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An easy access to enantio-enriched α-substituted aldehydes by carbolithiation of β-phenyl or β-silyl-α,β-ethylenic aldehydes, protected with the monolithioamide of a chiral diamine

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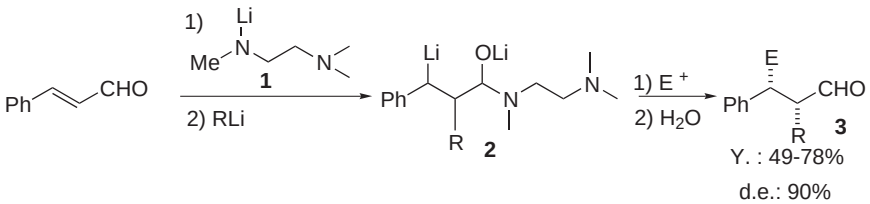
Abstract—Lithium amide derived from *N*,*N*,*N*′-trimethyl-1,2-diphenylethanediamine converts cinnamaldehyde to a lithium alkoxyamide which undergoes a regio- and stereoselective carbolithiation upon addition of various organolithiums. Subsequent hydrolysis or trapping with MeI delivers α-mono-, or α,β-disubstituted 3-phenylpropanals with e.e.s of 76–96%. Extension to a silylated α-enal is possible. © 2001 Published by Elsevier Science Ltd.

The preparation of α,β-disubstituted carbonyl compounds of high optical purity is an important synthetic objective. Methods involving chiral catalysts or covalently bonded chiral auxiliaries are numerous and deal mainly with conjugate 1,4-additions, followed by trapping of the intermediate enolate. In this paper we describe a new carbometalation reaction as a single step method for such an objective.

We have recently reported that cinnamaldehyde, once blocked as a lithium aminoalkoxide, via the amide of *N*,*N*,*N*′-trimethylethanediamine[1] **1** undergoes a regioselective addition of alkyllithiums on the carbon–carbon double bond, which delivers a benzyllithium derivative **2**. Various electrophiles reacted with the latter to give the *syn* compounds **3** with good yields (49–78%) and good diastereoselectivities (90% d.e.)[1] (Scheme 1).

We had previously shown that RLi/(−)-sparteine complexes added regio- and enantioselectively to cinnamyl alcohols, ethers, amines,[2] and amides,[3] so that we were interested to know whether intramolecular chirality, brought into the intermediate **4** by a chiral analog **5** of the amide **1** would allow a diastereoselective carbolithiation leading to the benzyllithium intermediate **6** and to the homochiral aldehydes **3** after quenching and hydrolysis. (*R*,*R*) or (*S*,*S*) - 1,2 - diphenyl - *N*,*N*,*N*′ - trimethylethanediamine[4] was selected for the preparation of the chiral reagent **5**.

Two equivalents of the chiral amide **5** are added to 1 equivalent of cinnamaldehyde at −40°C and the temperature is raised to 0°C. The mixture is cooled to −20°C and 4 equivalents of RLi in different solvents (see Table 1) are added. The mixture is stirred for 3 h at −20°C



Scheme 1.

Keywords: aldehyde; carbometalation; diastereoselection.

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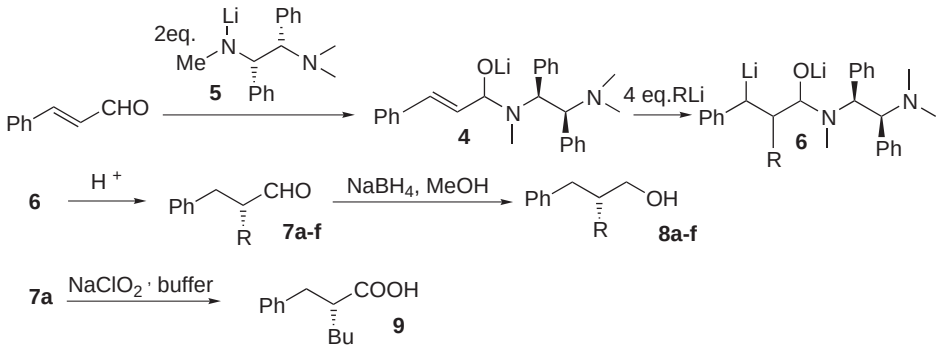
Table 1. Addition of organolithiums to α-aminoalkoxide **4**

Entry	RLi	Solvent	**7a–f**	Yield (%)	e.e. **7**[a] (%)
1	*n*-BuLi	Et_2O	**7a**	78	93
2	*n*-BuLi	THF	**7a**	65	59
3	EtLi	Et_2O	**7b**	75	92
4	*i*-PrLi	Hexane	**7c**	51	35
5	*i*-PrLi	Et_2O	**7c**	77	84
6	*s*-BuLi	Et_2O	**7d**	90	84[b]
7	*t*-BuLi	Et_2O	**7e**	65	76
8		Et_2O	**7f**	49	96[c]

[a] Measured from the corresponding alcohol **8**.[5]
[b] As a mixture of two diastereoisomers (4*S*/5*S*).
[c] After immediate reduction to the alcohol.

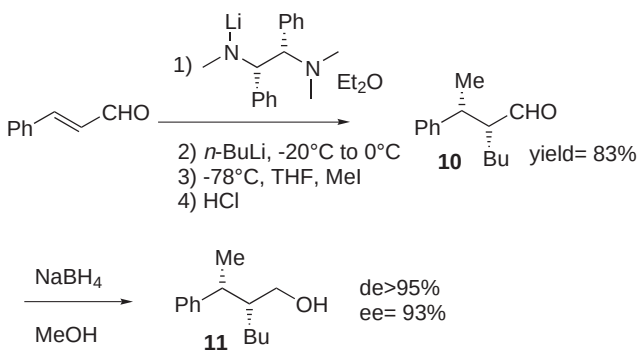


Scheme 2.

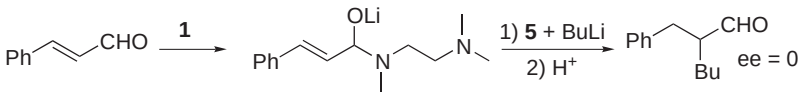
and 2 h at 0°C. Acidic quench delivers aldehydes **7a–f**, which are reduced to the alcohols **8a–f** (Scheme 2). The enantiomeric purities of the latter are measured from the ^{31}P NMR spectrum of a derived chiral diaminophosphite according to Alexakis et al.[5] From *n*-BuLi, 2-benzylhexan-1-ol **8a** is obtained with 88% yield and 93% e.e. An excess of chiral amide **5** is preferable indeed, if 1.3 equiv. are used instead of 2 equiv. the yield is similar (78% for BuLi, entry 1, Table 1), but the e.e. is lowered to 85%.

The raw aldehydes **7a** can be isolated after a rapid filtration on silica gel (78% yield, 93% e.e.). Meanwhile the chiral diamine used for the preparation of **5** is retrieved from the acidic aqueous layer. Moreover, the α-substituted aldehyde **7a** has been oxidized[6] ($NaClO_2$, pH 7 buffer) to the corresponding 2-benzylhexanoic acid **9** with no loss of optical purity (93% e.e.). The absolute configuration of **9** is determined by comparison with the literature data: (*R*)-2-benzylhexanoic acid[7] is formed from (*S*,*S*)-1,2-diphenyl-*N*,*N*,*N*′-trimethylethanediamine. It is worth noting that both enantiomers of the chiral diamine are available, thus both enantiomers of aldehydes **7a–f** can be obtained.

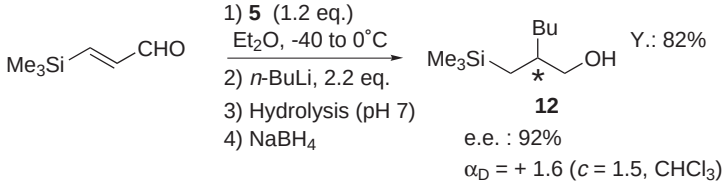
Contrary to the carbolithiation of cinnamyl derivatives by RLi/(−)-sparteine, which had to be run in hydrocarbons, diethylether as a solvent is used for this reaction. In THF, the reaction takes place with lower yield (65%) and lower e.e. (59%) as shown in Table 1. In hexane the enantioselectivity is worse (compare entries 4 and 5). Various organolithiums can be used with good yields and enantioselectivities: primary, secondary and tertiary alkyllithiums. Even cyclohexenyl lithium, prepared from 1-chlorocyclohexene reacts in ether (49% yield, 96% e.e.). In this case the reduction of the corresponding aldehyde must be performed immediately after hydrolysis, in order to avoid epimerization of the labile allylic Hydrogen atom.



Scheme 3.



Scheme 4.



Scheme 5.

One example of trapping the benzyllithium intermediate **6** (R = *n*-Bu) has been tested by reacting it with excess MeI. Aldehyde **10** is then obtained with good yield and good diastereomeric purity[8] (Scheme 3). The e.e. has been determined from the corresponding alcohol **11**.

Our attempts to trap the intermediate alcoholate **4** by TBDMSOTf or TMSCl failed,[9] and we could not establish whether it is present as a single diastereomer or not, which could explain the origin of enantio-enrichment. However, the intramolecular induction was proven by adding a mixture of the chiral amide **5** and *n*-BuLi to the racemic α-aminoalcoholate derived from **1**, whereby aldehyde **7a** was obtained as a racemate (0% e.e., Scheme 4).

Finally, we have shown that the phenyl group present in the starting cinnamaldehyde was not compulsory, and could be replaced by other anion-stabilizing residues. For example, β-trimethylsilylacrolein can be submitted to the amidation–carbolithiation sequence (with the chiral amide **5**) with success, and leads, after reduction, to 2-trimethylsilylmethylhexan-1-ol **12** of 92% e.e., in 82% overall yield[10] (Scheme 5).

In conclusion, we have designed a new methodology to synthesize enantio-enriched α,β-substituted aldehydes, not limited to the α-benzyl ones. Work is under way to extend the scope of this reaction.

Acknowledgements

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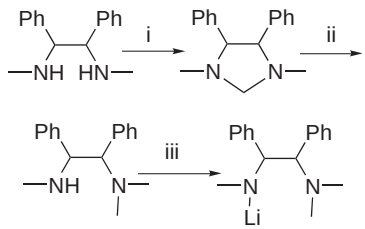
4. The amide **5** was prepared from (*R*,*R*) or (*S*,*S*)-1,2-diphenylethanediamine (global yield: 88% for the first two steps), as follows:



i: $(CH_2O)_n$ aq. CH_2Cl_2; ii: $NaBH_3CN$,TFA, MeOH; iii *n*BuLi

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10. The absolute configuration is not established as yet.