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Stereoselective Addition of R_2CuLi to *ortho*-Substituted Methyl Cinnamates Intramolecular Assistance and Solvent Effects

Beritte Christenson, Gerd Hallnemo# and Christina Ullenius*

Department of Organic Chemistry, Chalmers University of Technology, 412 96 Göteborg, Sweden

Present address: Astra Research Centre AB, S-151 85 Södertälje, Sweden

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Abstract *High chemical yields are obtained on the addition of the ortho-substituted enoates 1, 2, 3, and 4 to Me_2CuLi or Ph_2CuLi in non-coordinating solvents, CH_2Cl_2 or toluene. The results underline the strong effect of solvent on reactions between organocuprates and enoates as the corresponding reactions in diethyl ether afforded low yields and moderate stereoselectivity. No reaction was observed when THF was used. The high stereoselectivity observed with the dimethylaminoethyl substituted enoate 4 in non-coordinating solvents can be accommodated by a mechanistic model for the reaction based on chelation control, within a copper-alkene π-complex.*

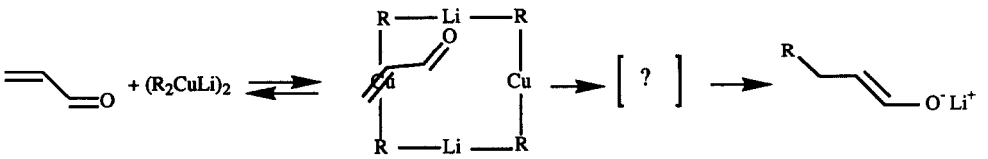
Considerable efforts to clarify the mechanistic pathway[1] of the copper-mediated conjugate addition of carbon nucleophiles to α,β-unsaturated ketones and esters have been made, facilitating the prediction of the stereoselectivity in these reactions. However, a clear mechanistic understanding is still lacking and further investigations are required. The structure of the reacting organocopper species is still a matter of uncertainty, although considerable progress has been made lately towards establishing the structure of simple cuprates in the solid state[2]. NMR investigations[3] make it possible to compare the solution structures with the solid state structures.

We have demonstrated the fast and reversible formation of an alkene-copper π-complex as an initial step in the conjugate addition of lithium diorganocuprates to methyl cinnamate by ^1H and ^{13}C NMR investigations of solutions at low temperature. On the basis of large upfield chemical shifts for the alkene carbons 2 and 3, an η^2 configuration was suggested for the π-complex[4]. Corey and coworkers have isolated solid copper-enone complexes and demonstrated that they can be transformed to the conjugate addition products[5]. The complexes were described as d,π*-complexes involving copper as a d^{10}-base and the enone as a π-acid in an η^3 -π-allyl configuration[1k].

The cuprates probably participate in the π-complex formation in their dimeric form, $(R_2CuLi)_2$, (we use the monomeric formula in the text for simplicity). This dimeric form offers several positions for coordination and/or bonding to the substrate molecule. The copper-alkene π-complex has proved to be a useful transition state model for the following rate-limiting step of the reaction. A copper(III) ß-adduct, which can undergo C-C bond formation by reductive elimination, is often suggested as the transient intermediate preceding the first observable product of the reaction sequence[1c], *i.e.* the enolate.

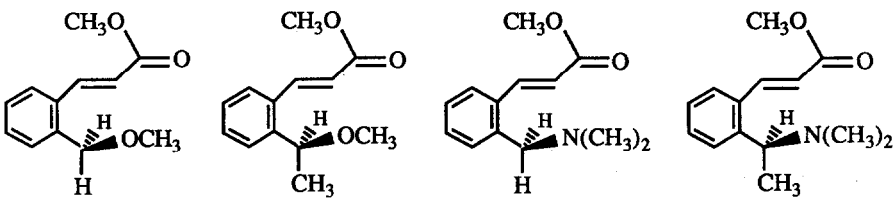
Our hypothesis, that the fast reversible formation of a π-complex is the first step of the 1,4-addition

reaction, is further corroborated by a recent investigation using ^{13}C NMR spectroscopy.[10] In this work copper-alkene π-complex formation between Me_2CuLi and an enone, 10-methyl-$\Delta^{1,9}$-2-octalone, was demonstrated.



Our interest in the mechanism of the cuprate addition to enoates and enones stems from our ambition to find a mechanistic basis for predictions of stereoselectivity in the C-C bond forming reaction. In preliminary communications we have reported the effect of bulky chelating substituents in the substrate on the rate of 1,4-addition of lithium dimethylcuprate, Me_2CuLi, to *ortho*-substituted methyl cinnamates[6]. On the basis of the observed rate enhancement for the cinnamates having a nitrogen or an oxygen containing *ortho*-side chain, we suggested that intramolecular assistance from the built-in ligand lowers the energy of the transition state. The side chain heteroatom is thought to compete with solvent molecules for coordination sites on the lithium atoms of the cuprate.

This model for the transition state prompted us to explore the possibility of exploiting this intramolecular assistance in stereoselective synthesis. In the present investigation the regio- and chemoselectivity of reactions of the achiral enoates **1** and **3** were compared with the reactions of their chiral analogues **2** and **4**. The stereoselectivity of the cuprate additions to enoates **2** and **4** was studied in order to find the best reaction conditions. Non-coordinating solvents were employed in this study, as previous work in this group had demonstrated the beneficial effect of such solvents on reaction rate and chemoselectivity.[3d]



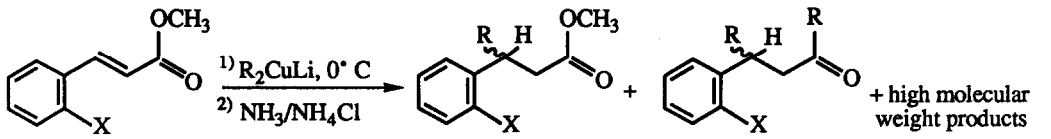
1 **2** **3** **4**

The ^1H and ^{13}C NMR spectroscopic investigation of the reactions of enoates **1**, **2**, **3** and **4** with Me_2CuLi and Ph_2CuLi has already been published[4c].

Results

The results of the addition of the *ortho*-substituted methyl cinnamates **1**, **2**, **3** or **4** to lithium dimethylcuprate, Me_2CuLi, or lithium diphenylcuprate, Ph_2CuLi, are summarized in Table1. All reactions were carried out several times to ensure reproducibility. Standard reaction conditions, *i.e.* addition of one equivalent of the cinnamate, dissolved in diethyl ether, Et_2O, to two equivalents of the cuprate, (2 R_2CuLi), prepared in Et_2O at 0 °C, were used initially. When other solvents were used, Et_2O was evaporated before addition of the new solvent. The reactions were monitored by GC analyses and quenched when no further reaction was observed, typical reaction times being 60 - 90 minutes. Three major types of products were identified while normally only traces of the starting material remained. The diastereomeric excess, d.e., of the products formed were determined from the NMR spectra of the crude reaction mixtures and compared with GC or HPLC data. The first diastereomer to be eluted from the GC was always the major one. According to their ^1H NMR spectra the major isomers also have the same relative configuration.

Cinnamate **1** reacted cleanly with Me_2CuLi in diethyl ether, Et_2O, to give the 1,4-addition product **5a**, Table 1, expt. 2. For reactions in Et_2O without TMSI, this was the only case where clean addition with negligible by-product formation, was observed.



a: R = Me **b**: R = Ph

	X	Conjugate adduct	Ketone by-product
1	- CH_2OCH_3	**5**	**9**
2	- $CH(CH_3)OCH_3$	**6**	**10**
3	- $CH_2N(CH_3)_2$	**7**	**11**
4	- $CH(CH_3)N(CH_3)_2$	**8**	**12**

On addition of **2**, **3** or **4** to Me_2CuLi or Ph_2CuLi in Et_2O at 0 °C the formation of the expected 1,4-addition products **6**, **7** or **8** was accompanied by formation of the ketones **10**, **11** or **12** and substantial amounts of high molecular weight products, Table 1 expt. 4, 6, 7, 8, 11, 16. The ketones are most probably the result of an initial substitution on the ester function by the cuprate followed by a rapid 1,4-addition to the newly formed enone.

$$\text{enoate} + [R_2CuLi]_2 \longrightarrow \text{enone} \xrightarrow{[R_2CuLi]_2} \mathbf{9, 10, 11, 12}$$

An increase in the cuprate to substrate ratio from 2:1 to 4:1 caused a substantial increase in the formation of the ketones **9** - **12**. However, the formation of ketones as well as the formation of high molecular weight products can be controlled and reduced to a minimum by a careful choice of reaction conditions as shown in Table 1, expt. 5, 9, 12, 13, 17.

The solvent is an important variable as seen from the experiments in Table 1. In tetrahydrofuran (THF) no reaction takes place at 0 °C and the starting material is recovered after 90 minutes. Reaction does occur in Et_2O, however at much lower rate than in dichloromethane, CH_2Cl_2, or toluene. The relative rate of consumption of **4** on addition to Me_2CuLi at 0 °C in Et_2O and CH_2Cl_2 was compared by GC analysis of the reactions mixtures.

After 5 minutes in Et_2O ca 80 % of **4** remained while in CH_2Cl_2 only 11 % of unreacted **4** remained. In contrast, a fast and clean reaction takes place on addition of compounds **2**, **3** or **4** to Me_2CuLi or Ph_2CuLi in CH_2Cl_2 or toluene leading to a complete conversion of the enoates to the 1,4-addition products **6a**, **7b**, **8a** and **8b** respectively. No significant by-product formation was observed in CH_2Cl_2 or toluene.

The best results obtained in this study, in terms of both chemical yield and stereoselectivity, were obtained in the addition of the chiral cinnamate **4** to either cuprate in CH_2Cl_2 or toluene, affording the products **8a** and **8b**. The yields were on average, 80-85% and the d.e. > 75%.

The diastereomeric excess observed on formation of **6a** or **6b** by addition of enoate **2** to Me_2CuLi or Ph_2CuLi was low and varied only moderately with changes in reaction conditions from 5 to 25%, expt. 4, 5, and 6. Attempts to increase the d.e. by lowering the reaction temperature to -78 °C were futile.

Reactions of **4** in Et_2O were not as stereoselective as in CH_2Cl_2 or toluene. For example, in the addition of **4** to Me_2CuLi in Et_2O, expt. 11, the diastereomeric excess of the ester product **8a** was 68%, (the d.e. of the ketone product **12a** was only 28%). The reaction of Ph_2CuLi with **4**, expt. 16, afforded similar results. Low reaction temperatures, -45 °C to -78 °C, did not change the final d.e. However the d.e. of **8a** varied with the conversion of **4**.The formation of products **8a**, corresponding to enolates **13**, see Figure 1, in the reaction between Me_2CuLi and **4** in Et_2O was therefore carefully monitored by capillary GC. We found low d.e. values, <35%, for **8a** after very short reaction times, 0.5 minutes, and low conversion of the substrate. As the reaction proceeded the d.e. of **8a** increased slowly to reach the observed value of 68-70%. A few representative results

Table 1. Addition of *ortho*-Substituted Methyl Cinnamates **1**, **2**, **3** or **4** to $[Me_2CuLi]_2$ or $[Ph_2CuLi]_2$.

Expt.	Enoate	R_2CuLi	Solvent	Yield of conjugate addition products **5**, **6**, **7**, **8**			Yield of ketone by-products **9**, **10**, **11**, **12**			Comments
				(%)[a]	(%)[b]	d.e.[c] %	(%)[a]	(%)[b]	d.e.[c] %	
1	**1**	Me	THF	< 1	< 1	–	< 1	–	–	91 % s.m.
2	**1**	Me	Et_2O	84	83	–	<1	–	–	–
3	**2**	Me	THF	< 1	< 1	–	< 1	< 1	–	68 % s.m.
4	**2**	Me	Et_2O	59	48	< 5	< 2	_	0	34% h.p.
5	**2**	Me	CH_2Cl_2	86	85	10	< 1	–	–	–
6	**2**	Ph	Et_2O	68	56	26	26	18	16	
7	**3**	Me	Et_2O	56	55	–	12	4	–	< 24 % h.p.
8	**3**	Ph	Et_2O	–	43	–	–	20	–	35 % h.p.
9	**3**	Ph	CH_2Cl_2	81	78	–	–	–	–	–
10	**4**	Me	THF	< 1	< 1	–	< 1	<1	–	60 % s.m.
11	**4**	Me	Et_2O	23	18	68	25	17	28	50% h.p.
12	**4**	Me	CH_2Cl_2	96	80/94	79/69	< 1	–	–	6 % s.m.
13	**4**	Me	Toluene	94	91	82	< 1	–	–	–
14	**4**	Me	Et_2O	89	83	0	2	–	0	TMSI added
15	**4**	Me	Et_2O	22	10	72	28	15	28	LiI removed 65% h.p.
16	**4**	Ph	Et_2O	46	30	25	20	19	3	40% h.p.
17	**4**	Ph	Toluene	90	70	74	–	–	–	6 % s.m.

All reactions were carried out at 0 °C for 60-90 min. a = estimated by GC, b = isolated yield, c = determined from NMR, s.m. = isolated yield of starting material, h.p. = isolated yield of high molecular weight product.

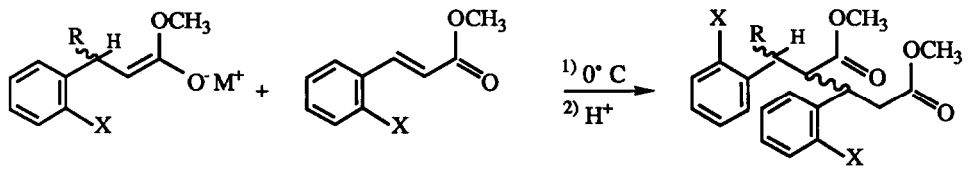
are summarized in Table 2. As seen from Table 2 the ketone **12a** is formed almost as fast as the normal 1,4-addition product together with increasing amounts of high molecular weight products. No change in d.e. was observed for product **12a** during the reaction.

The data in Table 2, indicates a correlation between the yield and d.e. of **8a** and the yields of high molecular weight products. It was possible to separate the high molecular weight products from **8a** and **12a**, however, no further separation of the individual components proved possible. Capillary GC analysis of this mixture showed several closely spaced peaks. The ^1H NMR spectrum of this mixture is similar to that of the 1,4-addition product **8a**. The mass spectrum of the mixture showed that the two major components had molecular masses of 466 and 482 respectively. The mass 482 is in agreement with structure **14** formed in a reaction sequence where the initially formed enolates, **13**, react with another substrate molecule **4**, see Figure 1, *i. e.* a double Michael reaction[7c], MIMI, to give diastereomeric products. As the d.e. of the enolates remaining in the solution is

Table 2. Variation in product composition and diastereoselectivity with reaction time on addition of enoate **4** to $[Me_2CuLi]_2$ in Et_2O at 0 °C. The relative ratios of components were measured by capillary GC.

Time min	reactant **4** %	**8a** yield %	d.e. %	**12a** yield %	d.e. %	Heavier products yield %
3	87	4	**40**	6	26	-
30	50	21	**62**	17	26	7
60	28	23	**70**	22	26	24

increased, it must be concluded that the second Michael reaction, enolate addition to substrate **4**, is stereoselective and that the minor diastereomer of **13** reacts faster than the major diastereoisomer. The compound with mass 466 is the product obtained in the analogous reaction between the enolates **13** and the unsaturated ketone formed *in situ*.



13 **14**

Figure 1.

To test this hypothesis another addition of **4** to Me_2CuLi in Et_2O was performed. The reaction was complete after 1.5 hours. GC analysis of a hydrolysed aliquot showed, **4**: 0%, **8a** 40%, d.e. 67%; **14**: 35%. The remaining reaction solution was stirred for another 4 hours at 0 °C whilst being monitored by GC. The composition remained unchanged with the d.e. of **8a** still being 67 %. At this point 0.3 equivalents of cinnamate **4** was added. Ten minutes after addition the d.e. of the remaining **8a** was 73 % and increased further as long as some **4** was present in the solution. The amount of **8a** in the solution decreased to 24% and the amount of the double Michael products increased to 48% as the added 0.3 equivalents of **4** reacted and disappeared. After 75 minutes **8a** was obtained in a low yield, 24%, but with a d.e. as high as 84 %.

The experiment was repeated with **2**. A similar increase in the yield of MIMI products was observed but the d.e. of product **6a** remained unchanged.

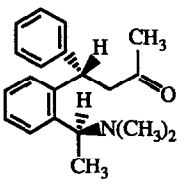
Some attempts were made to affect the chemo- and stereoselectivity by modification of the reagents. Removal of LiI, formed in the preparation of Me_2CuLi, from the cuprate before addition of **4** caused no change in d.e., expt. 15. No increase in the formation of **8a** was observed but instead the yield of the high molecular weight products increased substantially.

The addition of **4** to an ether solution of Me_2CuLi containing 2 equivalents of iodotrimethylsilane, TMSI, afforded a very high chemoselectivity and **8a** was obtained in high yield. The reaction is fast even below -20 °C. However, the stereoselectivity was completely lost, expt. 14.

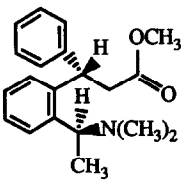
On addition of **4** to the organocopper reagent MeCu·LiI in Et_2O at 0 °C the yellow colour of the solid immediately changed to an orange-brown. The precipitate was unchanged after stirring for 4 h. Addition of Me_2CuLi to this precipitate afforded the previously observed product mixture, *cf* expt. 11, Table 1. The d.e. of **8a** increased as before and reached 67% after complete conversion of **4**. The addition of **4** to MeCu·LiI in Et_2O was repeated in the presence of iodotrimethylsilane. The temperature was raised from -78 °C to -40 °C (3h), followed by -40 °C to 0 °C (2h). Only a very low yield, *ca* 20%, d.e.0%, of the 1,4-addition product, **8a**, and

followed by -40 °C to 0 °C (2h). Only a very low yield, *ca* 20%, d.e.0%, of the 1,4-addition product, **8a**, and some starting material, ca 30%, was isolated while roughly 50% of the material was lost as water soluble products.

The diastereomeric 1,4-addition products **8b** from addition of **4** toPh_2CuLi, expt. 16, d.e. 25%, were separated and their ^1H NMR spectra compared with that of an authentic sample of *S,S*-4-(2-(1-dimethylaminoethyl))phenyl-4-phenyl-2-butanone, **15**, which is a ketone analogue of **8b**. The absolute configuration of **15** has been determined by X-ray diffraction.[8] On the basis of similarities in their ^1H NMR spectra (*cf.* the experimental part) the major diastereomer of **8b** was assigned the *S,S*-configuration.



15 (S,S)



8b (S,S)

Discussion

Synthetic aspects

The strong effect of solvent variation on reaction rate, chemical yield and stereoselectivity observed in this study, is consistent with previous findings.[3d, 9, 10] The relative reactivity of the cuprate was found to increase in the order THF < Et_2O < CH_2Cl_2, toluene.[3d]

In the early cuprate literature[11] enoates were considered less useful as substrates for 1,4-additions of organocuprates. In the light of our results this is not very surprising since the solvent of choice was often THF. Enones and enals are generally more reactive towards organometallic reagents than ester groups. Thus the combination of a slow-reacting cuprate in THF and a slow reacting carbonyl compound is not good. Our results clearly demonstrate that quantitative yields of 1,4-addition products can be obtained even from sterically crowded, slow-reacting enoates provided the proper solvent is used.

The presence of TMSI in the reaction of **4** with Me_2CuLi very favourably increased the reaction rate and the chemoselectivity of the reaction while stereoselectivity was completely lost in this particular case.

Solvent effect on cuprate structure

The following discussion on the mechanistic implications of our work is based on the model of dimeric lithium diorganocuprates.[2i,3,12] Me_2CuLi and Ph_2CuLi used in this investigation were prepared from recrystallized CuI[13] in diethyl ether using the appropriate organolithium compound without removal of LiI, except in expt. 15. This mode of preparation ensures the formation of a single observable species, $(R_2CuLi)_2 \cdot (Et_2O)_n$,[3d,e] assumed to be the reacting species in Et_2O. On exchange of Et_2O for THF as solvent, the coordinating ether molecules are displaced by THF (NMR observation) with simultaneous polarisation of the C - Li bonds within the dimeric cuprate.[1m] A loss of reactivity is observed. The structure of the cuprate in THF could be described as a double ion pair, R_2Cu^- and $Li^+(THF)_n$, whereas in non-coordinating solvents at least one molecule of Et_2O per lithium remains coordinated to the cuprate, and the dimeric structure with relatively strong covalent bonds is retained. The cuprates show higher reactivity in non-coordinating solvents than in Et_2O in spite of low solubility.[3d] The low reactivity of the cuprates in THF can at least be partially attributed to strong coordination of THF oxygens to lithium in the cuprate, thus preventing coordination to the carbonyl oxygen of the enoate. The coordination of a Lewis acid to the carbonyl oxygen is suggested to be necessary for reaction to take place.[1c] In CH_2Cl_2 or toluene coordination of the carbonyl oxygen can easily compete with the few diethyl ether molecules for coordination sites on lithium.

Enolate structure and reactivity

The unusual increase in the ratio of the diastereomers of **8a** obtained on addition of **4** to Me_2CuLi in Et_2O with consumption of **4** could have at least two explanations; equilibration of products, enolates, a thermodynamic phenomenon, or alternatively a subsequent step after formation of enolates consuming one of the diastereomeric enolates faster than the other. Equilibration as a rationale for the increase in d.e. requires that the carbon-carbon bond forming step is reversible. However, we have not been able to observe any increase in d.e. on prolonged reaction times, see above, consistent with such an equilibration and thus we rule out this explanation.

The increased diastereomeric excess observed in the reaction of **4** in Et_2O is consistent with a stereoselective secondary reaction in which the minor stereoisomer of the initially-formed enolate **13** reacts faster with additional molecules of **4**. As observed previously the rate of the secondary Michael reaction is sensitive to the choice of solvent.[3d] The MIMI reaction may afford the major reaction products from enoates in THF[9b] while it has not been observed in reactions performed in non-coordinating solvents. The formation of MIMI products in THF[9b] probably reflects the low reactivity of the cuprate in this solvent, allowing competition for substrate molecules by the enolate formed.

The high reactivity observed for the metal enolates in diethyl ether is attributed to the presence of the chelating methoxy and dimethylamino groups. House *et al.* discussed the nature of the enolate formed by addition of cuprates to enones.[14] Seebach has recently discussed the effects of the counter ion and solvent on the aggregate structure as well as on the reactivity of enolates.[15] However, a detailed mechanistic understanding of our observations must await information about the enolate aggregate structure.

Mechanistic aspects

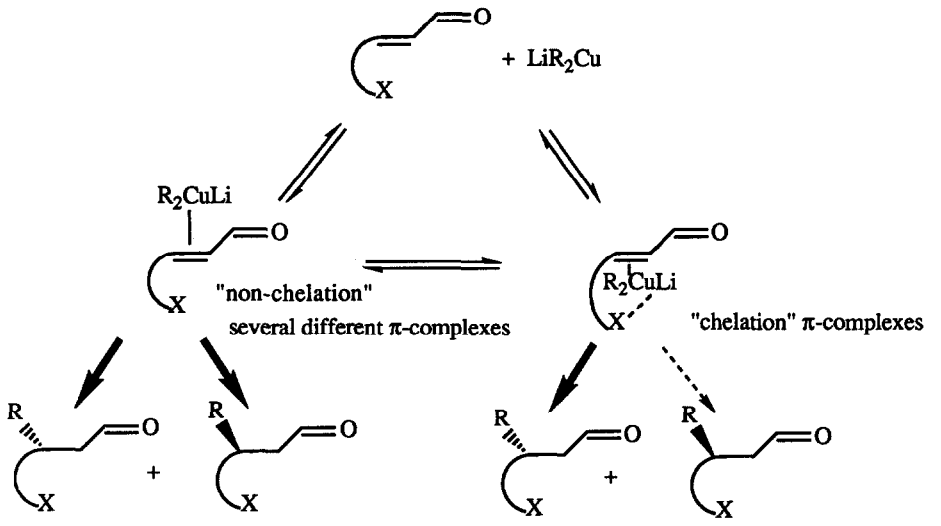
The results from our attempts to use chelation control from chiral substituents, to obtain high stereoselectivity in the reactions of R_2CuLi with enoates **2** and **4** in Et_2O, were disappointing. The inherent stereoselectivity was found to be low in this solvent, Table1, expts. 4 and 11 and Table 2. However, a change to non-coordinating solvents made reactions of **4** highly stereoselective, Table 1.

The initial steps in the reaction between an organocuprate and a substituted enoate can be summarized in a set of equilibria involving the cuprate and the alkene bond, see Figure 2, where X denotes a chelating substituent on the benzene ring. The actual number of π-complexes is greater than those shown in Figure 2 as the two major types, called "non-chelation" and "chelation" π-complex respectively,[16] each can exist in isomeric forms. "Non-chelation" refers to the function of the side chain hetero atom. The relative rates of transformation of the different π-complexes in the carbon-carbon bond forming step will determine the diastereoselectivity of the reactions. The influence of various reaction parameters, *e.g.* temperature, solvent and the presence of additives, will be discussed in relation to the equilibria pictured in Figure 2.

With the solvent system used for the NMR investigation, CD_2Cl_2/THF-d_8, of the solutions of **1**, **2**, **3** or **4** with Me_2CuLi or Ph_2CuLi, only the "non-chelation" π-complexes have been observed since THF occupies all coordination sites on the cuprate lithium atoms.[4c] At temperatures below -60 °C each individual π-complex gives rise to a separate NMR signal, 3 to 5 species were observed, while equilibration of the π-complexes is observed on raising the temperature slightly. Besides the two diastereomeric π-complexes there are conformational isomers which can equilibrate by rotation around single bonds in the enoate. Upon further increase of the temperature the equilibration between reactants and π-complexes is observed and simultaneously carbon-carbon bond formation starts.[4c]

In Et_2O, the presence of the "chelation" π-complexes is invoked on the basis of the reactivity relationship of substituted methyl cinnamates, *vide supra*.[6] With **2** and **4**, two diastereomeric "chelation" π-complexes are possible. As chelation of the side chain heteroatom limits the rotational freedom of the substrate molecules, conformational isomers of these π-complexes do not have to be taken into account. The equilibrium between "non-chelation" and "chelation" π-complexes has not been observed directly but is very likely. The low stereoselectivity obtained with **2** or **4** in Et_2O (d.e. *ca* 5% and <35% respectively) indicates that the rate

difference in the transformation of various π-complexes is small in this solvent. From NMR data we know that at least five π-complexes are formed from **2** on addition to Me_2CuLi.[4c] The side chain oxygen atom can compete with solvent oxygens for coordination to lithium atoms of the cuprate and thus "non-chelation" as well as "chelation" π-complexes may be present in equilibrium. With **4**, the dimethylamino group can be expected to be the slightly stronger Lewis base shifting the equilibrium towards the "chelation" side.



With the change of solvent from THF or Et_2O to CH_2Cl_2 or toluene the chelation of the dimethylamino group to lithium should be strongly favoured, shifting the equilibria towards the "chelation" π-complexes. Based on our earlier observation of the effect of intramolecular assistance from chelating side chains on the rate of the reaction, a chelating π-complex should be expected to react faster than a non-chelating π-complex.[6] This hypothesis is strongly supported by the observed stereoselectivity with **4**, expt. 13, Table 1, as the S,S-configuration of the major diastereomer of **8b** can be accommodated with a chelation controlled transition state. Several examples of heteroatom-assisted reactions between cuprates and organic compounds have been reported recently.[16, 17] Chelation control of the stereoselectivity has been invoked.

The rate enhancement and chemoselectivity observed when TMSI is present in the reaction between Me_2CuLi and **4** are in good agreement with results with TMSCl and TMSI reported by other groups.[18] The rate enhancement indicates the participation of TMSI in the rate determining step. Further discussion of the specific mode of action will be postponed until a more thorough investigation has been completed.

Alexakis *et al.* have studied the stereochemistry of related reactions.[16] The reactions between Me_2CuLi and some *ortho*-substituted ethyl cinnamates in Et_2O showed high stereoselection that was attributed to chelation control. The reversed stereoselectivity in the presence of TMSCl was attributed to the intervention of TMSCl in the equilibration between "non-chelation" ("kinetic" in their paper) and "chelation" π-complexes. It was suggested that TMSCl reacts with the "non-chelation" π-complex before an equilibrium is established and the stereochemistry will then be determined by the steric effects of the side chain, *i.e.* reaction occurs on the less shielded face of the substrate.

Our result with Me_2CuLi, TMSI and **4** can be accommodated within the hypothesis presented by Alexakis *et al.* if it is assumed that the diastereomeric, "non-chelation" π-complexes are transformed into products at an equal rate. This agrees well with the result obtained with **2**, *vide supra*. The stereodifferentiation obtained by Alexakis *et al.* in the kinetically-controlled reaction of the "non-chelation" π-complex is due to the bulky *ortho*-side chain compared to **2** or **4**.

Conclusion

We have demonstrated the favourable effect that can be obtained on chemoselectivity and stereoselectivity of cuprate additions to enoates by a careful choice of solvent. The temperature of the reaction is of less importance. In THF the cuprates show low reactivity. With Et_2O the cuprates show moderate reactivity while the metal enolates, the products of the reaction, show unusual high reactivity. Solvents like CH_2Cl_2 or toluene afford highly reactive cuprates and allow for intramolecular assistance in the stereodifferentiating step from built-in ligands.

Experimental

All handling of organometallic reagents was carried out under argon and with dried equipment. Diethyl ether, THF and toluene were distilled from sodium benzophenone ketyl and CH_2Cl_2 from CaH_2. Commercial methyllithium in diethyl ether and phenyllithium in benzene/ether (Aldrich) were used. Copper (I) iodide was recrystallized prior use.[13] ^1H and ^{13}C NMR spectra were recorded on a Varian XL 400 MHz, Brucker 270 or 500 MHz spectrometer, gas chromatograms on a Varian 3300 chromatograph (30 m DB-1, FID), mass spectra on a Finnigan 1020 (E.I. 70 eV), and IR spectra on a Perkin Elmer 1600 FTIR.

Syntheses

Synthesis of methyl 3-(2-methoxymethylphenyl)propenoate 1

1-Bromo-2-(methoxymethyl)benzene.[19] To a solution of sodium (1.49 g, 62.5 mmol) dissolved in dry methanol (30 ml), 2-bromobenzylbromid (14.8 g, 59.2 mmol) was added and the mixture was refluxed for 3 h. After cooling to room temperature NaBr was filtered of, 1 ml water was added and most of the methanol was evaporated in vacuo. The residue was diluted with 100 ml water and extracted with dichloromethane, dried (Na_2SO_4), evaporated in vacuo and finally purified by kugelrohr distillation (0.8 torr/ 55 °C). (10.4 g, 87.5%).

2-Methoxymethyl benzaldehyde. A solution of 1-bromo-2-(methoxymethyl)benzene (8 g, 39.8 mmol) in diethyl ether (30 ml) was cooled to - 78 °C and butyllithium (24.2 ml, 1.65 M) was added. After 1.5 h at -78 °C freshly distilled DMF (5 ml, 66 mmol) was added. The solution was stirred and the temperature slowly raised to 20 °C before quenching with HCl (15 ml, 2 M). After 30 min, the phases were separated, the ether phase dried (Na_2SO_4) and evaporated in vacuo. The crude reaction product was used without further purification in the next step. Yield > 95% (GC analysis of crude product). (7.4 g, 97%). IR (film): 1690 cm^{-1}

3-(2-Methoxymethylphenyl)propenoic acid. 2-Methoxymethyl benzaldehyde from the preceding step and 2 equiv. malonic acid (10.4 g, 100 mmol) were dissolved in pyridine (30 ml).[20] Piperidine (1 ml) was added and the mixture was heated to 80 °C during 30 min and kept there for 1 h. The temperature was then raised to 110 °C. After 3 h. the reaction mixture was cooled to room temperature and poured into cold water and HCl (30 ml, conc) was added. The crystals were filtered off and dried in vacuo. (6.5 g, 69.5%). mp: 142-143 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 3.44 (3H, s) 4.59 (2H, s) 6.42 (1H, d, J 16 Hz) 7.36-7.40 (3H, m) 7.64 (1H, m) 8.12 (1H, d, J 16 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 58.3, 72.5, 119.0, 127.0, 128.4, 129.6, 130.3, 133.3, 137.2, 143.9, 172.1.

Methyl 3-(2-methoxymethylphenyl)propenoate 1. A solution of 3-(2-methoxymethylphenyl)propenoic acid (6.5 g, 33.8 mmol) in methanol (75 ml) and traces of H_2SO_4 was refluxed for 12 h. The solvent was evaporated in vacuo and the residue was distilled by kugelrohr (0.3 torr/110-120 °C). (6.1 g, 87.5%). MS (m/Z): 206 (M^+, 2%) 174 (52) 131 (33) 115 (100) 103 (35) 59 (23). Found: C, 69.88; H, 6.93. Calc for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. ^1H NMR (270 MHz, $CDCl_3$) δ 3.42 (3H, s) 3.81 (3H, s) 4.56 (2H, s) 6.38 (1H, d, J 15.8 Hz) 7.34 (3H, m) 7.58 (1H, m) 7.99 (1H, d, J 15.8 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 51.34, 57.97, 72.22, 119.49, 126.54, 128.05, 129.25, 129.62, 133.41, 136.95, 141.56, 166.93.

Synthesis of Methyl 3-[2-(1-methoxyethyl)phenyl]propenoate 2.

1-Methoxy-1-phenylethane. 1-Phenylethanol (15 g, 122.8 mmol), (EGA-Chemie), was added to a slurry of NaH (246 mmol) in 200 ml THF and refluxed for 30 min. The reaction was cooled to room temperature and methyliodide (34.9 g, 246 mmol) in 30 ml THF was added. After 12 h the reaction was cooled to 0 °C and 2 M HCl was added to pH < 3. The mixture was extracted with diethyl ether, the organic layer dried (Na_2SO_4), and the solvent evaporated in vacuo. (14.6 g, 87 %). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.8, 56.3, 79.5, 126.1 (2C), 127.3, 128.3 (2C), 143.4.

2-(1-Methoxyethyl)benzaldehyde. *tert*-Butyllithium (4.4 ml, 1.7 M, 7.3 mmol) was added to a solution of 1-methoxy-1-

phenylethane (1 g, 7.3 mmol) in pentane (10 ml). After 2 h the deep red solution was cooled to -78 °C and freshly distilled DMF (0.55 ml, 8.3 mmol) was added. The temperature of the solution was raised to room temperature and after 45 min the reaction was quenched with HCl (3 M) to pH = 2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated in vacuo. As the product is very easily oxidized, the crude reaction product was used immediately in the next step, without further purification. Yield > 60% (GC analysis of the crude product). IR (film): 1695 cm^{-1}. MS (m/Z): 164 (M^+, 3%) 149 (84) 132 (83) 104 (100) 91 (60) 77 (78) 51 (59).

3-[2-(1-Methoxyethyl)phenyl] propenoic acid. 2-(1-Methoxyethyl)benzaldehyde (ca 3.3 mmol) and malonic acid (0.7 g, 6.6 mmol) were dissolved in pyridine (8 ml). After addition of piperidine (0.5 ml) the mixture was heated to 80 °C, kept with stirring for 1 h followed by reflux at 110 °C for 3h.[20] After cooling, the reaction mixture was poured into cold water and conc. HCl was added to pH<1. The crude crystals were dissolved in NaOH (1 M), washed with diethyl ether and finally HCl (conc) was added and the white crystals were filtered off. (400 mg, 59 %). mp: 148-150 °C. IR (KBr): 1680, 1620 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.45 (3H, d, J 6.5 Hz) 3.27 (3H, s) 4.71 (1H, q, J 6.5) 6.38 (1H, d, J 15.8) 7.80, 7.92 (2H, t, J 7.4 Hz) 7.97, 8.08 (2H, d, J 7.8 Hz) 8.24 (1H, d, J 15.8 Hz).

Methyl 3-[2-(1-methoxyethyl)phenyl]propenoate 2. 3-[2-(1-methoxyethyl)phenyl] propenoic acid (1.2 g, 5.8 mmol) was dissolved in methanol (30 ml) traces of conc. H_2SO_4 was added and the solution refluxed for 12 h. The solvent was evaporated under reduced pressure and the residue distilled by kugelrohr (0.1 torr/70 °C). (1.0 g, 78%). mp: 30-32 °C. IR (KBr): 1718, 1638 cm^{-1}. MS (m/Z): 220 (M^+, 1%), 205 (14) 161 (58) 129 (100) 115 (78) 59 (42). Found: C, 70.96; H, 7.39. Calc for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.42 (3H, d, J 6.5 Hz) 3.25 (3H, s) 3.82 (3H, s) 4.70 (1H, q, J 6.5 Hz) 6.35 (1H, d, J 15.8 Hz) 7.30, 7.42 (2H, t, J 7.6 Hz) 7.48, 7.55 (2H, d, J 7.7 Hz) 8.10 (1H, d, J 15.8 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 23.4, 51.6, 56.5, 76.2, 119.8, 126.1, 126.7, 127.5, 130.2, 132.4, 141.6, 142.7, 167.1.

Synthesis of Methyl 3-(2-dimethylaminomethylphenyl)propenoate 3.

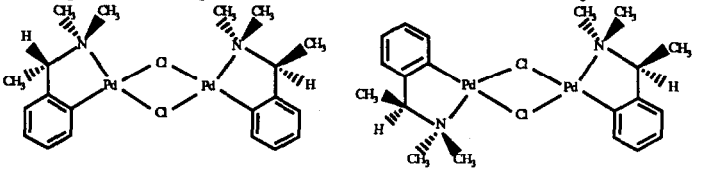
μ-(Dichloro)-bis(N,N-dimethylbenzylamine-2-C,N) dipalladium (II). The Pd-complex was prepared according to the literature[21] from N,N-Benzyldimethylamine (Fluka), (15 g, 110 mmol), and palladium dichloride (Janssen Chimica), (9.8 g, 55 mmol) in methanol. (82 %). mp: 181-182 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.85 (6H, d) 3.95 (2H, s) 6.8-7.2 (4H, m)

Methyl 3-(2-dimethylaminomethylphenyl)propenoate 3. See methyl (S)-3-[2-(1-dimethylaminoethyl)phenyl] propenoate. Pd-complex (1.0 g, 1.8 mmol), methyl acrylate (0.6 g, 7.2 mmol) and Et_3N (1.0 g, 7.2 mmol). (160 mg, 43%). MS (m/Z): 219 (M^+, 14%) 218 (17) 204 (42) 174 (34) 144 (33) 117(50) 115 (100) 58 (75). Found: C, 71.05; H, 7.88; N, 6.21. Calc. for $C_{13}H_{17}N_1O_2$: C, 71.15; H, 7.81, N 6.38. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.25 (6H, s) 3.5 (2H, s) 3.82 (3H, s) 6.37 (1H, d, J 16 Hz) 7.30 (3H, m) 7.58 (1H, d, J 7 Hz) 8.18 (1H, d, J 16 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 45.3 (2C), 51.6, 61.8, 118.7, 126.5, 127.5, 129.6, 130.7, 134.1, 138.3, 142.6, 167.4.

Synthesis of Methyl (S)-3-[2-(1-dimethylaminoethyl)phenyl]propenoate 4.

(S)-(-)-N,N-Dimethyl-1-phenylethylamine. The dimethyl amine was prepared by Eschweiler-Clarke methylation[22] of (S)-(-)-1-phenethylamine, Aldrich. (96 %). The dimethyl amine was further purified by recrystallisation with picric acid,[23] from $[\alpha]^{25}_D$ - 65 ° (neat) to $[\alpha]^{25}_D$ -70.6° (neat). (66 %).

μ-(Dichloro)bis[(S)-N,N-dimethyl-(1-phenylethyl)amine-2 C,N] dipalladium (II). The Pd-complex was prepared according to the literature[24] from the amine (5.0 g, 33.5 mmol) and palladium dichloride (2.7 g, 15.2 mmol) in dry methanol. (85%).
mp: 181-183 °C. The NMR spectra show the presence of two isomers of the dimeric Pd-complex, one of them in slight excess.



a = major product, a' = minor product. ^{13}C-NMR (125 MHz, $CDCl_3$) δ 18.5 (a') 18.7 (a) 46.8 (a') 47.2 (a) 52.1 (a') 52.4 (a) 75.2 (a+a') 121.9 (a+a') 124.6 (a) 125.2 (a') 132.9 (a) 133.4 (a') 143.3 (a') 143.4 (a) 152.1 (a') 152.3 (a).

Methyl (S)-3-[2-(1-dimethylaminoethyl)phenyl]propenoate 4. Et_3N (5.7 ml, 41 mmol) and methyl acrylate (3.5 g, 41 mmol) were added to the Pd-complex (1.2 g, 4.1 mmol) dissolved in dry toluene (50 ml). The solution was refluxed for 24 h, during which time a mirror of metallic Pd was deposited in the flask. After cooling to room temperature, the solvent was decanted and the

precipitate was washed with toluene. The toluene was evaporated and the residue was dissolved in diethyl ether and the salts were filtered off. The ether was evaporated and the residue was flash chromatographed (EtOAc/Pentane, 1/3, 1% TEA). (450 mg, 47%). $[\alpha]^{25}_D$ -57°, (c=4.0, $CHCl_3$). IR (film): 1720, 1640 cm^{-1}. MS (m/Z): 233 (M^+, 5%), 218 (41) 129 (49) 115 (49) 72 (100). Found: C, 71.92; H, 8.27; N, 5.92. Calc for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, d, J 6.6 Hz) 2.23 (6H, s) 3.61 (1H, q J 6.6 Hz) 3.84 (3H, s) 6.33 (1H, d, J 15.7 Hz) 7.26 (1H, t, J 7.6 Hz) 7.38 (1H, t, J 7.6 Hz) 7.51-7.54 (2H, m) 8.33 (1H, d J 15.7 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 19.5, 43.2 (2C) 51.5, 61.7, 119.0, 126.66, 126.74, 127.3, 129.9, 133.0, 142.9, 144.4, 167.3.

General procedure for the conjugate addition of lithium diorganocuprates:

A solution of Me_2CuLi (prepared from methyllithium (1 ml, 1.6 M) and CuI (167 mg, 0.88 mmol) in 10 ml diethyl ether was stirred at 0 °C for 10 min.. The enoate (0.4 mmol), dissolved in 2 ml diethyl ether was then added at 0 °C and the reaction left with stirring for 60 - 90 min., unless otherwise specified. NH_3/NH_4Cl (5ml) was then added and stirring continued for another hour. The phases were separated and the water phase extracted with ether (3x15 ml). The combined organic layer was washed with brine, dried (Na_2SO_4), and the solvent evaporated in vacuo. The crude product was analysed by GC. The same protocol was used for lithium diphenylcuprate (phenyllithium, 0.8 ml, 2 M).

Reactions in the presence of TMSI: When TMSI was used, 2 equivalents was added to Me_2CuLi at -78 °C followed by the addition of the substrate. The temperature of the solution was then raised to -20 °C and the general procedure was followed.

Reactions performed after removal of LiI: Methyllithium (0.5 ml, 1.6 M) was added to a slurry of CuI (167 mg, 0.88 mmol) in 3 ml diethyl ether at 0 °C. The yellow precipitate, CH_3Cu, was allowed to settle and the solvent was removed by a syringe. The precipitate was washed with 3x1.5 ml ether before 11 ml of fresh solvent and a second equivalent of methyllithium were added. The general protocol was then followed.

Change to solvents other than diethyl ether: The cuprate was prepared according to the general procedure but in 3 ml diethyl ether. After stirring for 10 min at 0 °C the ether was evaporated in vacuo at 0 °C for 30-60 min. The new solvent (2 ml) was added, the mixture stirred and the solvent evaporated at 0 °C for 30 min. Finally 11 ml of the new solvent was added to the pale yellow solid and the reaction was run as described above. The cuprate is a suspension in CH_2Cl_2 or toluene and retains at least one equivalent of diethyl ether coordinated to each lithium according to NMR. When THF is used as the second solvent all diethyl ether is removed by this procedure and the cuprate dissolves on addition of THF.

Procedure for the conjugate addition of methyl copper-TMSI.

MeCu·LiI was prepared by addition of methyllithium (0.4 ml, 1.6 M) to a slurry of CuI (125 mg, 0.4 mmol) in 10 ml diethyl ether at 0 °C. The solution was cooled to -78 °C before addition of TMSI (0.1 ml, 0.8 mmol). After 5 min at -78 °C, the enoate (0.4 mmol) dissolved in 2 ml diethyl ether was added. The temperature was slowly raised to -20 °C and after 3 h the reaction was quenched with NH_3/NH_4Cl and stirred at 0 °C. The workup procedure described above was followed.

Products.

Methyl 3-[2-methoxymethylphenyl] butanoate **5a** IR (film): 1738 cm^{-1}. MS (m/Z): 222 (M^+, 1%) 207 (4) 159 (6) 131 (15) 121 (100) 91 (22). Found: C, 70.7; H, 8.2. Calc for $C_{13}H_{18}O_3$: C, 70.2; H, 8.1. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.28 (3H, d, J 6.7 Hz) 2.54 (1H, dd, J 8; 15 Hz) 2.67 (1H, dd, J 6.5; 15.5 Hz) 3.40 (3H, s) 3.58 - 3.6 (1H, m, partly hidden), 3.62 (3H, s) 4.48 (1H, d, J 11.5 Hz) 4.62 (1H, d, J 11.5 Hz) 7.14-7.53 (4H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 21.8, 30.8, 42.4, 51.5, 58.1, 72.8, 125.6, 126.1, 128.3, 129.4, 135.0, 144.7, 172.9.

4-[2-methoxymethylphenyl]-2-pentanone **9a** IR (film): 1719 cm^{-1}. MS (m/Z): 206 (M^+, 2%) 174 (12) 159 (45) 148 (98) 133 (68) 121 (100) 91 (95). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.24 (3H, d, J 6.8 Hz) 2.07 (3H, s) 2.64 (1H, dd, J 6; 16 Hz) 2.79 (1H, dd, J 6; 16 Hz) 3.39 (3H, s) 3.61 (1H, m) 4.51 (1H, d, J 11.4 Hz) 4.56 (1H, d, J 11.4 Hz) 7.15 (1H, m) 7.22-7.31 (3H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 21.9, 29.8, 30.3, 51.9, 58.1, 73.0, 125.6, 125.9, 128.3, 129.5, 134.9, 145.2, 207.8.

Methyl 3-[2-(1-methoxyethyl)phenyl] butanoate **6a** The two diastereoisomers (a+a'), have not been separated. IR (film): 1738 cm^{-1}. MS (m/Z): 236 (M^+, 1%) 221 (13) 175 (22) 144 (27) 135 (100) 129 (90). Found: C, 70.5; H, 8.3. Calc for $C_{14}H_{20}O_3$: C, 71.1; H, 8.5. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.26 (a, 3H, d, J 6.8 Hz) 1.27 (a', 3H, d, J 6.4 Hz) 1.42 (a, 3H, d, J 6.6 Hz) 1.46 (a', 3H,d, J 6.4 Hz) 2.53-2.68 (a+a', 4H, m) 3.22 (a', 3H, s) 3.24 (a, 3H, s) 3.54-3.64 (a+a', 2H, m, partly hidden) 3.61 (a, 3H, s) 3.62 (a', 3H, s) 4.71 (a', 1H, q, J 6.4 Hz) 4.77 (a, 3H, q, J 6.4 Hz) 7.19-7.26 (a+a', 6H, m) 7.42-7.45 (a+a', 2H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) (a+a') δ 22.0, 22.6, 23.4, 23.8, 30.0, 30.2, 41.6, 42.7, 51.55 (2C), 56.4, 56.5, 75.2 (2C), 125.1, 125.4, 125.6, 125.8, 126.6 (2C), 127.37, 127.45, 140.4 (2C), 142.75, 142.85, 172.7 (2C).

4-[2-(1-methoxyethyl)phenyl]-2-pentanone **10a** The two diastereoisomers separate on GC-MS, identical spectra. MS (m/z): M^+ (not seen) 205 (10) 173 (14) 145 (44) 135 (100%) 131 (65) 91 (31). Structures tentatively assigned on the basis of analogy to **9a**.

Methyl 3-[2-(1-methoxyethyl)phenyl]-3-phenyl-propanoate **6b** The crude product was flash chromatographed on silica gel (70-230 mesh), Et_2O/Pentane (15/85 to 20/80).

Diastereoisomer **6b**: IR (film): 1738 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.44 (3H, d, J 6.4 Hz) 2.72 (3H, s) 3.00 (1H, dd, J 7; 17 Hz) 3.07 (1H, dd, J 8; 17 Hz) 3.59 (3H, s) 4.64 (1H, q, J 6.5 Hz) 4.76 (1H, t) 7.15-7.46 (8H, m) 7.43 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.7, 41.0, 41.9, 51.7, 55.9, 74.8, 125.9 - 128.6, 139.9, 142.1, 144.2, 172.1. Diastereoisomer **6b'**: IR (film): 1738 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, d, J 6 Hz) 3.0-3.1 (2H, m) 3.18 (3H, s) 3.58 (3H, s) 4.76 (1H, q, J 6.4 Hz) 4.90 (1H, t) 7.14-7.36 (8H, m) 7.45 (1H, m).

3-[2-(1-methoxyethyl)phenyl]-1,3-diphenyl-1-propanone **10b** Diastereomer **10b**: IR (film): 1687 cm^{-1} ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.49 (3H, d, J 6.4 Hz) 2.74 (3H, s) 3.63 (1H, dd, J 6.5; 18 Hz) 3.81 (1H, dd, J 7.7; 18 Hz) 4.70 (1H, q, J 6.5 Hz) 5.04 (1H, t) 7.13-7.30 (7H, m) 7.42-7.48 (4H, m) 7.56 (1H, m) 7.93-7.95 (2H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.6, 40.8, 45.1, 55.9, 74.9, 125.9, 126.1, 126.3, 127.1, 128.0 (3C), 128.1 (2C), 128.5 (2C), 128.6 (2C), 133.1, 136.9, 139.9, 142.1, 144.3, 197.8. Diastereomer **10b'**: IR (film): 1687 cm^{-1} ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, J 6.5 Hz) 3.20 (3H, s) 3.69 (1H, dd, J 7; 16 Hz) 3.78 (1H, dd, J 7; 17 Hz) 4.84 (1H, q, J 6.6 Hz) 5.16 (1H, t) 7.15-7.47 (11H, m) 7.54-7.55 (1H, m) 7.93-7.94 (2H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.1, 40.8, 45.5, 56.3, 74.6, 125–128, 133.1, 136.9, 140.5 141.6, 144.1, 197.8.

Methyl 3-[2-dimethylaminomethylphenyl] butanoate **7a** IR (film): 1738 cm^{-1}. MS (m/Z): 235 (M^+, 21%) 220 (18) 175 (34) 159 (55) 130 (83) 58 (100%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, d, J 7 Hz) 2.22 (6H, s) 2.51 (1H, dd, J 9; 18 Hz) 2.68 (1H, dd, J 9; 18) 3.39 (1H, d, J 13 Hz) 3.53 (1H, d, J 13 Hz) 3.62 (1H, s) 3.74 (1H, m) 7.14 (1H, m) 7.22-7.27 (3H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.6, 30.7, 42.5, 45.4, 51.4 (2C) 61.9, 125.5, 125.7, 127.5, 130.5, 136.2, 145.2, 173.1.

4-[2-dimethylaminomethylphenyl]-2-pentanone **11 a** MS (m/Z): 219 (M^+, 4%) 202 (22) 176 (44) 131 (100%) 91 (51) 58 (83). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.23 (2H, d, J 6.8 Hz) 2.09 (3H, s) 2.21 (6H, s) 2.6 (1H, dd, J 8.0; 8.4 Hz) 2.8 (1H, dd, J 5.7; 6.0) 3.4 (1H, d, J 12.8 Hz) 3.5 (1H, d, J 12.6 Hz) 3.78 (1H, m) 7.13 (1H, m) 7.21-7.27 (3H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.7, 29.8, 30.1, 45.3 (2C), 52.2, 62.1, 125.6 (2C), 127.5, 130.6, 136.0, 145.7, 208.3.

Methyl 3-[2-dimethylaminomethylphenyl]-3-phenyl-propanoate **7b** mp: 45-46 °C. IR (KBr): 1731 cm^{-1}. MS (m/Z): 297 (M^+, 19%) 238 (8) 192 (19) 178 (100%) 165 (13). Found: C, 76.8; H, 7.7; N, 4.7. Calc for $C_{19}H_{23}O_2N$: C, 76.7; H, 7.7; N, 4.7. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.20 (6H, s) 3.01 (1H, dd, J 8.4; 15 Hz) 3.06 (1H, dd, J 7; 15 Hz) 3.33 (1H, d, J 13) 3.47 (1H, d, J 13 Hz) 3.57 (3H, s) 5.20 (1H, t) 7.14-7.25 (9H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 40.9, 41.4, 45.4 (2C), 51.6, 62.1, 126.1, 126.2, 127.13, 127.35, 127.9 (2C), 128.3 (2C), 130.7, 136.9, 142.7, 143.6, 172.4.

3-[2-dimethylaminomethylphenyl]-1,3-diphenyl-1-propanone **11b** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.17 (6H, s) 3.30 (1H, d, J 12.6 Hz) 3.53 (1H, d, J 12.6 Hz) 3.70 (2H, dd, J 6; 7.5 Hz) 5.43 (1H, dd, J 6; 7.5 Hz) 7.12-7.27 (9H, m) 7.43 (2H, t) 7.53 (1H, t) 7.94 (2H, d).

Methyl 3-[2-(1-dimethylaminoethyl)phenyl]-butanoate **8a** The two diastereoisomers was separated on preparative HPLC (Waters 600E multisolvent system equipped with a Waters 490 UV-detector and a Spherosorb column, S10W (25 cm, i.d. 20 mm)), EtOAc/Hexane (5/95), 1% TEA; flow rate 10 ml/min.; λ=270 nm. Major diastereomer: IR (film): 1740 cm^{-1}. MS (m/Z): 249 (M^+, 5%) 234 (52) 175 (47) 144 (70) 129 (62) 72 (100). Found: C, 72.03; H, 9.17; N, 5.59. Calc. for $C_{13}H_{17}N_1O_2$: C, 72.24; H, 9.22, N 5.62. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, d, J 7 Hz) 1.33 (3H, d, J 6.5 Hz) 2.21 (6H, s) 2.57 (1H, dd, J 8; 15.5 Hz) 2.63 (1H, dd, J 7; 15.5) 3.59 (1H, q, J 6.5 Hz, partly hidden) 3.61 (3H, s) 3.77 (1H, m) 7.18-7.22 (3H, m) 7.47 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.5, 22.1, 30.1, 42.1, 43.7 (2C), 51.5, 60.63, 125.2, 126.3, 126.7, 126.9, 142.5, 142.9, 172.9. Minor diastereomer: IR (film): 1738 cm^{-1}. MS (m/Z): 249 (M^+, 6%) 234 (65) 175 (58) 144 (85) 129 (78) 72 (100). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, d, J 6.8 Hz) 1.32 (3H, d, J 6.6 Hz) 2.21 (6H, s) 2.54 (1H, dd, J 9; 15 Hz) 2.69 (1H, dd, J 6; 15 Hz) 3.59 (1H, q, J 6.6 Hz) 3.64 (3H, s) 3.78 (1H, m) 7.18-7.21 (3H, m) 7.48 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.6, 22.0, 30.2, 42.2, 43.6 (2C), 51.5, 60.8, 125.3, 126.4, 126.8, 127.0, 143.0, 144.6, 172.9.

4-[2-(1-dimethylaminoethyl)phenyl]-2-pentanone **12a** a = major diastereomer; a' = minor diastereomer. IR (film): 1717 cm^{-1} (a+a'). MS (m/Z), (a+a'): 233 (M^+, 8%) 218 (58) 173 (26) 159 (43) 145 (100) 131 (44) 72 (48). MS (m/Z): 233 (M^+, 5%) 218 (48) 173 (25) 159 (37) 145 (100) 131 (37) 72 (54). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.21 (a', 3H, d, J 5.4 Hz) 1.22 (a, 3H, d, J 5.5 Hz)

(a', 1H, q, J 5.2 Hz) 3.80 (a', 1H, m) 3.83 (a, 1H, m) 7.15-7.22 (a+a', 6H, m) 7.44-7.47 (a+a', 2H, m).

MIMI products **14**. The mixture of high molecular weight products, MIMI, was isolated from **8a** and **12a** by flash chromatografy, EtOAc/Pentane (1/3), 1% TEA. MS (positive FAB, PEG 400): M + 1 = 451, M + 1 = 467, M + 1 = 483, corresponding to $C_{29}H_{42}O_2N_2$, $C_{29}H_{42}O_3N_2$ and $C_{29}H_{42}O_4N_2$ respectivly. The amount of M + 1 = 467 was about 10 times more than of the two other.

Methyl 3-[2-(1-dimethylaminoethyl)phenyl]-3-phenyl propanoate **8b** The crude product was flash chromatographed on silica gel (70-230 mesh), EtOAc/Pentane (1/3), 1% TEA. Further separations of the ester isomers (SS, SR) and the ketone isomers (12B) were performed with semipreparative HPLC, (Waters M-45 solvent delivery system, Waters U6K injector, Waters R-401 differential refractormeter, and a Spherosorb column, 10 µm particles, 25 cm, i.d. 4.6 mm), EtOAc/Hexane (1/9), 1% TEA, flow rate, 3ml/min. Under these conditions the major stereoisomers of the ester and the ketone, respectively, separated and were isolated pure while a mixture of the minor stereoisomers of the ester and the ketone was obtained.

Major diastereomer of **8b**, (SS)

mp: 46-48 °C. IR (KBr): 1735 cm^{-1}. MS (m/Z): 311 (M^+, 11) 193 (100) 178 (48) 115 (53) 91 (55) 72 (82). Found: C, 77.03; H, 8.16; N, 4.28. Calc for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09, N, 4.50. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, d, J 6.4 Hz) 1.93 (6H, s) 3.02 (2H, d, J 7.6 Hz) 3.54 (1H, q, J 6.4 Hz) 3.59 (3H, s) 4.96 (1H, t, J 8 Hz) 7.16-7.26 (8H, m) 7.53-7.55 (1H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 20.6, 41.2, 41.6, 43.4 (2C), 51.6, 60.7, 126.3, 126.5, 126.6, 126.9, 127.2, 128.1 (2C), 128.3 (2C), 139.7, 143.7, 143.9, 172.2. The diasteromer was assigned the *S,S*-configuration on the basis of the comparison of ^{1}H NMR data for protons A and B with the corresponding values for ketone **15**, of known absolute configuration,[8] *vide infra*.

		δ_A	δ_B		δ_A	δ_B
Ketone **15**	S, S	1.93	1.35			
Product **8b**	S, S	1.94	1.37	S, R	2.21	0.98
Ketone **12b**	S, S	1.93	1.34;	S, R	2.22	0.94

Minor diastereomer of **8b**, (SR)

IR (film): 1740 cm^{-1}. MS (m/Z): 311 (M^+, 6) 296 (4) 192 (100) 178 (35) 115 (15) 72 (23). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.94 (3H, d, J 6.6 Hz) 2.22 (6H, s) 3.01 (1H, dd, J 8.4; 16 Hz) 3.07 (1H, dd, J 7.5; 16) 3.57 (3H, s) 3.58 (1H, q, J 6.7 Hz) 5.07 (1H, t) 7.14-7.54 (9H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.7, 41.2, 42.0, 43.6 (2C), 51.6, 60.5, 126.1-128.6, 139.98, 143.44, 143.9, 172.2, assigned the *S,R*-configuration on the basis of ^{1}H NMR data, *vide supra*.

3-[2-(1-dimethylaminoethyl)phenyl]-1,3-diphenyl-1-propanone **12b** Major diastereomer of **12b** (SS) IR (film): 1688 cm^{-1}. MS (m/Z): 357 (M^+, 2%) 252 (16) 192 (72) 178 (28) 129 (28) 105 (100). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.37 (3H, d, J 6.5 Hz) 1.94 (6H, s) 3.57 (1H, q, J 6.5 Hz) 3.66 (1H, dd, J 7.3; 17 Hz) 3.73 (1H, dd, J 7.4; 17 Hz) 5.23 (1H, t) 7.14-7.56 (12H, m) 7.92-7.94 (2H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.9, 40.6, 43.6 (2C), 45.3, 60.9, 126.1-128.6 (13C), 133.1, 137.0, 140.2, 143.7, 144.2, 197.9. The absolute configuration *S,S* was assigned on the basis of ^{1}H NMR data, *vide supra*.

Minor diastereomer of **12b** (SR) IR (film): 1688 cm^{-1}. MS (m/Z): 252 (16) 192 (78) 178 (32) 129 (30) 105 (100). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, d, J 6.0 Hz) 2.21 (6H, s) 3.68-3.71 (3H, m) 5.33 (1H, m) 7.13-7.55 (12H, m) 7.93-7.95 (2H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.3, 41.0, 43.4 (2C), 45.3, 60.5, 126.1, 126.6, 126.6, 126.7, 127.4, 128.0 (2C), 128.1 (2C), 128.4 (2C), 128.5 (2C), 133.0, 136.9, 140.7, 143.1, 144.3, 197.9. The absolute configuration was assigned on the basis of ^{1}H NMR data, *vide supra*.

(S, S)-4-[2-(1-Dimethylaminoethyl)phenyl]-4-phenyl-2-butanone **15**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, d, J 6 Hz) 1.93 (6H, s) 2.08 (3H, s) 3.12 (2H, d, J 8 Hz) 3.53 (1H, q, J 6 Hz) 5.00 (1H, dd, J 7.5; 7.5 Hz) 7.11-7.52 (9H, m).

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