Tetrahedron Vol. 48, No. 17, pp. 3623-3632, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Addition of Me_2CuLi to Enones and Enoates Effects of Solvent and Additives on the Yield and Stereoselectivity

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(*Received in UK* 6 *March* 1992)

Key words: lithium diorganocuprates; conjugate addition; stereoselectivity; solvent effects; effects of additives.

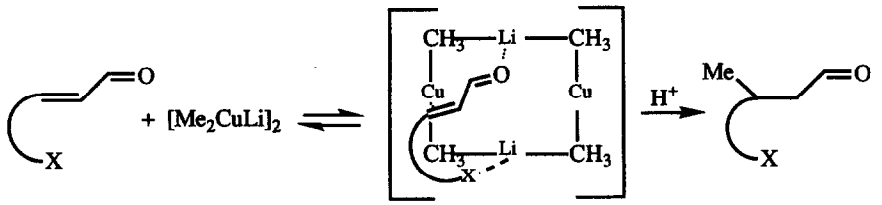
Abstract *High yields of diastereomeric 1,4-addition products are obtained on addition of* ***1, 2 or 3*** *to* $[Me_2CuLi]_2$ *in toluene, hexane or* CH_2Cl_2. *The stereoselectivity is strongly influenced by the choice of solvent as well as by addition of TMSCl or TMSI. The diastereoselectivity of the reaction between S-1 and* $[Me_2CuLi]_2$ *changed from 13.5 : 1 RS:SS ratio when the reaction was performed in thiophene, to 10 : 1 in toluene, to 1 : 14 in* CH_2Cl_2 *with TMSI. The RS configuration obtained with non-polar solvents such as toluene is attributed to chelation control of the stereoselectivity while the reaction under "non-chelation" conditions, i e ether and TMSCl or TMSI, shows low stereoselectivity.*

The addition of lithium diorganocuprates, R_2CuLi, to activated alkenes, mostly enones or enoates, is a simple and well established procedure for the elaboration of the carbon skeleton of an organic compound.[1] The classical and most commonly used reaction conditions, *i e* the use of diethyl ether, Et_2O, or tetrahydrofuran, THF, as solvent and temperatures ≈0° C or below, are often successful. However, a large variety of solvents and additives have been tested and found to be advantageous in special cases, *e g* the addition of boron trifluoride etherate has been found to modify the reactivity of the lithium diorganocuprates.[2] The addition of chlorotrimethylsilane, Me_3SiCl, has been found to improve the regioselectivity of the addition to enals, to affect the reaction rate of the cuprates in THF, and also to change the stereoselectivity of some 1,4-addition reactions.[3]

We have previously shown that the choice of solvent for the addition of R_2CuLi to enones or enoates has a strong influence on the chemoselectivity[4] as well as on the stereoselectivity of the addition reaction.[5] The use of non-coordinating (non-polar) solvents such as dichloromethane, CH_2Cl_2, toluene or hexane favours the formation of highly reactive cuprates that form the expected products selectively.[4,5] In these solvents only one cuprate species, the dimeric $[R_2CuLi]_2$ solvated by two to four Et_2O molecules, can be detected.[4a,6] It has not been possible to prove that these dimers are the reacting species in 1,4-additions but the dimeric structure has been successfully used in our transition state model for reactions with *ortho*-substituted methyl cinnamates.[4b] This model is based on the observation of a reversible formation of a copper-alkene π-complex as the first step in the 1,4-addition reaction of R_2CuLi with alkenoates.[7]

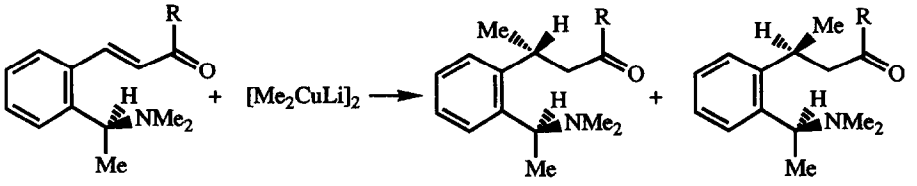
Furthermore, the choice of solvent is of great importance with less reactive or sterically hindered

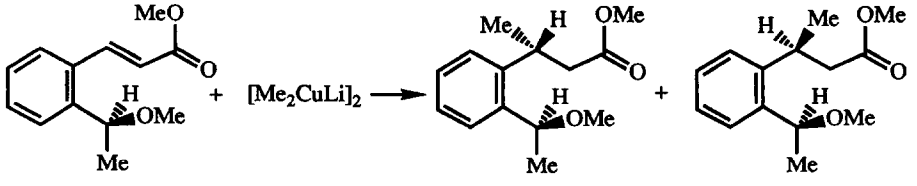
substrates. The addition of the chiral methyl (S)-3-[2-(1-dimethylaminoethyl)phenyl]-propenoate, **1**, to lithium dimethylcuprate, $[Me_2CuLi]_2$, in diethyl ether afforded only a low yield of the diastereomeric 1,4-addition products with an unsatisfactory diastereomeric ratio of ≈ 2 : 1. The same reaction performed in toluene gave the expected 1,4-addition products in a quantitative yield with a diastereomeric ratio of 10 : 1. The stereoselectivity was suggested to arise from chelation control. A model for the transition state of the product-determining step based on intramolecular coordination of the chiral side chain heteroatom of the substrate to lithium within a cuprate-alkene π-complex in non-polar solvents was presented.[5]



RESULTS AND DISCUSSION

We now report the results of an extended investigation with the dual objective firstly to find optimum conditions for the reaction between Me_2CuLi and sterically crowded substrates to obtain high chemo- and stereoselectivity, secondly to further test the mechanistic model suggested above.[5] The parameters investigated are the reaction temperature, the choice of solvent, the addition of iodo- or chlorotrimethylsilane, TMSI or TMSCl respectively, and the removal of lithium iodide in reactions with the chiral compounds **1**, **2** and **3** giving the corresponding 1,4-addition products **4**, **5** and **6**. The results are summarized in Table 1. Some representative results from previous work have been included for comparison. The ratio of diastereomers is given in the order of elution from the GC capillary column.





Most of the reactions reported in Table 1 have been monitored by capillary GC over a wide temperature range, -78° to -10° C, in order to study the effect of temperature on the stereoselectivity. Generally no such effect could be detected. However, the reactions performed in the presence of TMSI showed some variation in the

Table 1. Addition of chiral *ortho*-substituted substrates **1**, **2** and **3** to $[Me_2CuLi]_2$, ratio 1 : 1, in various solvents and in the presence of 1 to 2 equiv of TMSX The isolated yields of the corresponding products **4**, **5** and **6** are given together with the ratio of diastereomers determined from ^1H NMR spectra of crude products.

Entry	Substrate	Solvent	Additive	Temp. °C	Time h	Yield %	Ratio of diastereomers	Comments
1	1	Et_2O	-	0	1.0	18	≈2:1	*
2	1	Et_2O	TMSCl	0	2.5	80	1 : 1.1	
3	1	Et_2O	TMSCl	-78 to -15	6.0	70	1 : 1.4	
4	1	Et_2O	TMSI	-78 to -40	4.5	83	1 : 1	*
5	1	Toluene	-	0	2.0	91	10 : 1	*
6	1	Toluene	TMSCl	-40	6.0	82	11 : 1	
7	1	Toluene	TMSI	-78	4.0	86	1 : 5	fast
8	1	CH_2Cl_2	-	0	1.0	94	9 : 1	*
9	1	CH_2Cl_2	TMSCl	-40 to -10	7.0	-	1.2 : 1	50% conversion
10	1	CH_2Cl_2	TMSI	-78 to -40	4.0	c	1 : 14	50% conversion
11	1	Thiophene	-	-78 to 0	1.0	77	13.5 : 1	
12	1	Thiophene	TMSI	-10	3.0	30	1 : 3.5	50% conversion
13	1	THT [a]	-	-78 to 0	9.5	16	2 :1	
14	1	THF	TMSI	-78	4.0	25	1 : 1.2	25% unreacted **1**
15	2	THF	-	0	2.5	51[b]	1 : 1	
16	2	Et_2O	-	0	4.0	>95	1.5 : 1	
17	2	Et_2O	TMSCl	-78 to -20	4.5	48[b]	2 : 1	
18	2	Et_2O	TMSI	-40	3.0	-	-	Cuprate reacts
19	2	Toluene	-	0	2.0	95	9 : 1	
20	2	Toluene	- LiI	0	3.0	99	2 : 1	LiI removed
21	2	Toluene	TMSCl	-78 to -20	4.5	91	9 : 1	
22	2	Toluene	TMSI	-78 to -40	20.0	>36	6 : 1	slow
23	3	Et_2O	-	0	4.5	48	1 : 1.1	*
24	3	Et_2O	TMSI	-78	2.0	68	1 : 3.5	
25	3	Hexane	-	-40, 0	5.0	98	1 : 1.4	
26	3	Hexane	TMSCl	-40, 0	5.0	85	1 : 1.1	
27	3	Toluene	TMSCl	-40	3.5	79	1 : 1.2	
28	3	Toluene	TMSI	-78 to -40	8.5	70	1 : 1.1	
29	3	CH_2Cl_2	TMSI	-78	4.0	50[c]	1 : 5.5	

a = Tetrahydrothiophene, b = isolated by prep TLC, c = *ca* 50% yield within 2 min, no further reaction, * = data from reference 5.

composition of products.

The yields reported in Table 1 reflect the general difficulty of recovering amino-substituted compounds, partly water-soluble, from small scale reactions. In several of the reactions the yields of **4**, **5** or **6** were quantitative according to the GC analysis.

As observed previously[5] the use of dichloromethane or hydrocarbon solvents has a very strong effect on the reactivity of the reagents and chemical yields of products **4**, **5** and **6**, expts 5, 8, 19 and 25. With substrates **1** and **2** the high yields are combined with a tremendous increase in diastereoselectivity in comparison with reactions performed in ethers, expts 1, 15 and 16.

The sulphur-containing solvents thiophene and tetrahydrothiophene, THT, were included in order to study any possible effects of sulphur coordination on reactivity or stereoselectivity. THT is an alternative to dimethyl sulfide, which has been suggested by Bertz *et al* to be a useful solvent for reactions with organocopper compounds[8] and equivalent to diethyl ether for lithium diorganocuprates.[3i] As seen from Table 1 the results obtained with thiophene are very similar to those with toluene, *cf* expts 5 and 11, and thiophene can probably be considered to behave essentially as an aromatic solvent. The reactions are fast in thiophene, toluene and CH_2Cl_2 in spite of the low solubility of the cuprate. In thiophene as well as in CH_2Cl_2 a yellow slurry is formed, *i e* most of the $(Me_2CuLi)_2$ is in the solid state. The cuprate is slightly more soluble in toluene. The reactions with **1** and **3** in THT afforded only very low yields of the 1,4-addition products even after complete consumption of starting materials as side reactions prevailed. Thus the sulphur analogues of ethers do not offer any advantages compared to Et_2O or hydrocarbon solvents in these reactions.

The presence of TMSCl or TMSI in the reactions of **1** performed in Et_2O, expts 2, 3 and 4, improved the yield of **4**, *cf* expt 1, while the stereoselectivity was essentially lost. The improved yield of **4** is most probably due to the trapping of a reaction intermediate, thus maintaining a very low concentration of the lithium enolate. We have previously shown the low yield of the expected diastereomeric 1,4-addition products, **4**, obtained in the reaction between $[Me_2CuLi]_2$ and **1** in diethyl ether, expt 1, to be due to the rapid reaction between the initially formed enolate and remaining **1** forming MIMI-type products[9] in a stereoselective reaction.[5]

TMSCl in toluene, expt 6, causes a slight increase in stereoselectivity relative to expt 5, while in CH_2Cl_2, expt 9, a slow and incomplete reaction afforded a low yield of the diastereomers in roughly equal amounts.

Similar sequences of reactions were run with the ketone **2** and the ester **3**. The ketone **2** shows a higher reactivity than the corresponding ester **1**, expt 15, as the 1,4-addition products **5** are obtained in 51% isolated yield (after preparative TLC) when **2** is added to Me_2CuLi in THF at 0° C, while the ester **1** is unreactive under these conditions.[5] The higher reactivity of **2** is also manifested in reactions performed in Et_2O as a lower $[Me_2CuLi]_2$ to substrate ratio (1 : 2 for **2** instead of 1 : 1 for **1**) can be used to obtain a quantitative conversion of **2** to product **5**. The reactivity of ketone **2** towards the cuprate also prevents the formation of MIMI products as long as there is any cuprate available in solution.

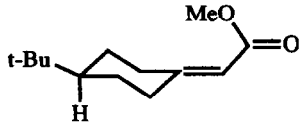
The stereoselectivity observed in the formation of **5** in THF or Et_2O is very low, expts 15, 16 and 17, while toluene, with or without TMSCl, exerts a very favorable influence, expts 19 and 21, on the diastereomeric ratio in agreement with results obtained with ester **1**.

Only a few examples of reactions with the chiral ester **3**, carrying an oxygen atom, have been included in Table 1. The stereoselectivity in the reactions of **3** is consistently low with diastereomeric ratios typically in the range 1 : 1.2. The only exceptions observed are the reactions between **3** and $[Me_2CuLi]_2$ in the presence of TMSI in Et_2O or CH_2Cl_2, expt 24, 29, with the best results being a diastereomeric ratio of 1 : 5.5.

Thus the two halosilanes have different effects on the reactivity as well as on the chemo- and stereoselectivity. The results obtained from reactions performed in the presence of TMSI are strongly dependent on the choice of solvent, reaction temperature and the structure of the alkenone or alkenoate. For example high yields of **4** were obtained from **1** in Et_2O or toluene at -78° C, expt 4 and 10, while the reaction of **2** in Et_2O at -40° C yielded no **5** but a complex mixture of products, expt 18. The presence of TMSI in reactions with **1** in toluene, CH_2Cl_2 or thiophene, expts 7, 10 and 12, reverses the stereoselectivity, the best result, 1 : 14, being obtained with CH_2Cl_2. However, the favourable stereoselectivity seems to be obtained at the expense of chemical yields, expts 10, 12.

The results obtained raise questions about the composition of the reagents in various solvents, *i e* the compatibility of TMSI with Me_2CuLi in different solvents and with the substrates, and their mode of action.

The unreactive β,β-disubstituted ester **7** was included for comparison of the effect of the added halosilanes on the reactivity of the cuprate in some reactions with a sterically hindered enoate lacking the coordinating side chain.



7

No 1,4-addition was observed in solutions of $[Me_2CuLi]_2$ and **7** in diethyl ether or toluene, not even if the temperature was increased to 0 °C. In the presence of TMSCl in Et_2O the reaction is still very slow. A very modest yield of the expected product, 20% **8**, was isolated together with 80% of the unreacted starting material **7** in a reaction run for 15 hours at -78° followed by 9 h when the temperature was slowly raised to 0° C. In contrast, the addition of **7** to $[Me_2CuLi]_2$ in Et_2O in the presence of TMSI afforded a high yield, 81% after isolation, of the 1,4-addition product **8** after 2 h at -78° C.

The ^1H, ^{13}C and ^{29}Si NMR spectra were recorded for solutions of TMSI and $[Me_2CuLi]_2$, in a 1 : 1 ratio, in THF at -70° C. On the addition of TMSI to the clear solution of $[Me_2CuLi]_2$ in THF at -70° C a rapid change takes place with the initial formation of a yellow precipitate which dissolves to a clear solution that slowly turns slightly red. The ^{29}Si NMR spectrum of this solution at -70° C shows no signal at 11.5 ppm characteristic of TMSI but two new signals, one at 0 ppm, attributed to the formation of tetramethylsilane, TMS, and the second at 16 ppm relative to TMS.

Possible interactions between TMSI and enoates were also investigated. ^1H and ^{13}C NMR spectra for CD_2Cl_2 solutions of TMSI were recorded at -70° C. No shift changes were observed when TMSI was added to methyl cinnamate or to **3**. The carbonyl carbon signals of both compounds are shifted less than 1 ppm. Thus we conclude that there are no strong interactions between TMSI and any of these two enoates. The effect observed in the ^{13}C NMR spectrum on addition of TMSI to **1** is in strong contrast as the carbonyl carbon and the alkene carbon signals quickly disappear with the appearance of many new signals attributed to several new species. The ^1H NMR spectrum shows the same type of changes.

As amines can be expected to react with the halosilanes the spectra for CD_2Cl_2 solutions of TMSI or TMSCl and triethylamine, Et_3N, were recorded at -70° C. On addition of TMSI to Et_3N in CD_2Cl_2 at -78° C a white solid is formed that is dissolved on warming. The ^{29}Si NMR spectrum shows two signals; one at 11.5 ppm, unreacted TMSI, the other at 44.5 - 46 ppm indicating the formation of a silylammonium salt. The ^1H and ^{13}C NMR spectra confirm the presence of a new species.

The addition of TMSCl to Et_3N in CD_2Cl_2 yields a clear solution showing only one signal at 31 ppm in the ^{29}Si NMR spectrum at -70° C, in accordance with the ^{13}C NMR spectrum which shows three signals, 3.5 and 11.8, 46 ppm corresponding to TMSCl and Et_3N respectively.

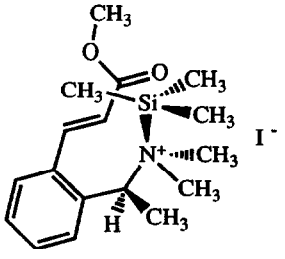


Figure 1

On the basis of the NMR experiments we conclude that TMSI is not Lewis acidic towards the carbonyl oxygens of the enoates. TMSI and cuprates interact even at low temperatures in THF. However, the normal cuprate reactivity is retained in toluene and Et_2O. Neither can interactions between amino-substituted compounds and TMSI be neglected. One possible reaction in the case of **1** or **2** is the nucleophilic substitution on silicon by the amino group forming a silylammonium salt, Figure 1.

There are also reports that TMSI can be successfully used to cleave ethers and esters.[10] The direct Michael addition of silyl groups to α,β-unsaturated ketones and lactones in the presence of organocuprates have also been reported.[11] These processes may well compete in our reactions and cause the formation of by-products, some of which are highly water-soluble, thus preventing their observation or isolation. The results obtained with ester **7** show however, that side reactions are not a problem in the absence of the nucleophilic side chain, as the presence of TMSI in the reaction of **7** has a very positive effect on the formation of **8**.

Contrary to TMSI, TMSCl is compatible with the cuprate as well as the amino-substituted enoate and enone at *low temperatures* in some solvents.[3b] The most advantageous effect observed with TMSCl in this investigation is the increase in yield in the reaction of **1** with $[Me_2CuLi]_2$ in Et_2O, *cf* expts 1 and 2. Neither TMSI nor TMSCl seem to be compatible with the cuprate in CD_2Cl_2 or thiophene as only 50% conversion could be obtained irrespective of reaction time, expts 9, 10 12.

For the mechanistic interpretation of the observed stereoselectivity it is essential to determine the absolute configuration of the diastereomeric products. To this end experiment 5 in Table 1, reaction between *S*-**1** and Me_2CuLi in toluene, was repeated and the major isomer isolated and recrystallized as its HCl salt. The unit cell was found to contain two independent molecules, both of which have the *R*-configuration at the new stereocentre. The independent molecules prove to be two conformers of the major isomer of expt 5 which thus is methyl 3(*R*)-[2-(1(*S*)-dimethyl-aminoethyl)phenyl]-butanoate. The structure of one of the two conformers of the molecules is shown in Figure 2.

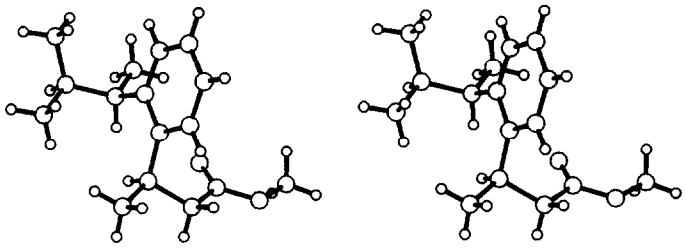


Figure 2

The major isomer of product **5**, expt 18, from *S*-**2** has been assigned the *R*-configuration at the new stereocenter on the basis of comparison of its NMR spectra with those of *R,S*-**4**. No attempt has been made to assign configuration to diastereomers of **6**, formed from ester **3**, which was used as the racemate.

MECHANISTIC IMPLICATIONS

We have previously proposed[5] that the reactions under study can be best described by the initial establishment of several equilibria between reagents and isomeric alkene-copper π-complexes followed by the irreversible monomolecular transformation[12] of the complexes in one or several steps with the ultimate formation of the new carbon-carbon bond. The stereoselectivity will be determined by the relative rates of the competing product forming paths.[5]

The formation of the 3-*R*-configuration at the new stereocenter in the reaction of *S*-**1** and $[Me_2CuLi]_2$ in

toluene agrees well with a transition state in which the substrate is oriented to allow copper-alkene bonding as well as intramolecular coordination of the side chain nitrogen to a cuprate lithium atom leading to chelation control of the stereoselectivity in non-polar solvents. A "chelation" π-complex is the most reactive species existing in equilibrium with the reagents as well as with other "non-chelation" π-complexes.

In ether solvents the "non-chelation" isomeric π-complexes are the major species in solution[7c] due to the competion for coordination sites on lithium from the solvent oxygens as observed previously by NMR spectroscopy. The diastereomeric π-complexes react with roughly equal rates as only minor stereoselectivity is observed with **1** or **2**.

The observation of *S,S*-**4**, as the major diastereomer in *e g* expts 7 and 10, indicates that product formation has taken place via a "non-chelation" route. The reversed stereoselectivity in the product has to be attributed to steric control exerted by a bulky and sterically demanding side chain[5] blocking one side of the enoate, in agreement with observations reported by Alexakis *et al.*[3j] Presently we find that the observation is best explained by postulating the formation of a quaternary ammonium ion by the nucleophilic attack on the Si of the TMSI by nitrogen in the side chain in agreement with the NMR signals observed, *see above*. The side chain is transformed to a sterically demanding group without the capacity for coordination, but effectively blocking one side of the enoate.

CONCLUSIONS

We have demonstrated the feasibility of control of chemo- and stereoselectivity in 1,4-addition reactions of lithium diorganocuprates to alkenones and alkenoates. Hydrocarbon solvents or dichloromethane always favour high rates and high chemical yields. The present level of understanding of the reaction mechanism allows strategies to be designed for sterically controlled formation of products (*e g* by use of Et2O or THF and TMSCl) or alternatively control of stereochemistry by intra-molecular coordination in non-polar solvents, preferably hydrocarbons. The temperature of the reaction should be kept as low as possible.

EXPERIMENTAL

All handling of organometallic reagents was carried out under argon and with dried equipment. Diethyl ether and toluene were distilled from sodium benzophenone ketyl and CH_2Cl_2 and hexane from CaH_2. Freshly distilled thiophene was used. Commercial methyllithium in diethyl ether, TMSCl and TMSI (Aldrich) were used. Copper(I) iodide was recrystallized prior to use. ^1H and ^{13}C NMR spectra were recorded on a Varian XL 400 MHz spectrometer and gas chromatograms on a Varian 3300 chromatograph (30 m DB-1, FID).

General procedure for the reaction of lithium dimethylcuprate in diethyl ether.

A solution of Me_2CuLi, prepared from methyllithium (1 ml, 1.6 M) and CuI (167 mg, 0.88 mmol), in 13 ml diethyl ether was stirred at 0° C for 10 min. When TMSCl (0.2 ml, 1.6 mmol) or TMSI (0.15 ml, 1.0 mmol) was used, the solution was cooled to -40° C or -78° C, respectively, before the addition, and the solution was then allowed to stand with stirring for 30 min. The enoate (0.4 mmol), dissolved in 2 ml diethyl ether was added and the reaction temperature and time varied as shown in Table 1. NH_3/NH_4Cl (5 ml) was then added and stirring continued for another hour.

General procedure for reactions in solvents other than diethyl ether.

The cuprate was prepared according to the procedure above but in 3 ml diethyl ether. After stirring the solution for 10 min at 0° C the ether was evaporated in vacuo at 0° C for 30 min. The new solvent (2-3 ml) was added, the mixture stirred for 10 min and the solvent evaporated at 0° C for 30 min. Finally 13 ml of the new solvent was added to the white/pale yellow solid and the mixture stirred at 0° C as described above. The cuprate which is a yellow suspension in CH_2Cl_2, hexane, thiophene and tetrahydrothiophene and a colloidal solution in toluene and retains at least one equivalent of diethyl ether coordinated to each lithium according to NMR. When TMSCl (0.2 ml, 1.6 mmol) or TMSI (0.15 ml, 1.0 mmol) was used, the solution was cooled to -40° C or -78° C, respectively, before the addition, and the solution was then allowed to stand with stirring for 30 min. The enoate (0.4 mmol), dissolved in 2 ml of the solvent chosen, was added and the reaction temperature and time varied as shown in Table 1. The general quench and work-up procedure above was then followed.

Isolation and characterization of 1,4-addition products 4, 5, 6 and 8.

After quenching with NH_3/NH_4Cl and stirring for one hour the phases were separated and the water phase extracted with ether (3 x 15 ml). The combined organic solutions were washed with brine, dried (Na_2SO_4), and the solvent evaporated in vacuo. The crude product was analysed by GC and NMR, and products isolated after flash chromatography on silica gel (230-400 mesh ASTM), EtOAc/Pentane (1/3) + 1 % triethylamine, TEA, for the products **4** and **5**; Et_2O/Pentane (7/93) for product **6**. As indicated in Table 1 preparative TLC was used in a few cases.

Products **4, 5,** and **6** (all in ref 5) have all been reported previously and their NMR data agree with the literature. For product **8** see ref 14; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (9H, s) 0.9 (1H, m) 1.0 (3H, s) 1.1-1.2 (4H, m) 1.5-1.7 (4H, m) 2.3 (2H, s) 3.6 (3H,s). ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.54, 22.73, 27.29, 27.36, 27.55, 29.62, 32.38, 32.87, 38.48 (2C), 40.49, 47.92, 51.08, 173.25.

Synthesis of the substrates 1, 2, 3 and 7.

The methyl esters **1** (*S*-configuration)[5], **3** (racemic)[5] and **7**[13] were prepared according to literature procedures. Ketone **2**, (S)-4[2-(1-dimethylaminoethyl)phenyl]-3-butene-2-one[5,14] was prepared via the same route as used for ester **1** starting from *S*-1-dimethylaminoethylbenzene. Yield: 0.74 g, 49 %. ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, d, J 6.6 Hz) 2.21 (6H, s) 2.40 (3H, s) 3.57 (1H, q, J 6.6 Hz) 6.56 (1H, d, J 16 Hz) 7.26 (1H, t, J 7.6 Hz) 7.38 (1H, t, J 7.6 Hz) 7.43 (1H, d, J 7 Hz) 7.48 (1H, d, J 7 Hz) 8.30 (1H, d, 16 Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.94, 27.40, 43.18, 62.62, 126.82, 126.97, 127.67, 128.30, 130.04, 133.29, 142.01, 144.50, 198.66.

Preparation of the HCl salt of methyl 3(R)-[2-(1(S)-dimethylamino-ethyl)phenyl]-butanoate, 4. A solution of $Li(CH_3)_2Cu$ (prepared from methyllithium (6.8 ml, 1.6 M) and CuI (1.14 g, 6.0 mmol) in 7 ml diethyl ether was stirred at 0° C for 10 min, and the ether was then evaporated. Toluene (4 ml) was added, the mixture was stirred for 10 min and the toluene evaporated. Finally, 80 ml toluene was added. Methyl (S)-3-[2-(1-dimethyl-aminoethyl)phenyl]propenoate (2.7 mmol) dissolved in toluene (4 ml) was added to the cuprate at 0° C, and the reaction was allowed to stand with stirring for 2 h. NH_3/NH_4Cl (30 ml) was then added, and stirring continued for another hour. The phases were separated and the water phase extracted with toluene (3x20 ml). The combined organic layer was washed with brine and dried (Na_2SO_4), and the solvent evaporated. The crude product was flash chromatographed on silica gel (70-230 mesh), ethyl acetate/pentane 1/3, 1 % TEA. Yield: oil, 0.62 g, 91 %; d.e. 80 %. The oil (0.13 g) was dissolved in diethyl ether (5 ml), and diethyl ether saturated with HCl(g) was added dropwise to give the HCl-salt of **4**. A white precipitate was obtained. This product was recrystallized from toluene/ethanol 10/1 to give small white needles. Recrystallization of these from dimethoxyethane afforded colourless plates. One of these plates was analyzed by X-ray diffraction. This plate was then dissolved in 5 ml saturated $NaHCO_3$, and the water phase was immediately extracted with 20 ml diethyl ether. GC analysis of the ether phase showed the plate to be the major diastereomer, > 95% .

Crystal Structure Analysis - Crystal Data.

$C_{15}H_{24}ClO_2N$, M_r = 285.8, monoclinic, space group $P2_1$, a = 13.726(4), b = 7.561(10), c = 16.222(5) Å, β = 104.12(2)°, V = 1633(3) $Å^3$, Z = 4, D_{calcd} = 1.16 g cm^{-3}, μ(CuKα) = 20.7 cm^{-1}. Colourless plates. A crystal with the approximate dimensions 0.60 x 0.30 x 0.05 mm was mounted on a glass fiber. Diffracted intensities (+h,+k,±l) were measured at 23° C for 2Q < 120°, using a Rigaku AFC6S diffractometer and graphite-monochromated CuKα radiation. The ω/2θ scan mode was employed with an ω scan rate of 4 ° min^{-1} and a scan width of (1.05 + 0.30 tanθ)°. Weak reflections ($I < 10\sigma(I)$) were rescanned twice and counts accumulated to improve counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time vs. background counting time was 2:1. Of the 2646 independent reflections measured, 1747 had $I > 3\sigma(I)$ and were regarded as being observed. That the crystal was not subject to decay during measurement of intensities was checked by monitoring three reflections at regular intervals (after measurement of 150 reflections). Intensity data were corrected for Lorentz and polarization effects. An empirical correction based on azimuthal scans for several reflections was made for absorption (min., max. transmission factors: 0.69, 1.00). Unit-cell parameters were obtained from diffractometer setting angles for 25 reflections in the range 54.2° < 2θ < 77.9°.

Structure Determination and Refinement.

The structure was solved by direct methods (MITHRIL).[15] Full-matrix least-squares refinement of positional and anisotropic thermal parameters for the chlorine atoms and of positional and isotropic thermal parameters for the remaining non-hydrogen atoms gave a final R = 0.079, R_w = 0.088 for 162 parameters and 1747 reflections, hydrogen atoms being included as a fixed contribution in calculated positions. Atomic scattering factors were taken from International Tables for X-ray Crystallography,[16] and the F_o values

Table 2. Positional parameters for the non-hydrogen atoms in $C_{15}H_{24}ClNO_2$. Origin fixed by y for Cl(1). Estimated standard deviations are given in parentheses.

Atom	x	y	z
Cl(1)	0.6422(2)	0.1718	0.4840(2)
Cl(2)	0.1445(2)	0.0735(7)	0.2562(2)
O(1)	0.4167(6)	0.222(1)	0.7628(5)
O(2)	0.2696(6)	0.290(1)	0.7880(6)
O(3)	0.159(1)	0.586(3)	-0.033(1)
O(4)	0.123(2)	0.461(3)	0.070(1)
N(1)	-0.0803(6)	0.227(1)	0.6880(5)
N(2)	0.4338(6)	0.141(1)	0.3650(5)
C(1)	0.462(1)	0.217(3)	0.853(1)
C(2)	0.3210(9)	0.259(2)	0.7378(7)
C(3)	0.2846(8)	0.262(2)	0.6445(7)
C(4)	0.1711(8)	0.238(2)	0.6108(7)
C(5)	0.1419(8)	0.260(2)	0.5159(7)
C(6)	0.1388(7)	0.066(2)	0.6409(6)
C(7)	0.1788(9)	-0.088(2)	0.6126(8)
C(8)	0.1567(9)	-0.254(2)	0.6345(8)
C(9)	0.0936(8)	-0.277(2)	0.6873(7)
C(10)	0.0535(8)	-0.128(2)	0.7170(7)
C(11)	0.0746(7)	0.043(2)	0.6941(7)
C(12)	0.0291(7)	0.193(2)	0.7313(6)
C(13)	0.0427(8)	0.185(2)	0.8285(7)
C(14)	-0.0952(8)	0.267(2)	0.5972(7)
C(15)	-0.1540(8)	0.089(2)	0.6985(7)
C(16)	0.071(2)	0.691(5)	-0.047(2)
C(17)	0.182(2)	0.480(4)	0.023(2)
C(18)	0.277(2)	0.421(4)	0.053(2)
C(19)	0.297(1)	0.232(2)	0.1082(9)
C(20)	0.257(2)	0.092(4)	0.058(1)
C(21)	0.4104(8)	0.221(2)	0.1386(7)
C(22)	0.470(1)	0.194(2)	0.0804(8)
C(23)	0.575(1)	0.196(2)	0.1058(8)
C(24)	0.6232(9)	0.218(2)	0.1886(8)
C(25)	0.5654(8)	0.238(2)	0.2472(7)
C(26)	0.4619(7)	0.239(2)	0.2248(6)
C(27)	0.4057(7)	0.276(2)	0.2934(7)
C(28)	0.428(1)	0.460(2)	0.3277(9)
C(29)	0.3742(7)	0.169(2)	0.4299(7)
C(30)	0.420(1)	-0.043(2)	0.3329(8)

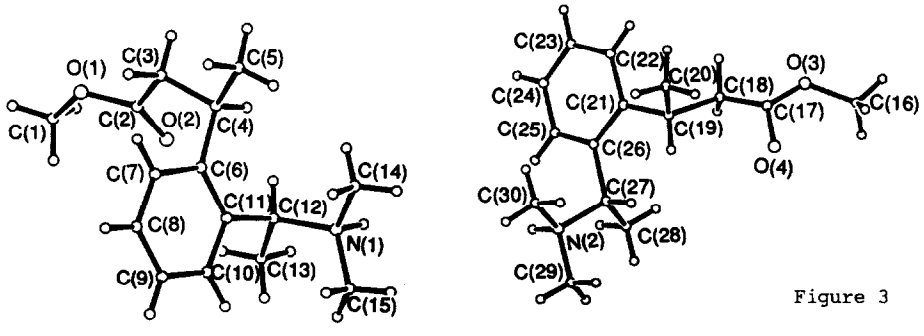


Figure 3

were weighted according to $w = [\sigma^2(F_o)]^{-1}$. A final difference map showed a max., min. residual density of 0.46 and -0.33 e $Å^{-3}$, respectively. All calculations were carried out with the TEXSAN program system.[17] Atomic coordinates for the non-hydrogen atoms are given in Table 2.

The unit cell contains two independent molecules, both of which can be assigned the *R*-configuration at the new stereocentre of the alkanoate side chain relative to the known *S*-configuration of the aminosubstituted side chain. The two molecules in the unit cell are conformational isomers. Both conformers exhibit normal bond lengths and angles. Data can be obtained from SJ. The crystallographic numbering is shown for the two conformers in Figure 3.

NMR-experiments

Solutions of $[Me_2CuLi]_2$ were prepared by addition of methyllithium (4 mmol) to a slurry of copper(I) iodide (2.2 mmol) in Et_2O (3 ml) at 0° C followed by stirring for 10 min. The Et_2O was evaporated under reduced pressure at 0° C. The new deuterated solvent (1 ml) was added, mixture stirred for 10 min and the solvent evaporated at 0° C for 30 min. Finally 1 ml of fresh, deuterated solvent was added, the sample divided and transferred to two NMR tubes and cooled to -78° C. ^1H and ^{13}C NMR spectra were recorded at low temperature before addition of TMSI, 1 mmol, 0.14 ml to each NMR tube.

ACKNOWLEDGEMENTS

We thank Mrs. Ann-Charlotte Klintenberg for her contribution to the experimental work with ketone 2. Financial support from the Swedish Natural Science Research Council is gratefully acknowledged.

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