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Addition of Organocopper Reagents to Allylic Acrylates - the Preparation of γ, δ-Unsaturated Acids and Subsequent Functionalization to γ-Lactones

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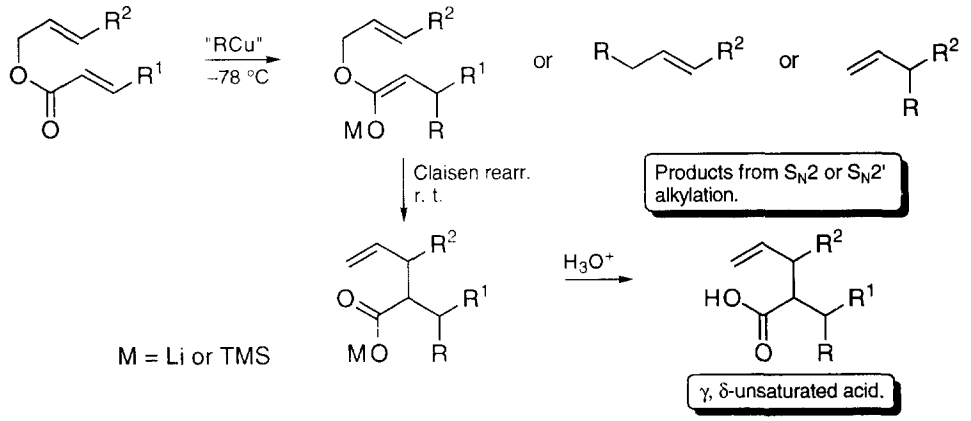
Abstract: Conjugate addition of monoorganocopper compounds with iodotrimethylsilane (TMSI) or lithium diorganocuprates, with or without halosilanes, to allylic acrylates give allylic silyl ketene acetals/ester enolates. These can undergo Claisen rearrangement to give diastereomeric mixtures of γ, δ-unsaturated acids after aqueous work-up. For organocuprates, the diastereomeric ratio is strongly affected by the halosilane. Either diastereomer can be obtained as major product by proper choice of copper reagent. Cyclization of the acids followed by reduction gives γ-lactones in good yields. A copper iodide/dimethyl sulfide complex is introduced as an excellent precursor to organocopper reagents.

INTRODUCTION

Conjugate addition of organocopper compounds to α, β-unsaturated carbonyl compounds continues to be a most versatile method for making new carbon-carbon bonds. Many different types of organocopper reagents can be used and generally give high yields of conjugate adducts.[1] Over the past ten years, the use of additives, such as halosilanes (*e.g.* TMSI, TMSCl) and BF_3, in combination with organocopper compounds has become increasingly popular. Our work in this field focuses on the application of monoorganocopper compounds, RCu(LiI), together with iodotrimethylsilane (TMSI). In several reports, we have demonstrated additions, at low temperature, to ketones and esters giving high yields of silyl enol ethers and silyl ketene acetals, respectively.[2] The RCu(LiI)-TMSI reagent is also effective in stereoselective additions to chiral esters, [3] imides and amides.[4] Recently, we reported the first example of conjugate addition of copper acetylides to enones and enals.[2a, 5]



Scheme 1. Reactions of allylic α, β-unsaturated esters with organocopper reagents.

Allylic α, β-unsaturated esters as substrates give the copper reagent two possible reaction paths, conjugate addition or S_N2/S_N2' alkylation of the allylic group (Scheme 1). When conjugate addition is preferred, the

primary product is an allylic ester enolate or an allylic silyl ketene acetal (an allyl vinyl ether), which is expected to undergo Claisen rearrangement at higher temperature, [6] to give γ, δ-unsaturated carboxylates or silyl esters, respectively. Hydrolytic work-up should give γ, δ-unsaturated acids. We have recently demonstrated the usefulness of the RCu(LiI)-TMSI reagent in this kind of reaction. It provides an efficient one-pot procedure for the diastereoselective preparation of γ, δ-unsaturated acids.[7] This has also been demonstrated by Kuwajima and Aoki, [8] who reported copper-catalyzed addition of Grignard reagents promoted by TMSCl to allylic crotonates and acrylates, affording γ, δ-unsaturated acids after Claisen rearrangement and hydrolytic workup. Subsequent iodolactonization of the γ, δ-unsaturated acids should give di- or trisubstituted γ-lactones depending on substituents on the starting allylic α, β-unsaturated ester.

The other possible reaction path for allylic α, β-unsaturated esters is the S_N2/S_N2' alkylation of the allylic group. Substitution reactions of allylic substrates with organometallic reagents are well-known and have been reviewed by Magid.[9] The substrates studied are generally allylic halides, [10] vinylic epoxides, [11] phosphates[12] or esters, such as acetates.[13] To our knowledge, only one earlier report has demonstrated S_N2/S_N2' alkylation of allylic α, β-unsaturated esters.[8] They reported that lithium dimethylcuprate gave exclusive S_N2/S_N2' alkylation of allyl and *i*-butenyl crotonate to afford high yields of crotonic acid. Recently, we reported that Me_2CuLi(LiI)-TMSCl gives both conjugate addition and S_N2/S_N2' alkylation with crotyl crotonate whereas it gives conjugate addition to crotyl acrylate.[7] However, MeCu(LiI)-TMSI gives conjugate addition to crotyl crotonate as well as to allyl cinnamate. More important is that the Me_2CuLi(LiI)-TMSCl reagent gives opposite diastereoselectivity of the γ, δ-unsaturated acids, from conjugate addition followed by Claisen rearrangement, when crotyl acrylate is used as compared with the MeCu(LiI)-TMSI reagent. Given the assumption that the Claisen rearrangement proceeds *via* a chair-like transition state, at least for acyclic allyl vinyl ethers, [14] the switch of diastereoselectivity implies that the conjugate addition of R_2CuLi(LiI)-TMSCl reagents to allylic acrylates occurs mainly *via* an *s-cis* conformation whereas addition of RCu(LiI)-TMSI reagents occurs mainly *via* an *s-trans* conformation.

In this paper we report an extended study of different organocopper reagents in reactions with allylic acrylates. We also report the further tranformation of γ, δ-unsaturated acids to trisubstituted γ-lactones and some new observations regarding the CuI used for these reactions.

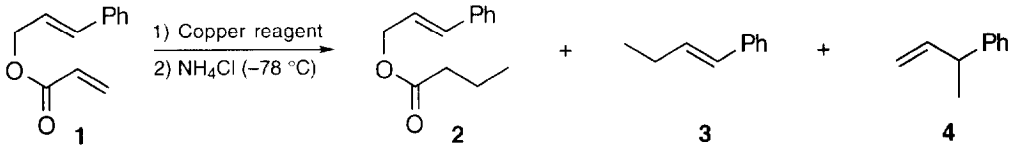
RESULTS

We have investigated lithium diorganocuprates, R_2CuLi(LiI), and monoorganocopper compounds, RCu(LiI), with various additives in reactions with cinnamyl acrylate and crotyl acrylate. Cinnamyl acrylate was chosen as a model substrate in order to facilitate the identification and isolation of products from S_N2/S_N2' alkylation. Crotyl acrylate was chosen mainly due to its high reactivity in these reactions. In all reactions involving additives, we used a 1:1 ratio of additive to monoorganocopper compound/organocuprate.

Conjugate Addition Followed by Hydrolysis

The results for different monoorganocopper/organocuprate reagents, in reactions with cinnamyl acrylate, are summarized in Table 1. These reactions were quenched at −78 °C by addition of saturated NH_4Cl. Iodotrimethylsilane with lithium dimethylcuprate or methylcopper gives the most regioselective reactions (entries 4 and 6). Lithium dimethylcuprate and TMSCl or the cuprate alone are also effective in these reactions although some S_N2 product is observed (entries 1 and 2). Notable is that BF_3 is not effective, neither for organocuprate nor for monoorganocopper reagents. The difference in reactivity for MeCu(LiI)-TMSX (X = I or OTf) using CuI or CuI•0.75DMS should also be noted (*cf.* entries 5 and 6 and 9 and 10).

Table 1. Conjugate addition of different copper reagents to cinnamyl acrylate (**1**). All reactions were run in diethyl ether at –78 °C for 18 h using equimolar amounts of copper reagent, additive and substrate and quenched with saturated NH_4Cl at low temperature. The yields were measured by quantitative GC using undecane as the internal standard. CuI was used in all cases except for the following: entries 6 and 10; CuI•0.75DMS, entry 7; CuBr•DMS and in entry 8; CuCN to which 1 eq. DMS was added.



Entry	Copper Reagent	Rec. of **1**(%)	Yield of **2**(%)	Yield of **3**(%)	Yield of **4**(%)
1	$Me_2CuLi(LiI)$	–	67	21	–
2	$Me_2CuLi(LiI)$-TMSCl[a]	–	75	7	–
3	$Me_2CuLi(LiI)$-BF_3	–	49	trace	9
4	$Me_2CuLi(LiI)$-TMSI[a]	–	98	–	–
5	MeCu(LiI)-TMSI	80	19	–	–
6	MeCu(LiI)-TMSI[b]	35	64	–	–
7	MeCu(LiBr)-TMSI	38	61	–	–
8	MeCu(LiCN)-TMSI	71	10	–	–
9	MeCu(LiI)-TMSOTf	51	2	–	–
10	MeCu(LiI)-TMSOTf[b]	84	15	–	–
11	MeCu(LiI)-BF_3	54	3	–	2

a. The reaction is fast at –78 °C as judged by the precipitation of MeCu which starts within a few minutes after addition of the acrylate. b. CuI•0.75DMS was used.

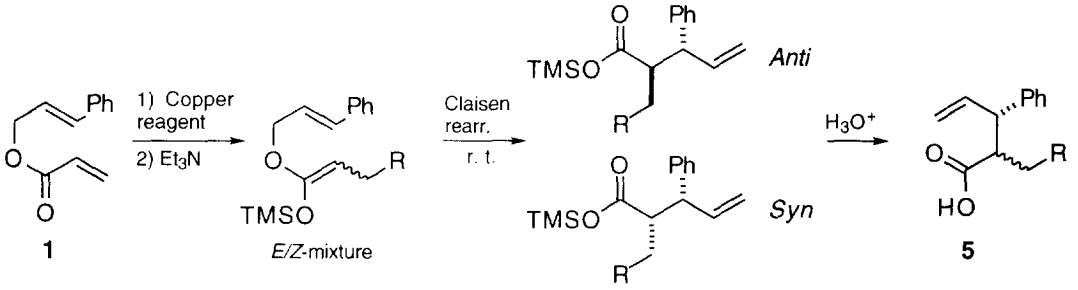
Conjugate Addition Followed by Claisen Rearrangement

When the reaction mixtures are stirred at room temperature, without being quenched with NH_4Cl, the silyl ketene acetals/ester enolates rearrange to γ, δ-unsaturated TMS-esters/carboxylates. The *E/Z*-ratio will then determine the diastereomeric ratio of the products.

The system for assignment of the diastereomers from these reactions calls for some comment. In reactions with crotyl acrylate and MeCu(LiI)-TMSI or $Me_2CuLi(LiI)$-TMSCl, the products can be assigned using the *erythro/threo* system. However, this only gives a consistent discussion as long as the vinyl group takes preference over the other groups in the molecule. For clarity, we use the γ, δ-unsaturated acid as the basic carbon-chain, irrespective of the substituents, and assign the products as *syn* or *anti* (see Fig, Table 2). This makes it easier to follow the stereochemical results in connection with RCu(LiI) or $R_2CuLi(LiI)$ reagents.

Our results for selected organocopper reagents are presented in Table 2. Lithium dimethylcuprate in Et_2O, with or without TMSCl, gives mainly the *syn* form of the γ, δ-unsaturated acid, whereas $Me_2CuLi(LiI)$-TMSCl in THF (entry 3) gives only a small preference for the *syn* form. In contrast, TMSI or TMSBr in combination with the cuprate gives predominantly *anti* form, as does the MeCu(LiI)-TMSI reagent. Monoorganocopper compounds with TMSCl or TMSI give mainly the *anti* form both in Et_2O and THF although the ratios in THF are lower. These results suggest that $Me_2CuLi(LiI)$ or $Me_2CuLi(LiI)$-TMSCl in Et_2O favour the reaction *via* an *s-cis* conformation of the acrylate whereas the cuprate and TMSBr or TMSI favour reaction *via* an *s-trans* conformer. Monoorganocopper reagents appear to favour reaction via an *s-trans*

Table 2. Conjugate addition of different copper reagents to cinnamyl acrylate (**1**) followed by Claisen rearrangement at room temperature. All reactions were run at –78 °C for 18 h, except where indicated otherwise, followed by 6-24 h at room temperature. Equimolar amounts of copper reagent and substrate were used in the organocuprate reactions whereas a 50% excess of monoorganocopper reagent *versus* substrate was used.



Entry	Copper Reagent	Solvent	Yield of **5** (%)	*Anti:Syn* ratio of **5**
1	$Me_2CuLi(LiI)$	Et_2O	76	24:76
2	$Me_2CuLi(LiI)$-TMSCl		75	20:80
3	$Me_2CuLi(LiI)$-TMSCl[a]	THF	82	46:54
4	$Me_2CuLi(LiI)$-TMSBr	Et_2O	90	90:10
5	$Me_2CuLi(LiI)$-TMSI		89	88:12
6	$Me_2CuLi(LiI)$-BF_3		47	66:34
7	MeCu(LiI)-TMSI		88	90:10
8	MeCu(LiI)-TMSI[b]	THF	95	67:33
9	MeCu(LiI)-TMSCl[c]		38	55:45
10	MeCu(LiBr)-TMSI	Et_2O	42	87:13

a. 4h (–78 °C) then Et_3N and r.t. b. 2h (–78 °C) then Et_3N and r.t. c. 8h (–78 °C) then Et_3N and r.t.

conformation and more strongly so with MeCu(LiI)-TMSI in diethyl ether (entry 7).

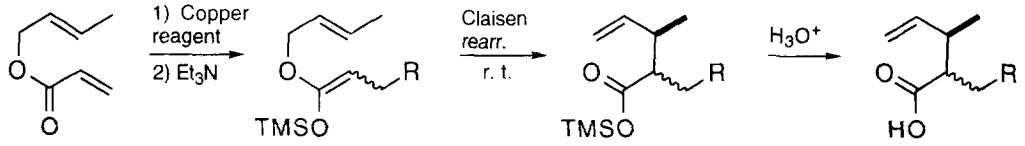
Triethylamine is generally added at –78 °C. The addition of Et_3N seems more important in those reactions that involve an excess of copper reagent *versus* substrate than in those involving equimolar amounts. The reactions with RCu(LiI)-TMSI reagents, where an excess of reagent is used, generally gave higher yields with Et_3N than without. Triethylamine probably forms a silylammonium salt with the halosilane, [15] thus lowering the reactivity of the monoorganocopper reagent and preventing side-reactions at higher temperature (*e. g.* S_N2/S_N2').

The opposed selectivity for $R_2CuLi(LiI)$-TMSCl as compared with RCu(LiI)-TMSI appears to be general as seen from Table 3. In our hands, phenyl cuprates prepared from CuI or CuBr•DMS in ether gave irreproducible results and only small amounts/traces of γ, δ-unsaturated acids. However, the phenylcuprate, $Ph_2CuLi(LiCN)$ prepared from CuCN, with excess TMSCl, [16] gave ca 20% γ, δ-unsaturated acid along with substantial amounts of phenyltrimethylsilane. The stereochemical result for **9b** was, however, in accordance with that of **8b** or **7b**.

Determination of stereochemistry

Epimerisation of the *anti* and *syn* acids under work-up does not occur. This was verified by treatment of an ether solution of a *anti:syn* = 85:15 mixture with either 10% NaOH or 10% HCl for 4h at room temperature.

Table 3. Conjugate addition of RCu(LiI)-TMSI and $R_2CuLiI(LiI)$-TMSCl to crotyl acrylate (**6**) followed by Claisen rearrangement at room temperature. All reactions were run in Et_2O. CuI was used in all cases except for entries 5 (CuI•0.75DMS) and 6 (CuCN). A 20% excess of organocopper reagent *versus* crotyl acrylate was used in all reactions except for entries 5 and 6 where equimolar amounts were used.

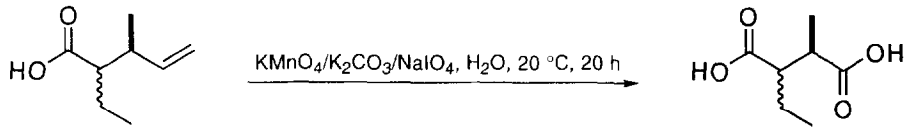


6 **7-9**

Entry	Copper Reagent	Condition	Product	Yield (%)	*Anti:Syn* Ratio
1	MeCu(LiI)-TMSI[a]	–78 °C, 4 h	**7a**	68	83:17
2	$Me_2CuLiI(LiI)$-TMSCl	–78 °C, 4 h	**7b**	93	18:82
3	BuCu(LiI)-TMSI	–78 °C, 2 h	**8a**	84	88:12
4	$Bu_2CuLiI(LiI)$-TMSCl	–78 °C, 2 h	**8b**	66	19:81
5	PhCu(LiI)-TMSI	–78 °C, 3 h	**9a**	68	82:18
6	$Ph_2CuLiI(LiCN)$-2TMSCl	–78 °C, 3 h	**9b**	24[b]	14:86

a. *Ca* 13% starting material recovered. b. *ca.* 85% pure by NMR.

The ^{1}H-NMR spectra for these separately treated samples clearly showed that the *anti:syn* ratio remained unchanged. The stereochemical assignment of the *anti* and *syn* forms of the γ, δ-unsaturated acids were originally based on the work by Ireland *et al.*[6] and by experiments with methyl acrylate where conjugate addition of MeCu(LiI)-TMSI gives mainly the *E*-silyl ketene acetal whereas $Me_2CuLi(LiI)$-TMSCl gives mainly the *Z*-silyl ketene acetal.[7] In order to confirm the tentative stereochemistry, γ, δ-unsaturated acid **10** was oxidized to the disubstituted succinic acid **11** following the procedure of Lemieux and Rudloff (Scheme 2).[17]



10 **11**

Anti : *Syn* = 85 : 15

Scheme 2. Oxidation to 2-ethyl-3-methyl-succinic acid.

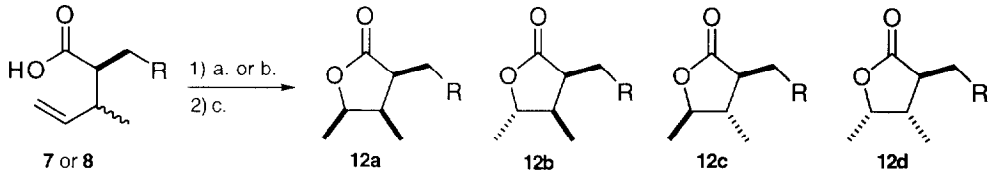
The major as well as the minor ^{13}C resonances for **11** were in excellent agreement with data published by Ernst and Trowitzsch for *anti*- and *syn*-**11**, respectively.[18] Thus it was confirmed that addition of MeCu(LiI)-TMSI to crotyl acrylate gives mainly the *anti* isomer whereas $Me_2CuLi(LiI)$-TMSCl gives predominantly *syn* isomer. The *anti/syn* assignments for the products from reactions with cinnamyl acrylate, as well as for the products from additions of butyl and phenyl reagents to crotyl acrylate, were then made by comparison of their ^{1}H-NMR spectra with those of **10**.

Lactonisations

The γ, δ-unsaturated acids readily undergo iodolactonisation to give γ-iodolactones in good yields. Subsequent reduction with $NaBH_4$ in DMSO[19] gives the corresponding lactones (Table 4). The iodolac-

tonisation generally gives a mixture of four diastereomers corresponding to the *anti/syn* ratio for the γ, δ-unsaturated acid used. By using a "kinetic" iodolactonisation procedure[20] with acids **7a** or **8a**, one obtains reasonable selectivity for the all-*syn* isomer **12a**. When a "thermodynamic" procedure[21] is used on acid **7b**, reasonable selectivity for the all-*anti* isomer **12c** is observed. Surprisingly, acid **8b** with a major *syn* configuration gave mostly isomer **12d** under "thermodynamic" conditions. In addition, lactonisation of **8b** gives small amounts of δ-iodolactone, with a γ:δ ratio of 90:10, which was supported by GC and EIMS. The reason for this is not understood but a possible explanation could be the increased steric demand of the pentyl group as compared with the ethyl group under the present conditions. The other lactonisations give only γ-lactones.

Table 4. Iodolactonization of γ, δ-unsaturated acids **7** or **8** followed by reduction to the corresponding γ-lactones. The yields given are based on the amount of γ, δ-unsaturated acid used.



Substrate	R	Method	Total yield (%)	Ratio of **12a-d**
7a	Me	a	59	69 : 13 : 1 : 17
7b	Me	b	84	3 : 13 : 76 : 8
8a	Bu	a	78	71 : 17: 2 : 10
8b	Bu	b	79	8 : 6 : 27 : 59

a. KI, $Na_2S_2O_8$, $NaHCO_3$, H_2O, r. t., 4h. b. I_2, CH_3CN, 0 °C, 24h. c. $NaBH_4$, DMSO, 45-50 °C, 5h.

A Useful Copper Iodide-Dimethyl Sulfide Complex

During this work we discovered that the pretreatment of CuI was important. Best results are obtained with copper iodide containing dimethyl sulfide. The preparation of the CuI/dimethylsulfide complex follows the method described by House *et al.*[22] When this complex is dried under vacuum (*ca.* 0.1 mbar) for 1-2 hours at room temperature, it rapidly loses dimethyl sulfide to give a new complex with an overall 1:0.75 stoichiometry.

Three batches of CuI/DMS complex were prepared independently and dried between 1.5 and 24 hours at room temperature. The elemental analyses of these three complexes confirmed the 1:0.75 stoichiometry. This 1:0.75 CuI/dimethyl sulfide complex remains stable at room temperature and does not spontaneously lose dimethyl sulfide on standing. However, attempts to deliberately prepare crystals, suitable for X-ray analysis, of such a 1:0.75 complex have so far been unsuccessful. It should be noted that the remaining dimethyl sulfide can be evaporated by heating under vacuum for 5-6 hours at 80-90 °C or by drying under vacuum at room temperature for longer periods, *ca* 2-3 weeks. The CuI•0.75DMS complex is stable and is an excellent precursor to lithium diorganocuprates but especially to monoorganocopper reagents.

DISCUSSION

One of the more important observations from this study is the significant influence of the additive. In terms of yield and regioselectivity, the best reagents appear to be organocuprates together with TMSBr or

TMSI and monoorganocopper compounds, prepared from CuI•0.75DMS, and TMSI. Monoorganocopper compounds prepared from CuBr•DMS or CuCN are not equally effective. Somewhat surprising are the poor results with BF_3. An explanation may be the strong influence of BF_3 on the composition of monoorganocopper/organocuprate reagents, as demonstrated by Lipshutz *et al.*[23] They showed that addition of BF_3 withdraws MeLi from the cuprate cluster. The sensitivity of acrylates to RLi-induced anionic polymerization, [24] could provide an explanation to the low yields as well as the incomplete mass balance observed in the BF_3-reactions (Table 1, entries 3 and 11). The fastest additions to cinnamyl acrylate in Et_2O were observed with the Me_2CuLi(LiI)-TMSX (X = Br or I) reagents, indicated by the immediate precipitation of MeCu. The addition of MeCu(LiI)-TMSI to cinnamyl acrylate in THF is quite fast and requires less than 1 hour at –78 °C, whereas it is considerably slower in Et_2O. Unfortunately, reactions with MeCu(LiI)-TMSI in THF give lower diastereomeric ratios (Table 2).[7] However, as RCu(LiI)-TMSI reagents give little or no competing S_N2/S_N2' alkylation, it is possible to use an excess of reagent to increase the reaction rate in Et_2O (*cf.* Table 1, entry 6 and Table 2, entry 7).

During this work, we observed that the rate of addition also depended on the CuI used. When we used CuI•0.75DMS as precursor, the addition of MeCu(LiI)-TMSI to cinnamyl acrylate was faster than with CuI alone (*cf.* Table 1, entries 5 and 6). The same trend was observed for the MeCu(LiI)-TMSOTf reagent (*cf.* Table 1, entries 9 and 10). However, in the additions of MeCu(LiI)-TMSI and BuCu(LiI)-TMSI to crotyl acrylate, CuI was successfully used (Table 3). Also, in our recent study on TMSI-promoted conjugate additions of copper acetylides to unsaturated ketones and aldehydes, [5] we observed no reactivity dependence on different CuI precursors. Nevertheless, it is likely that one obtains a more soluble organocopper reagent[25] when CuI•0.75DMS is used than with CuI, due to the DMS present. The higher reactivity of crotyl acrylate as compared with cinnamyl acrylate may also play a role. Our recommendation is to use CuI•0.75DMS as precursor to monoorganocopper reagents, whenever possible.

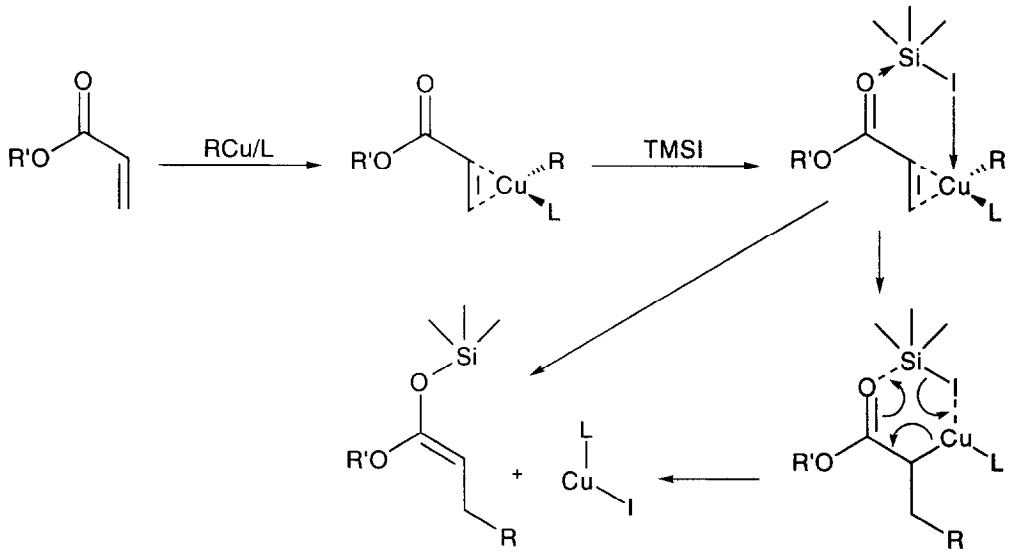
The choice of copper(I) salt for preparation of monoorganocopper compounds is important. Copper iodide is slightly more effective than CuBr•DMS or CuCN. This is in line with our results from TMSI-promoted conjugate addition of copper acetylides, where CuI was considerably more effective than CuBr•DMS, CuCN or CuOTf.[5] Furthermore, investigations by Bertz *et al.*[26] revealed that addition of BuCu(LiI) in THF to 2-cyclohexenone was faster than with BuCu(LiBr) or BuCu(LiCN). It is interesting to note that organocuprate reactivity does not seem as strongly affected by the Cu(I) salt used.[27]

In their work on copper precursors to lithium diorganocuprates, House *et al.* reported preparation of dimethyl sulfide complexes of CuBr, CuCl and CuI. While the CuBr•DMS complex was stable, the initial CuI•DMS complex was not and gradually lost weight on standing. San Filippo *et al.* have reported the formation of a 1:1 complex of CuI and DMS and in addition an 1:0.75 complex of CuI and diethyl sulfide.[28] However, only the 1:0.75 complex with diethyl sulfide was confirmed by X-ray crystallography. Kopf *et al.* recently reported the crystal structure for a CuI•DMS complex with a 1:1.5 stoichiometry.[29] The structure is reported to consist of polymeric chains with bridging Me_2S molecules between dimers of CuI. Another Me_2S molecule is coordinated end-on to each copper atom, giving the overall 1:1.5 stoichiometry. Our results indicate that half of the DMS of such a complex is easily evaporated whereas the other half appears much stronger coordinated to the CuI. However, if all end-on coordinated DMS molecules are removed, the overall stoichiometry would become 1:0.5 which is not consistent with our findings. It may be that the crystal structure significantly changes in going from 1:1.5 to 1:0.75, or the complex may simply collapse into an amorphous material when dried under vacuum. Nevertheless, the complex with 1:0.75 stoichiometry remains stable at room temperature and appears to compare in this regard with CuBr•DMS.

The diastereoselectivities observed for the γ, δ-unsaturated acids provide additional information which might help us to understand the mechanism for halosilane-promoted conjugate addition of monoorganocopper reagents. We believe that the diastereoselectivities observed in these additions are due to different conformations of the allylic acrylate in the transition state. This would mean that R_2CuLi(LiI) in Et_2O, with or

without TMSCl, preferably reacts via an *s-cis* conformation of the substrate in order to arrive at the *syn* form of the acid. On the other hand, RCu(LiI) compounds with TMSI or lithium diorganocuprates in combination with either TMSBr or TMSI prefer to react via an *s-trans* conformation, giving mostly the *anti* form. Lithium dimethylcuprate and TMSI are compatible in Et_2O at –78 °C for shorter periods (ca 10-15 min), whereas in THF they are not, rapidly giving MeCu(LiI) and Me_4Si.[15b] Thus, our results cannot be explained by TMSI- or TMSBr-promoted addition of reformed MeCu(LiI) as only one equivalent of halosilane *versus* cuprate is present (Table 1). Furthermore, the stereoselectivities for the γ, δ-unsaturated acids imply that the reactive conformation of the acrylate (*s-cis versus s-trans*) is strongly affected by the additive. The switch in stereoselectivity for organocuprates, in going from TMSCl to TMSBr or TMSI could indicate different modes of interaction with the cuprate cluster or a common way of interaction but less pronounced with TMSCl.

Several NMR investigations of the reaction between organocuprates and α, β-unsaturated carbonyl compounds have shown that formation of a π-complex most probably takes place prior to the actual transfer of the organic ligand.[30] A similar reaction path is most likely the case also for monoorganocopper reactions, although π-complexes have not been verified in these cases. Some very important differences exist for the two types of organocopper reactions; monoorganocopper reactions require an additive, preferably TMSI, [2–5] and organocuprate and monoorganocopper/TMSI reactions give opposite diastereomers when reacted with a chiral compound.[3a] This difference indicates that the two reagents react with the carbonyl compound adopting two different conformations, the cuprate reactions dominantly reacting with the enoate in the *s-cis* conformation[3a, 31] whereas the monoorganocopper/TMSI reactions prefers the *s-trans* conformation.[3a, 32] These observations together with the present results have led us to propose the following mechanism for TMSI-promoted monoorganocopper additions to enoates and enones:

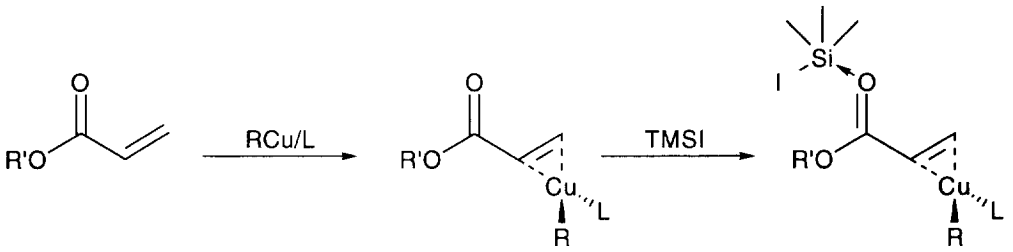


Scheme 3. Proposed reaction mechanism for monoorganocopper/TMSI addition to *s-trans* conformation of an enoate/enone. L represents either I^- from LiI present in the reaction mixture or a solvent molecule such as THF, DMS or diethyl ether.

We assume an initial formation of a π-complex, in which the enoate/enone can adopt either the *s-cis* or the *s-trans* conformation. Coordination of the silicon in TMSI to the carbonyl oxygen activates the enoate/enone for subsequent addition and a fast silylation.[33] The silicon coordinates to one of the electron pairs

on the carbonyl oxygen and for the *s-trans* conformation of the enoate/enone, this arrangement is suitable for additional intramolecular stabilisation of the π-complex as well as allowing for further reaction of the π-complex, either through direct decomposition yielding the conjugate addition product, or through formation of an α-cuprioketone[34] with subsequent decomposition to product (Scheme 3).

For the *s-cis* conformation, the additional stabilisation of the copper intermediate/transition state is not possible. For steric reasons, the silicon must coordinate to the electron pair pointing away from the double bond thus giving no intramolecular stabilisation and without a favourable path for decomposition to product (Scheme 4). However, stabilisation of the copper intermediate/transition state may still be important for both *s-cis* and *s-trans* conformations, but it would then require intermolecular coordination by another TMSI molecule.



Scheme 4. Monoorganocopper/TMSI addition to s-*cis* conformation of an enoate/enone without intramolecular stabilisation and without a favourable path for decomposition to product. L represents either I^- from LiI present in the reaction mixture or a solvent molecule such as THF, DMS or diethyl ether.

This mechanism accounts for the *s-trans* selectivity in these monoorganocopper reactions, the superiority of TMSI as additive, since it can coordinate well both to the carbonyl oxygen and to copper, and the importance of LiI, particularly in the absence of a good coordinating solvent.

Supported by NMR-investigations on $R_2CuLi(LiI)$-TMSCl mixtures in THF, Lipshutz *et al.*[35] suggest coordination of TMSCl to lithium in the presumed cuprate dimer, [36] thereby increasing the Lewis acidity of silicon towards the carbonyl oxygen. This scenario implies a simultaneous conjugate addition/silylation and formation of the silyl enol ether through a cyclic mechanism. In their study on conjugate addition of $BuCu_2Li(LiI)$ to 2-cyclohexenone, Bertz *et al.*[33, 37] demonstrate that the silylation by TMSCl is slower than the conjugate addition, in Et_2O as well as in THF. They propose that TMSCl accelerates the conjugate addition by coordination to copper in the transition state. In our study on conjugate addition of copper acetylides to enones and enals, we observed that $BF_3{\bullet}OEt_2$ as additive gave no reaction. We also observed a strong halide effect for halosilanes, with TMSI >>TMSBr >TMSCl (ineffective), [5] which gives support for coordination of halosilane to copper as an important factor of the mechanistic picture. The role of TMSCl may be to induce the collapse of a π-complex or to convert a π-complex into a possible Cu(III)-β-adduct.[38] Nevertheless, addition of TMSCl to $Me_2CuLi(LiI)$ in the reaction with cinnamyl acrylate affected neither the yield nor the diastereoselectivity to any significant extent (*cf.* Table 1 and 2, entries 1 and 2). This may be a reflection of a slow silylation process as compared to the conjugate addition.

In strong contrast, TMSBr or TMSI induces a dramatic change in combination with $Me_2CuLi(LiI)$. One may speculate that TMSI or TMSBr, in consonance with the proposal of Bertz *et al.*, [37] coordinates to copper in the transition state and that this favours product formation *via* an *s-trans* rather than an *s-cis* conformation. This would require that the ability of simultaneous coordination to the carbonyl oxygen and to copper in the transition state/intermediate is greater for TMSBr and TMSI than for TMSCl. The decomposition to product

may occur either *via* direct collapse of a π-complex, *via* a transient Cu(III) intermediate followed by reductive elimination or *via* a cyclic six-membered transition state/intermediate involving an α-cuprio ketone as discussed above.

CONCLUSION

The present work clearly shows that conjugate addition to reactive acrylates followed by Claisen rearrangement is a useful method to prepare substituted γ, δ-unsaturated acids in good yields. Both alkyl and aryl groups can successfully be added to reactive acrylates. It is shown that opposite diastereomers of the γ, δ-unsaturated acids can be obtained by using different organocopper reagents, although the diastereomeric ratios are moderate. A mechanism is presented which accounts for the observed results . This method also gives easy access to highly substituted γ-lactones in only a few steps. Furthermore, CuI•0.75DMS is a stable and useful precursor for both organocuprate and monoorganocopper reagents.

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EXPERIMENTAL SECTION

General. All reactions were performed under argon and in cooled oven-dried glassware (140 °C). NMR-spectra were recorded on Varian 400 or 500 MHz instruments using $CDCl_3$ as solvent and TMS as the internal standard (δ = 0). Coupling patterns are abbreviated as s, singlet; d, doublet; t, triplet; m, multiplet and *J* is the coupling constant given in Hertz (Hz). High resolution mass spectra were recorded on a VG Zabspec instrument. IR spectra were recorded on a Perkin-Elmer FTIR spectrometer. Gas chromatography was performed on a Varian GC equipped with a capillary column (DB-1) using nitrogen as carrier gas. Undecane (Aldrich, 99+%) was used as the internal standard. Elemental analyses were performed by Analytische Laboratorien in Engelskirchen, Germany.

Chemicals. All chemicals used are commercial and were used as received unless otherwise noted. CuBr•DMS complex was prepared according to House *et al.*[22] Diethyl ether and THF were distilled under nitrogen from sodium/benzophenone ketyl. Triethylamine (Et_3N) was distilled under nitrogen from calcium hydride (CaH_2) and used immediately. Methyl lithium (1.6 M in Et_2O) and butyl lithium (1.6 M in hexane) were purchased from Aldrich. Phenyl lithium (2.0 M in cyclohexane:ether = 70:30) was purchased from Fluka. All lithium reagents were titrated prior to use. Iodotrimethylsilane (TMSI) was purchased from JANSSEN, SIGMA or Aldrich and stored septum-capped at –25°C under argon. TMSOTf was purchased from JANSSEN and stored septum-capped at –25°C under argon. Chlorotrimethylsilane (TMSCl), Bromotrimethylsilane (TMSBr) and BF_3•OEt_2 were purchased from Aldrich and stored septum-capped at 4 °C under argon.

Preparation of CuI•0.75DMS. The procedure of House *et al.*[22] was used to prepare CuI•1.5DMS. This complex was dried under vacuum (*ca.* 0.1 mbar) for 1-24 h at room temperature to give $Cu_4I_4C_6H_{18}S_3$ (CuI•0.75DMS). Generally, 1-2 hours is sufficient. Anal. calc. for $Cu_4I_4C_6H_{18}S_3$; C; 7.60. H; 1.91.Three individually prepared samples gave the following elemental analysis data: 1) Dried for 24 h. C; 7.42. H; 1.76.

2) Dried for 3 h. C; 7.31. H; 1.62. 3) Dried for 1.5 h. C; 7.38. H; 1.69. However, prolonged drying (*ca* 2-3 weeks) at room temperature under vacuum eventually gives CuI completely free from DMS. As an alternative, the CuI can be heated at 90 °C under vacuum for 5-6 h.

Typical procedure for conjugate addition/Claisen rearrangement using RCu(LiI)-TMSI. Methyl lithium (3 mmol) was added at –15 °C to a stirred suspension of CuI or CuI•0.75DMS (3.3 mmol) in dry Et_2O (10 ml). The resulting yellow suspension was stirred at –15 °C for 45 min. The temperature was then lowered to – 78°C and iodotrimethylsilane (3 mmol) was added *via* syringe and the mixture was stirred for 2-3 min. The allylic α, β-unsaturated ester (2 mmol), dissolved in 4 ml of dry Et_2O, was slowly added *via* the flask wall so as to maintain a temperature of –78 °C. After the time indicated in the Tables, dry Et_3N (12 mmol) was added. The cooling bath was removed and the mixture was stirred at room temperature for 6-24 h. The mixture was hydrolyzed to pH = 1-2 using 3M HCl and filtered through Celite which was subsequently washed with several portions of Et_2O. The combined ethereal layer was extracted with 10% NaOH (5×15 ml). The NaOH solution was acidified with 3M HCl to pH = 1-2 and extracted with CH_2Cl_2 (5×15 ml). Drying of the organic solution over Na_2SO_4 followed by evaporation afforded the γ, δ-unsaturated acid in a high state of purity as determined from NMR.

When BuCu(LiI) was prepared, BuLi was added at –78 °C and the suspension was stirred at –60 °C for 45 minutes and TMSI was subsequently added at –78 °C. When PhCu(LiI) was prepared, PhLi was added at –78 °C and the reaction mixture was stirred at *ca* –40 °C for 1 h and TMSI was subsequently added at –78 °C. When TMSOTf or BF_3•OEt_2 were used, these were added at –78 °C to the RCu(LiI) suspension.

Typical procedure for conjugate addition/Claisen rearrangement using R_2CuLi(LiI)-TMSCl. Methyl lithium (4 mmol) was added at –15 °C to a stirred suspension of CuI or CuI•0.75DMS (2.02 mmol) in dry Et_2O (10 ml). The resulting colourless solution was stirred at –15 °C for 30-45 min. The temperature was then lowered to – 78°C and chlorotrimethylsilane (2 mmol) was added *via* syringe and the solution was stirred for 2-3 min. The allylic α, β-unsaturated ester (2 mmol), dissolved in 4 ml of dry ether, was slowly added *via* the flask wall so as to maintain a temperature of –78 °C. After the time indicated in the Tables, dry Et_3N (12 mmol) was added. The cooling bath was removed and the mixture was stirred at room temperature for 6-24 h. The work-up method is the same as for the RCu(LiI)-TMSI procedure.

Bu_2CuLi(LiI) was prepared by addition of BuLi at –78 °C. The temperature was raised to –50 °C and the mixture was stirred for 45 min to afford a solution of the cuprate. TMSCl was added at –78 °C and the above procedure was then followed.

Ph_2CuLi(LiCN) was prepared by addition of PhLi at –78 °C to CuCN in ether. The stirred mixture was gradually warmed to 0 °C over 1 h and stirred at 0 °C for 15 min. Two equivalents of TMSCl was added at –78 °C and the above procedure was then followed. **CAUTION**, the work-up of reactions involving CuCN should be carried out in a well-ventilated hood due to the risk of HCN formation.

When TMSI, TMSBr or BF_3 were used, these were added to the cuprate at –78 °C followed by the acrylate as described above.

1-Phenyl-1-butene. Prepared from cinnamylacetate by S_N2 alkylation using the procedure of Goering *et al.*[13a]

3-Phenyl 1-butene. Prepared from cinnamyl chloride by S_N2' alkylation using the procedure of Yamamoto *et al.*[10a]

Cinnamyl butanoate. Cinnamyl acrylate (2.0 mmol) in dry THF (3 ml) was added at –78 °C to a yellow suspension of MeCu(LiI)-TMSI (3.0 mmol) in dry THF (10 ml). The mixture was stirred at –78 °C for 2h and then quenched by addition of 5 ml saturated NH_4Cl. The reaction mixture was stirred at room temperature for 1 h and then diluted with Et_2O. The ethereal layer was washed once with aqueous 5% $Na_2S_2O_3$, once with brine and then dried over Na_2SO_4. Evaporation of the solvent followed by flash chromatography (5% ether in pentane, R_f = 0.25) gave 86% yield of cinnamyl butanoate as a colourless oil. ^{1}H-NMR: δ 7.42-7.22(m, 5H),

6.65(bd, J = 16, 1H), 6.29(dt, J = 16, 6.4, 1H), 4.74(dd, J = 6.4, 1.2, 2H), 2.34(t, J = 7.4, 2H), 1.74-1.63(m, 2H), 0.97(t, J = 7.4, 3H). ^{13}C-NMR: δ 173.7, 136.4, 134.2, 128.8, 128.2, 126.8, 123.5, 65.0, 36.4, 18.7, 13.9. IR(neat): 1736 cm^{-1}. HRMS(EI): Calculated: 204.115. Found: 204.115.

Cinnamyl acrylate. To a solution of cinnamyl alcohol (100 mmol) in dry Et_2O (300 ml) at –20 °C, BuLi (c = 1.6 M, 100 mmol) was added. The resulting suspension was stirred for 30 min at –20 °C after which acryloyl chloride (100 mmol) was added rapidly *via* syringe. The mixture was stirred for 15 min at –20 °C and then warmed to room temperature. Dilution with ether followed by washing with water, brine and subsequent drying over Na_2SO_4 gave a slightly yellow oil after evaporation of the solvent. Flash chromatography on silica gel with 10% ether in pentane (R_f = 0.46) gave 15.5 g (82%) of cinnamyl acrylate as a colourless oil. ^{1}H-NMR: δ 7.43-7.23(m, 5H), 6.68(bd, J = 16.0, 1H), 6.46(dd, J = 17.2, 1.2, 1H), 6.32(dt, J = 16.0, 6.4, 1H), 6.17(dd, J = 17.2, 10.4, 1H), 5.86(dd, J = 10.4, 1.2, 1H), 4.83(dd, J = 6.4, 1.2, 2H). ^{13}C-NMR: δ 166.2, 136.4, 134.5, 131.3, 128.8, 128.5, 128.3, 126.8, 123.2, 65.4. IR(neat): 1724 cm^{-1}. HRMS(EI+): Calculated for $C_{12}H_{12}O_2$: 188.084. Found: 188.080.

Crotyl acrylate. To a solution of crotyl alcohol (26 mmol) in dry Et_2O (100 ml) at –20 °C, BuLi (c = 1.50 M, 26 mmol) was added. The resulting white suspension was stirred for 15 min at –20 °C after which acryloyl chloride (26 mmol) was added rapidly *via* syringe. The mixture was stirred for 15 minutes at –20 °C and then warmed to room temperature. Dilution with ether followed by washing with water, brine and subsequent drying over Na_2SO_4 gave a slightly yellow oil after evaporation of the solvent. Flash chromatography on silica gel with 5% ether in pentane (R_f = 0.38) gave 1.83 g (56%) of crotyl acrylate as a colourless oil. ^{1}H-NMR: δ 6.42(dd, J = 17, 2, 1H), 6.13(dd, J = 17, 10, 1H), 5.83(dd, J = 10, 2, 1H), 5.88-5.78(m, 1H), 5.67-5.58(m, 1H), 4.59(dt, J = 7, 2, 2H), 1.74(dq, J = 7, 2, 3H). ^{13}C-NMR: δ 166.2, 131.8, 130.9, 128.7, 125.2, 65.5, 18.0. IR(neat): 1724 cm^{-1}. HRMS(EI+): Calculated for $C_7H_{10}O_2$: 126.068. Found: 126.070.

***anti*-2-Ethyl-3-phenyl-4-pentenoic acid.** ^{1}H-NMR: δ 7.26-7.14(m, 5H), 5.93-5.83(ddd, J = 17, 10, 10, 1H), 5.14-5.05(m, 2H), 3.45(dd, J = 10, 10, 1H), 2.65(ddd, J = 10, 10, 4, 1H), 1.83-1.71(m, 1H), 1.64-1.52(m, 1H), 0.92(t, J = 7, 3H). ^{13}C-NMR: δ 180.2, 142.1, 139.0, 128.7, 127.8, 126.9, 116.8, 52.9, 52.5, 24.0, 11.9. IR(neat): 1707 cm^{-1}. HRMS(CI+): Calculated for $C_{13}H_{17}O_2$(M+H): 205.123. Found: 205.121.

***syn*-2-Ethyl-3-phenyl-4-pentenoic acid.** ^{1}H-NMR: δ 7.35-7.16(m, 5H), 6.05-5.95(ddd, J = 17, 10, 8, 1H), 5.12-5.00(m, 2H), 3.44(dd, J = 10, 9, 1H), 2.68(ddd, J = 10, 10, 4, 1H), 1.52-1.40(m, 1H), 1.35-1.23(m, 1H), 0.85(t, J = 7, 3H). ^{13}C-NMR: δ 181.0, 141.4, 139.5, 129.0, 128.2, 127.0, 116.0, 53.2, 53.1, 24.0, 12.0. IR(neat): 1706 cm^{-1}. HRMS(CI+): Calculated for $C_{13}H_{17}O_2$(M+H): 205.123. Found: 205.122.

***anti*-2-Ethyl-3-methyl-4-pentenoic acid.** ^{1}H-NMR: δ 5.64(ddd, J = 17, 10, 8, 1H), 5.08-5.00(m, 2H), 2.41(m, 1H), 2.14(m, 1H), 1.59(m, 2H), 1.06(d, J = 7, 3H), 0.92(t, J = 7, 3H). ^{13}C-NMR: δ 181.7, 141.5, 115.3, 53.1, 40.6, 23.6, 18.8, 12.3. IR(neat): 1707 cm^{-1}. HRMS(CI+): Calculated for $C_8H_{15}O_2$(M+H): 143.107. Found: 143.103.

***syn*-2-Ethyl-3-methyl-4-pentenoic acid.** ^{1}H-NMR: δ 5.78(ddd, J = 17, 10, 8, 1H), 5.06-4.98(m, 2H), 2.45(m, 1H), 2.23(ddd, J = 9, 7, 5, 1H), 1.59(m, 2H), 1.06(d, J = 7, 3H), 0.94(t, J = 7, 3H). ^{13}C-NMR: δ 181.4, 141.3, 114.9, 53.0, 40.1, 22.4, 17.5, 12.3. IR(neat): 1702 cm^{-1}. HRMS(EI+): Calculated for $C_8H_{14}O_2$: 142.099. Found: 142.095.

***anti*-3-Methyl-2-pentyl-4-pentenoic acid.** ^{1}H-NMR: δ 5.64(ddd, J = 17, 10, 8, 1H), 5.08-5.00(m, 2H), 2.44-2.34(m, 1H), 2.20(q, J = 8, 1H), 1.58-1.49(m, 2H), 1.38-1.20(m, 6H), 1.06(d, J = 7, 3H), 0.90-0.84(m, 3H). ^{13}C-NMR: δ 181.6, 141.5, 115.3, 51.5, 40.9, 31.9, 30.4, 27.5, 22.7, 18.8, 14.2. IR(neat): 1712 cm^{-1}. HRMS(CI+): Calculated for $C_{11}H_{21}O_2$(M+H): 185.154. Found: 185.153.

***syn*-3-Methyl-2-pentyl-4-pentenoic acid.** ^{1}H-NMR: δ 5.77(ddd, J = 17, 10, 8, 1H), 5.07-4.97(m, 2H), 2.49-2.39(m, 1H), 2.33-2.25(m, 1H), 1.65-1.41(m, 2H), 1.37-1.20(m, 6H), 1.06(d, J = 7, 3H), 0.92-0.84(m, 3H). ^{13}C-NMR: δ 181.3, 141.3, 114.9, 51.3, 40.3, 32.0, 29.2, 27.6, 22.7, 17.5, 14.2. IR(neat): 1707 cm^{-1}. HRMS(CI+): Calculated for $C_{11}H_{21}O_2$(M+H): 185.154. Found: 185.158.

***anti*-2-Benzyl-3-methyl-4-pentenoic acid.** ^{1}H-NMR: δ 7.29-7.12(m, 5H), 5.73(ddd, *J* = 17, 10, 8, 1H), 5.14-5.04(m, 2H), 2.89(dd, *J* = 14, 4, 1H), 2.79(dd, J = 14, 10, 1H), 2.57-2.42(m, 2H), 1.10(d, *J* = 7, 3H). ^{13}C-NMR: δ 180.4, 141.2, 139.5, 128.9, 128.6, 126.5, 115.9, 53.5, 40.9, 36.4, 18.5. IR(neat): 1708 cm^{-1}. HRMS(CI+): Calculated for $C_{13}H_{17}O_2$(M+H): 205.123. Found: 205.122.

***syn*-2-Benzyl-3-methyl-4-pentenoic acid.** ^{1}H-NMR: δ 7.31-7.11(m, 5H), 5.88-5.78(m, 1H), 5.11-5.05(m, 2H), 2.88(dd, *J* = 14, 10, 1H), 2.79(dd, *J* = 14, 5, 1H), 2.69-2.64(m, 1H), 2.58-2.49(m, 1H), 1.13(d, *J* = 7, 3H). ^{13}C-NMR: δ 179.8, 140.5, 139.6, 129.1, 128.6, 126.5, 115.6, 53.0, 40.2, 35.2, 17.7. IR(neat): 1707 cm^{-1}.

3-Ethyl-4, 5-dimethyl-(2H)-furan-2-one. Obtained as a colourless oil in 84% yield in two steps from the corresponding γ, δ-unsaturated acid. Mixture of 4 diastereomers. The spectroscopic data refers to the major diastereomer **12c**. ^{1}H-NMR: δ 3.96-4.05(m, 1H), 2.13-2.20(m, 1H), 1.64-1.90(2m, 3H), 1.40(d, *J* = 6, 3H), 1.13(d, *J* = 7, 3H), 1.02(t, *J* = 7, 3H). ^{13}C-NMR: δ 178.5, 81.2, 49.4, 43.4, 21.5, 18.9, 15.7, 11.1. IR(neat): 1773 cm^{-1}. HRMS(EI+): Calculated for $C_8H_{14}O_2$: 142.099. Found: 142.099.

3-Ethyl-4, 5-dimethyl-(2H)-furan-2-one. Obtained as a colourless oil in 59% yield in two steps from the corresponding γ, δ-unsaturated acid. Mixture of 4 diastereomers. The spectroscopic data refers to the major diastereomer **12a**. ^{1}H-NMR: δ 4.47-4.55(m, 1H), 2.45-2.60(m, 2H), 1.80-1.90(m, 1H), 1.40-1.46(m, 1H), 1.33(d, *J* = 7, 3H), 1.02(t, *J* = 7, 3H), 0.84(d, *J* = 7.0, 3H). ^{13}C-NMR: δ 178.7, 78.0, 48.3, 36.9, 18.4, 15.7, 12.4, 8.0. IR(neat): 1766 cm^{-1}. HRMS(EI+): Calculated for $C_8H_{14}O_2$: 142.099. Found: 142.099.

3-Butyl-4, 5-dimethyl-(2H)-furan-2-one. Obtained as a colourless oil in 78% yield in two steps from the corresponding γ, δ-unsaturated acid. Mixture of 4 diastereomers. The spectroscopic data refers to the major diastereomer **12a**. ^{1}H-NMR: δ 4.48-4.54(m, 1H), 2.57-2.65(m, 1H), 2.42-2.52(m, 1H), 1.73-1.86(m, 1H), 1.25-1.50(m, 7H), 1.33(d, *J* = 7, 3H), 0.86-0.94(m, 3H), 0.84(d, *J* = 7, 3H). ^{13}C-NMR: δ 178.9, 78.0, 46.7, 37.2, 31.9, 27.5, 25.1, 22.7, 15.7, 14.2, 8.2. IR(neat): 1772 cm^{-1}. HRMS(EI+): Calculated for $C_{11}H_{20}O_2$: 184.146. Found: 184.146

3-Butyl-4, 5-dimethyl-(2H)-furan-2-one. Obtained as a colourless oil in 79% yield in two steps from the corresponding γ, δ-unsaturated acid. Mixture of 4 diastereomers. The spectroscopic data refers to the major diastereomer **12d**. ^{1}H-NMR: δ 4.68-4.60(m, 1H), 2.40-2.30(m, 1H), 2.25-2.15(m, 1H), 1.76-1.54(2m, 2H), 1.40-1.25(m, 6H), 1.25(d, *J* = 7, 3H), 1.05(d, *J* = 7, 3H), 0.92-0.87(m, 3H). ^{13}C-NMR: δ 179.3, 77.8, 46.1, 38.6, 32.0, 29.1, 26.8, 22.7, 15.8, 14.2, 14.1. IR(neat): 1774 cm^{-1}. HRMS(EI+): Calculated for $C_{11}H_{20}O_2$: 184.146. Found: 184.143.

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