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# Diastereoselective " contra-Michael " addition of (-)-sparteine/organolithium complexes to secondary chiral cinnamyl amides

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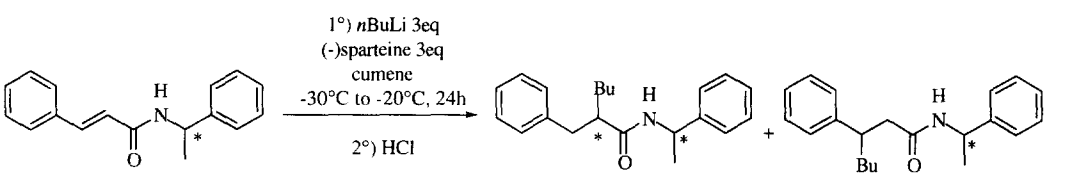
**Abstract** : " Contra-Michael " addition of (-)sparteine/organolithium reagents complexes to cinnamyl secondary amides derived from (R) or (S)-α-Methylbenzylamine occurs with matched or mismatched pairs, and allows an enantioselective access to 2-benzyl-amides,- acids, or- alcohols. © 1999 Published by Elsevier Science Ltd. All rights reserved.

*Keywords: alkyl lithium; (-)-sparteine; matched and mismatched pairs.*

In the preceding paper, we have shown that (-)sparteine induces a " contra-Michael " addition (3,4-addition) on cinnamyl secondary amides, much better than does TMEDA. However, the alkylated product showed disappointingly low enantiomeric excess. In order to take advantage of this (-)-sparteine induced reaction, we wondered whether a cinnamyl amide derived from a chiral amine would lead to a matched or mismatched transition state during the addition process.

Little is known whatsoever about the *conjugate* addition of lithium reagents to ethylenic amides derived from chiral amines [1]: the most efficient results have been obtained with α,β-unsaturated amides of (S)-2-(1-hydroxy-1-methylethyl)pyrrolidine, (S)-prolinol and (-)-ephedrine [2,3]. (S)-γ-trityloxymethyl-γ-butyrolactam was used as a chiral auxiliary in the conjugate addition of Grignard reagents to the corresponding α,β-unsaturated amides and imides in the presence of CuBr, $Me_2S$ [4,5]. Brown [6] reported good to excellent diastereoselective conjugate additions of alkyl Grignard reagents to the tertiary crotonamide and cinnamamide derived from (R)(-)-2-aminobutan-1-ol.

Herein, we shall concentrate exclusively on the 3,4- addition process (product **2** in scheme 1).




**1**-R or S **2** **3**

**Scheme 1**

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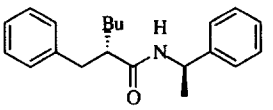
Table 1 shows our results with various ligands. With TMEDA in cumene (from –30°C to –20°C) or in diethylether (from –50°C to –20°C), 61/39 to 70/30 ratios of **2**/**3** were observed in 37-50% global yield (**1**+**2**). Product **2** was obtained as a major ***anti*** isomer (*anti/syn* = 80/20). In THF, the same major isomer was obtained (dr= 65/35) but with a lower yield, since 1,4 addition was predominant (73/27). Use of Tomioka ether [7] ((R, R)-1,2-dimethoxy-1,2-diphenylethane) instead of a diamine with (S)-**1** also gave the *anti* isomer as a 79/21 mixture in 39% yield, whereas (R)-**1** led with low yield to a 50/50 mixture of *anti/syn* isomers of **2**. With **(-)sparteine,** the addition of *n*butyllithium to (S)-**1** resulted in a good regioselectivity in favour of the 3,4 addition. Product **2** was obtained in 56% yield, in a 36/64 ratio of *anti/syn* isomers pointing to a " mismatched " pair of reagents. With (R)-**1**, not only the regioselectivity was enhanced to 84/16, but the overall yield was also improved up to 71% of isolated **2**. The *anti/syn* ratio now raises up to 22/78. Several cristallisations in hexane allowed isolation of the pure ***syn*** compound. Moreover, slow addition over 6 hours of the lithium reagent to the mixture of (R)-**1** and (-)-sparteine boosted the yield **to 79% with 88/12 regioselectivity** and still in a 23/77 *anti/syn* ratio.

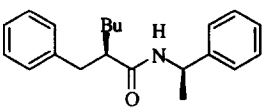
**Table 1.** Diastereoselective " contra-Michael " addition of *n*BuLi/ligand 1/1 complex (3 equivalents) to (R) or (S)-**1**.[a]

| Amide **1** | Ligand | Conditions | **2**/**3** | Yield **2**[b] | dr *anti/syn* | Major Diastereo isomer |
|---|---|---|---|---|---|---|
| (S) | TMEDA | Cumene, -30 to –20°C, 24h | 70/30 | 26% | 80/20 | *anti* (R,S) |
| (S) | TMEDA | $Et_2O$, -50 to –20°C, 24h | 61/39 | 30% | 81/19 | *anti* (R,S) |
| (S) | TMEDA | THF, -60 to –25°C, 24h | 27/73 | 9% | 65/35 | *anti* (R,S) |
| (R) | N,N-dimethylpiperazine | Cumene, -40 to –20°C, 24h | 36/64 | 20% | 43/57 | *syn* (R,R) |
| (S) | DBU | Cumene, -40 to –20°C, 24h | 77/23 | 36% | 71/29 | *anti* (R,S) |
| (S) | $[PhCH(OCH_3)]_2$ (R,R)[c] | Cumene, -40 to –30°C, 24h | 50/50 | **39%** | **79/21** | ***anti*** (R,S) |
| (R) | $[PhCH(OCH_3)]_2$ (R,R)[c] | Cumene, -40 to –20°C, 24h | 16/84 | 1% | 50/50 | - |
| (S) | (-)sparteine | Cumene, -40 to –20°C, 24h | 81/19 | 56% | 36/64 | *syn* (S,S) |
| (R) | (-)sparteine | Cumene, -40 to –20°C,24h | 86/14 | 71% | 22/78 | *syn* (R,R) |
| | | Cumene, -30°C, *n*BuLi added in 6h | **88/12** | 79% | **23/77** | *syn* (R,R) |

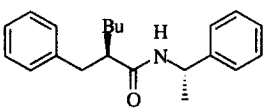
[a] see scheme 1. [b] yields refer to purified compounds. [c] one equivalent of ligand used, see text



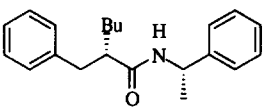
*anti* (S,R)



*syn* (R,R)

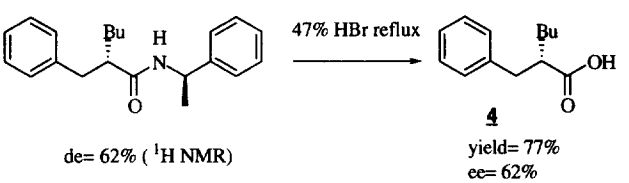


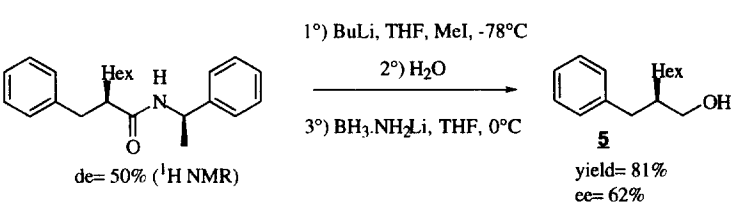
*anti* (R,S)



*syn* (S,S)

The diastereomeric ratio of the 3,4- products was easily established by $^{1}H$ and $^{13}C$ NMR. Amide **2** was hydrolysed with 47% HBr at reflux to yield the corresponding acid **4**. Its enantiomeric purity was assessed by means of $^{31}P$ NMR on a trivalent phosphorus derivative [8]. The absolute configuration was determined thanks to the optical rotations, compared with the literature [9]. The obtained chiral amides can also be converted to the corresponding alcohols **5**, after alkylation into a tertiary amide and reduction [10]. Scheme 2 summarises these derivatisations.




**Scheme 2**

Other lithium reagents have also been tested as shown in table 2, using a 1/1 ratio of (-)sparteine and organolithium in cumene at low temperature (-40°C to –20°C). The trimethylsilylmethyllithium reagent shows an excellent regioselectivity (exclusively 3,4- addition) and diastereoselectivity but the yield has to be improved. The vinyl reagent did add in good yield but with low regioselectivity (65/35) and low diastereoselection (37/63).

**Table 2.** Diastereoselective contra-Michael addition of organolithium reagents/(-)sparteine 1/1 complexes to **(R)-1** in cumene.

| RLi | 2/3 | Yield 2[a] | dr 2 | Derivatisation[c] |
|---|---|---|---|---|
| *n*BuLi | 86/14 | 71% | 22/78 (*syn*) | Acid, ee= 58% |
| *n*HexLi | 87/13 | 81% | 25/75 (*syn*) | Alcohol, ee= 62% |
| $Me_3SiCH_2Li$ | >95/5 | 34% | >5/95[d] | Alcohol, ee= 90% |
| Cyclohexenyllithium[b] | 65/35 | 54% | 63/37[d] | Alcohol, ee= 30% |

[a] yields refer to isolated pure compounds. [b] reaction run in $Et_2O$. [c] see text. [d] major diastereoisomer not determined.

In summary, the combined use of (-)-sparteine/organolithium complex, and cinnamyl amides derived from (-)(R)-α-Methylbenzylamine allows regioselective " contra-Michael " addition. A good diastereoselection is observed. The α–alkylated amides can be converted to the parent (R) acids or (R) alcohols with enantiomeric excess of 58% to 90% depending on the primary alkyllithium reagent used.

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