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Regioselective addition of *n*butyllithium on secondary cinnamyl amides : " Michael " versus " contra-Michael " process

Nathalie Bremand[a], Ilan Marek[b]*, and Jean F. Normant[a]*

a) Laboratoire de Chimie des Organoéléments, Université P. et M. Curie, Boîte 183, Tour 44-45

4 Place Jussieu, 75232 Paris Cedex 05, France

b) Department of Chemistry, Technion Institute of Technology

Technion City, 32 000 Haifa, Israel

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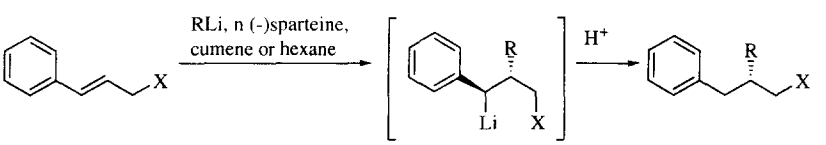
Abstract : Lithiated secondary cinnamyl amides undergo a preferred " contra-Michael " addition of *n*butyllithium, complexed with (-)sparteine, in a non polar solvent.

Keywords: alkyl lithium; (-)-sparteine; Michael addition; contra-Michael addition.

We have recently reported on the (-)sparteine mediated enantioselective carbolithiation of cinnamyl substrates (alcohols, ethers, amines) and of β-substituted styrenes [1] (Scheme1).



R= primary or secondary alkyl
n= 10% to 1 equivalent
X= OH, $OC(CH_3)_2OCH_3$, CH_2OH, OtBu, $N(CH_3)_2$, $N(Et)_2$, NHMe, NMeBn, CH_3, H

yield= 60-82%
ee= 66-95%

Scheme 1

As a follow up of this study we were intrigued by the " contra-Michael " type addition of various organolithium reagents on cinnamic acid or amides, initially disclosed by Klumpp *et al* [2], and more recently by Mortier *et al* [3] and Mestres *et al* [4]. These recent reports urge us to describe our own findings in this area. Some of the literature results, concerning 1,4 versus 3,4 addition of alkyllithium reagents to cinnamic acid are gathered in Scheme 2.

* Fax : (33) 01 44 27 75 67 E-mail : normant@ccr.jussieu.fr

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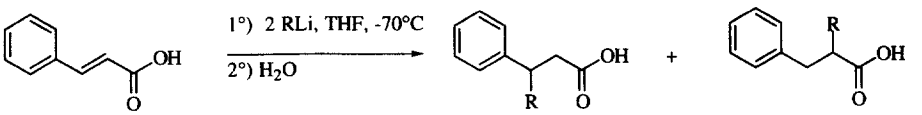


RLi	1,4/3,4[a]	yield (1,4)[b]	yield (3,4)[b]	ref
*t*Bu	60/40	38%	26%	2
	37/63	30%	37%	4
*n*Bu	95/5	33%	2%	2
	70/30	42%	18%	3
	95/5	50%	ε	4
*s*Bu	64/36	45%	25%	3

a ratios obtained from ^{1}H NMR spectra of crude mixtures

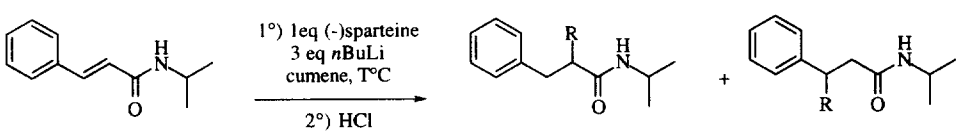
b yields refer to purified isolated compounds

Scheme 2

Although some 3,4- addition has thus been observed in THF at low temperature in the case of cinnamic acid, excellent 1,4- additions of various organolithium reagents to crotonamides (either secondary or tertiary) had been described by Snieckus [5] several years ago. Similarly Baldwin reacted alkyllithium reagents in the presence of TMEDA in THF with cinnamyl secondary amides in a 1,4- fashion [6]. However, in hexane / ether, Klumpp observed that with secondary amides of type R(R')C=CH-CO-NH-CH_3, " contra-Michael " (3,4- addition) was favoured (90%) when R=R'= Me_3Si, but was minor (14%) for R=R'= Ph and only 1,4- addition was observed when R=$SiMe_3$, R'=H [7].

These results have been considered as derived from an ionic mechanism as concerns the conjugate addition, and from a SET for the 3,4- addition [8]. However, for the latter, Mestres [4] also considers favourably an ionic mechanism related to a CIPE effect as already described for the β deprotonation of β aryl amides [9].

Following our previous methodology [1], we studied the addition of three equivalents of *n*butyllithium, and one equivalent of (-)-sparteine in cumene to cinnamyl-N-isopropyl amide and indeed, we observed a predominant 3,4- addition (versus 1,4-) leading to a benzyl lithium educt (Scheme 3).



Scheme 3

The two isomers are readily separated on silica gel, and display different signals for the CH-Bu group (δ^1H = 2,3 ppm for **A** and 3 ppm for **B**, δ^{13}C = 49 ppm for **A** and 43 ppm for **B**).

The rate of conversion is best when using concentrated solutions : 80% for a 0.2 M concentration (in cumene). The influence of temperature is not crucial for the overall yields, but lower temperatures (-20°C) favour the 3,4-

process : **A/B** = 53/47 at 25°C and 70/30 at –20 or –40°C. The amido group must be secondary or primary, otherwise 1,4- and 1,2- additions are observed, instead of 3,4- addition (table 1).

Table 1. Influence of the amido group on the regioselectivity of the addition of *n*butyllithium to cinnamyl amides

Amido group[a]	T°C (time)	**A/B**	Yield of **A** (A+B)[b]
CONHiPr	-20°C (5h)	70/30	47% (67%)
CONHMe	-30°C to –20°C (24h)	63/37	31% (49%)
$CONH_2$	-40°C to –20°C (5h)	66/34	29% (44%)
$CONMe_2$	-20°C (4h)	0/100	ε (27%)

[a] conditions: 3 equivalents of *n*BuLi, 1 equivalent of (-)sparteine, in cumene. [b]yields refer to isolated compounds

With secondary amides, the solvent and the diamine have also a significant influence (see table 2).

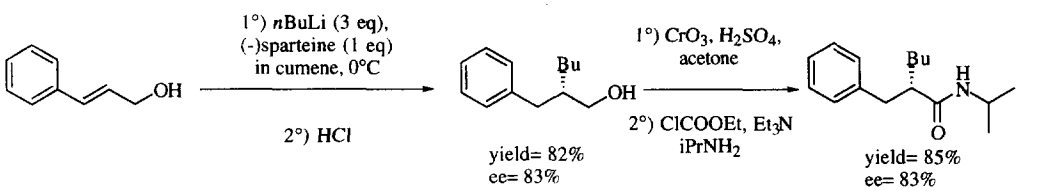
Table2. Influence of solvent and added diamine on the regioselectivity of the addition of *n*butyllithium (3 equivalents) to cinnamyl-N-isopropyl amides

Entry	Solvent	Diamine (n eq)	T°C(time)	**A/B**	Yield of **A**[a]
1	Et_2O/Hexane 1/1[b]	none	-40°C to rt (4h)	18/82	13%
2	Et_2O/Hexane 1/1	(-)sparteine (1)	-40°C to rt (4h)	62/38	44%
3	cumene	(-)sparteine (1)	-40°C to rt (4h)	68/32	45%
4	cumene	(-)sparteine (3)	-30°C to -20°C (24h)	86/14	56%
5	cumene	(-)sparteine (4)	-40°C to –20°C (24h)	89/11	42%
6	cumene	TMEDA (3)	-30°C to -20°C (24h)	45/55	19%

[a] Yields refer to isolated compounds. [b] Klumpp's conditions, see ref 7.

According to entry 4, " contra-Michael " product can be obtained in an acceptable 56 % yield, and surprisingly (-)-sparteine enhances the 3,4/1,4 ratio much more than TMEDA does: 86/14 versus 45/55.

Now that a substantial ratio of a chiral diamine inducing 3,4- addition was reached, the ultimate goal was to check enantioselection. An authentic sample of the chiral amide was prepared acccording to Scheme 4 from E-cinnamyl alcohol followed by oxidation and amidation of the acid. Comparison of the $[\alpha]_D^{25}$ thus measured, with those of products **A** showed that the induction obtained from cinnamyl-N-methyl amide, N-isopropylamide or from the primary cinnamylamide were very low : respectively 16%, 11% and 18% enantiomeric excess.



Scheme 4

In conclusion, the " contra-Michael " addition of *n*butyllithium to secondary cinnamyl amides is largely favoured when (-)sparteine is present in the reaction medium, in a non polar solvent.

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