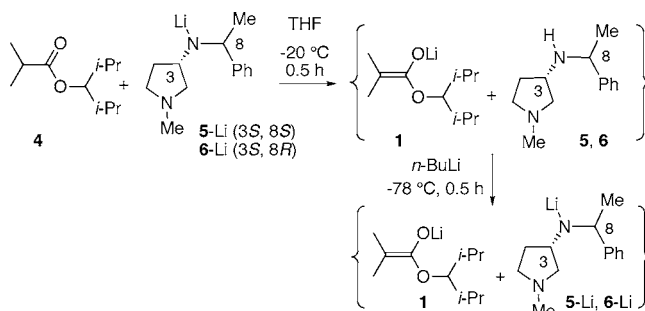
3-Aminopyrrolidines (3APLi) are known to form 1:1 noncovalent aggregates, 3APLi:RLi, the structure of which was established by NMR¹² and supported by DFT calculations.^{12,13} These aggregates have been used as chiral auxiliaries for the enantioselective 1,2-addition of alkyl-,¹⁴ aryl-,¹⁵ and vinylolithiums¹⁶ on aldehydes. We present here results suggesting that 3APLi can also form aggregates with lithium enolates of ester (Scheme 2), to be used in enantioselective Michael additions on α,β -unsaturated esters.

Scheme 2. Hypothesis of a Mixed Aggregate between a Lithium Enolate and 3APLi



The study was conducted with the lithium enolate **1** derived from 2,4-dimethylpentan-3-yl *iso*-butyrate **4** (Scheme 3). This choice circumvents the problem of the control of

Scheme 3. Protocol to Generate an Enolate:Amide Aggregate



the enolate double bond configuration and leads to the creation of a single asymmetric center.¹⁷ The protocol retained to run these experiments was designed to avoid, in a first set of experiments, any interference of the amine used to deprotonate the ester with the putative complex of enolate and amide. Therefore, the enolate was generated by adding 3APLi to the ester (30 min at -20 °C; see Supporting Information). The resulting 3APH (**5** or **6**) was then deprotonated in situ by 1 equiv of *n*-BuLi added atop (Scheme 3).

The first experiments were optimized using (*E*)-*tert*-butyl crotonate. Parameters to be considered included the solvent, the temperature, and the ratio between the enolate, the amide, and the substrate (Table 1). Preparing the enolate **1** with LDA and leaving the residual *i*-Pr₂NH in the medium led to a poor 13% yield after 6 h (entry 1). A similar result was obtained replacing LDA with **5**-Li (yield = 11%). In contrast, the presence of 1 equiv of lithium amide enhanced the yield of the transformation up to 86% (entry 2), as previously noted in the enantioselective 1,2-addition of comparable lithium enolates on imines.¹⁸ We next substituted LDA with the chiral **5**-Li and were delighted to note that the resulting ester (+)-**7** was obtained in 68% yield and 72% ee (entry 3). Increasing the chiral amide to enolate ratio improved slightly the yields but left the ee almost unaltered (entries 4 and 5). This observation supports the hypothesis of the formation of a 1:1 enolate:amide aggregate (Scheme 2). The best results (yield = 82%, ee = 76%) were obtained when increasing both the amide and enolate concentrations (entry 6). Interestingly, swapping from THF to toluene reversed the sense of the induction, albeit the performances of the reaction were somewhat decreased (entry 7). This inversion was also observed with the diastereomeric amide **6**-Li (entry 8), as noted previously during the 1,2-addition of alkylolithiums on

(8) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060–2061.

(9) Iguchi, M.; Tomioka, K. *Org. Lett.* **2002**, *4*, 4329–4331.

(10) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602–8604.

(11) (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) Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7829–7830. (c) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2459–2463. (d) Ramirez, A.; Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 10326–10336.

(12) Corruble, A.; Valnot, J. Y.; Maddaluno, J.; Prigent, Y.; Davoust, D.; Duhamel, P. *J. Am. Chem. Soc.* **1997**, *119*, 10042–10048.

(13) (a) Fressigné, C.; Maddaluno, J.; Marquez, A.; Giessner-Prettre, C. *J. Org. Chem.* **2000**, *65*, 8899–8907. (b) Fressigné, C.; Lautrette, A.; Maddaluno, J. *J. Org. Chem.* **2005**, *70*, 7816–7828.

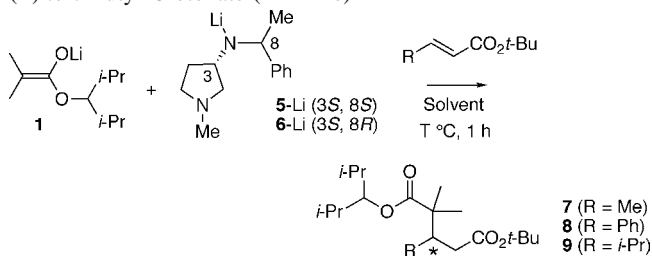
(14) (a) Corruble, A.; Valnot, J. Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63*, 8266–8275. (b) Corruble, A.; Davoust, D.; Desjardins, S.; Fressigné, C.; Giessner-Prettre, C.; Harrison-Marchand, A.; Houte, H.; Lasne, M.-C.; Maddaluno, J.; Oulyadi, H.; Valnot, J.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 15267–15279.

(15) Flinois, K.; Yuan, Y.; Bastide, C.; Harrison-Marchand, A.; Maddaluno, J. *Tetrahedron* **2002**, *58*, 4707–4716.

(16) Yuan, Y.; Harrison-Marchand, A.; Maddaluno, J. *Synlett* **2005**, 1555–1558.

(17) Kambara, T.; Hussein, M. A.; Fujieda, H.; Iida, A.; Tomioka, K. *Tetrahedron Lett.* **1998**, *39*, 9055–9058.

(18) Hussein, M. A.; Iida, A.; Tomioka, K. *Tetrahedron* **1999**, *55*, 11219–11228.

Table 1. Conjugate Addition of Lithium Enolate **1** on (*E*)-*tert*-Butyl Crotonate (R = Me)

entry	amide	ratio ^a	solvent	temp (°C)	7 (%) ^b	ee (%) ^c
1	LDA	0.0:1.3:1.0	THF	-78	13 ^d	
2	LDA	1.3:1.3:1.0	THF	-78	86	
3	5 -Li	1.3:1.3:1.0	THF	-78	68	72 (+)
4	5 -Li	1.7:1.3:1.0	THF	-78	83	74 (+)
5	5 -Li	2.6:1.3:1.0	THF	-78	81	71 (+)
6	5 -Li	2.4:2.0:1.0	THF	-78	82	76 (+)
7	5 -Li	1.7:1.3:1.0	toluene	-78	52	62 (-)
8	6 -Li	1.7:1.3:1.0	THF	-78	95	55 (-)
9	6 -Li	2.4:2.0:1.0	THF	-78	91	54 (-)
10	6 -Li	2.4:2.0:1.0	THF	-20	76	53 (-)
11	6 -Li	2.4:2.0:1.0	toluene	-78	45	45 (+)
12	6 -Li	2.4:2.0:1.0	toluene	-20	61	30 (+)

^a Ratio between amide:enolate:(*E*)-*tert*-butyl crotonate. ^b Isolated yields in **7**. ^c Measured by HPLC on a Daicel Chiralpak AD-H column (see Supporting Information). The absolute configuration of **7** remains to be determined. ^d Isolated yield after 6 h.

o-tolualdehyde.^{14b} However, the associated ee's are lower (entries 8–10). Finally, a “double inversion” was noticed when employing **6**-Li in toluene; the (+)-**7** enantiomer was recovered, but in a mediocre 30% ee (entry 12).

We next probed the influence of the structure of the substrate on the enantioselectivity of the reaction (Table 2).

Table 2. Conjugate Addition of Lithium Enolate **1** on (*E*)-*tert*-Butyl Cinnamate (R = Ph) and (*E*)-*tert*-Butyl 4-methylpent-2-enoate (R = *i*-Pr) in the Presence of Chiral 3APLi in THF

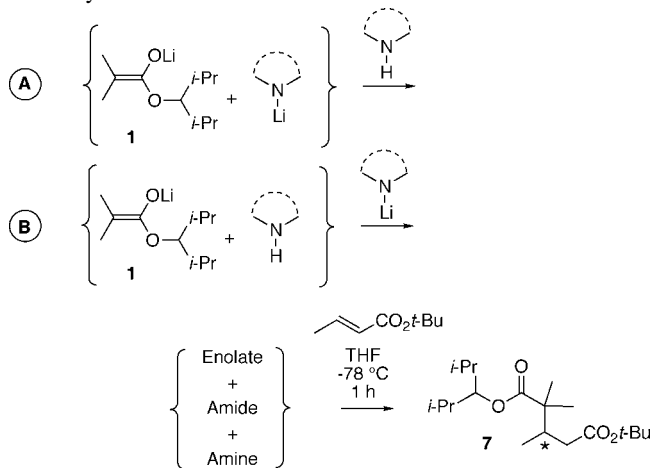
entry	R ^a	amide	temp (°C)	time (h)	yield (%) ^b	ee (%) ^c
1	Ph	5 -Li	-78	6	8 (52)	12 (+)
2	Ph	5 -Li	-20	2	8 (94)	2 (+)
3	Ph	6 -Li	-78	6	8 (52)	50 (-)
4	Ph	6 -Li	-20	2	8 (96)	6 (-)
5	<i>i</i> -Pr	5 -Li	-78	3	9 (75)	11 (+)
6	<i>i</i> -Pr	6 -Li	-78	3	9 (79)	15 (+)

^a R refers to the Scheme in Table 1. ^b Isolated yields in **8** or **9**. ^c Measured by HPLC on a Daicel Chiralpak AD-H column (see Supporting Information). The absolute configurations of **8** and **9** remain to be determined.

Applying the previous protocol to **5**-Li and *tert*-butyl cinnamate (R = Ph) required longer reaction times and led to very disappointing results inductionwise (entry 1). Raising the temperature increased significantly the reaction rate while the ee plummeted (entry 2). A similar observation was made with amide **6**-Li (entries 3 and 4).

The congested product resulting from the addition of our bulky enolate to cumbersome (*E*)-*tert*-butyl 4-methylpent-2-enoate (R = *i*-Pr) resulted in surprisingly good chemical yields; however, the associated ee's remained very low (entries 5 and 6). Overall, this reaction seems highly substrate sensitive and requires a re-optimization of its conditions in every new case.

In a last section, we ran complementary experiments to probe the possible formation of ternary enolate:amide:amine complexes, closer to the enolate:amide:chiral ether studied previously by Tomioka et al.^{7c} Thus, two new protocols were designed. The first (protocol A) was identical to that described above (Scheme 3), except that it was followed by the addition of an extra equivalent of an amine atop of the enolate-amide mixture. The second protocol (B) implied the deprotonation of the ester by a given lithium amide, resulting in an enolate-amine mixture, before a second equivalent of another lithium amide was added (Table 3). In all cases, the

Table 3. Conjugate Addition of Lithium Enolate **1** on *tert*-Butyl Crotonate in the Presence of Amide and Amine

entry	protocol ^a	first amine/amide	second amine/amide	7 (%) ^b	ee (%) ^c
1	A	5 -Li	<i>i</i> -Pr ₂ NH	79	71
2	B	5	LDA	72	67
3	A	5 -Li	5	94	62
4	A	LDA	5	60	19
5	B	<i>i</i> -Pr ₂ NH	5 -Li	47	66

^a See text for the definition of the protocols. ^b Isolated yields. ^c Measured by HPLC on a Daicel Chiralpak AD-H column (see Supporting Information). The (+) enantiomer was recovered in all of these experiments.

ratio amine/amide/enolate/*tert*-butyl crotonate was kept equal to 1.3:1.3:1.3:1.0, figures adapted from the above results. The data are presented in Table 3. Its entry 1 suggests that the addition of *i*-Pr₂NH to the enolate:**5**-Li complex is meaningless, the results being similar to those obtained in Table 1, entry 3. When the order of introduction of the additives is reversed (entry 2), the output is hardly altered. This suggests that LDA is more basic than **5**-Li and that a similar enolate:**5**-Li aggregate is obtained in entries 1 and 2. The latter seems to be poorly affected by the chiral amine

5, which exerts a slightly unfavorable effect on the ee (entry 3), suggesting a “mismatch” relationship between the amine and its corresponding amide. If the enolate is first aggregated with LDA and the free chiral amine **5** added atop of this complex (entry 4), the ee drops to 19%. This observation probably translates the mediocre induction power of the amine itself, which would hardly interact with the robust enolate:achiral amide mixed aggregate. Entry 5 finally supports the above assumptions, since the addition of **5**-Li to the enolate:*i*-Pr₂NH mixture once more affords the enolate:**5**-Li complex associated with a 66% ee.

Inspired by Seebach's pioneering works,^{7a} we finally attempted to form a ternary complex between LiBr, enolate **1**, and **5**-Li. However, generating the enolate with **5**-Li and then deprotonating the resulting amine with MeLi:LiBr (1:1) led to disappointing figures (yield = 15%, ee = 11%).

In conclusion, the above results show that 3APLi lithium amides act as chiral auxiliaries in the enantioselective conjugate addition of lithium enolate to α,β -unsaturated esters. Values for ee's of up to 76% were reached after optimization of the experimental conditions. The sense of the induction appears to be controlled both by the relative

configuration of the stereogenic centers borne by the amide and by the solvent. The analysis of the data suggests that, at low temperature, mixed aggregates form between the two lithiated entities. Within the limits of the Curtin–Hammett postulate, this complex can be held responsible for the observed inductions. Detailed NMR and theoretical studies will be necessary to describe the structure of this putative species and its interaction with the electrophiles.^{12,14b}

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Supporting Information Available: Detailed experimental procedures and ¹H and ¹³C NMR spectra of the synthesized new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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