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On the Mechanism of Cu-Catalyzed Enantioselective Extended Conjugate Additions: A Structure-Based Approach

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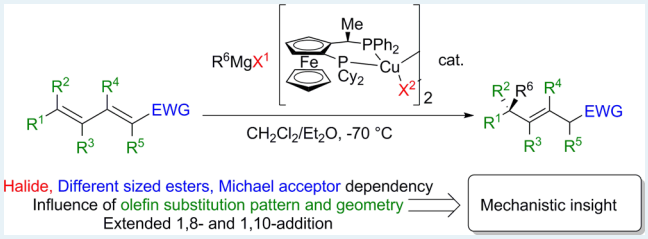
Supporting Information

ABSTRACT: The enantioselective 1,6-addition to unsaturated carbonyl compounds offers unique opportunities to study the range of selectivities one can obtain using Cu catalysis. Here, a substrate−reagent approach to obtain structural information on the mechanism of extended conjugate additions is reported. By studying the influence of several halides in the Grignard reagent and in the Cu source on the enantioselective 1,6-addition, it was shown that it is advantageous to use a combination of EtMgBr as Grignard reagent and CuI as Cu source. Furthermore, exploring substrates bearing several alkyl esters revealed that *t*Bu-ester substrates enhance the enantiodiscrimination in the 1,6-addition and allow the addition of $BnCH_2MgBr$. Substrates with a variety of electron-withdrawing groups were investigated as well, identifying that ester substrates are optimal for the 1,6-addition. Two other investigations feature Me-substituted olefin substrates and substrates with all possible olefin geometries. These studies show unprecedented high enantioselectivity in the 1,6-addition when α-Me substrates are used and give relevant insight into the 1,6-addition mechanism. Finally, substrates with three or four olefins in conjugation with the electron-withdrawing groups were studied. Here, a 1,8-addition is reported that gives the corresponding products in reasonable yield, regio- and stereoselectivity. With the combined results of these studies, elucidating key substrate and reagent parameters, an adapted mechanism for the enantioselective 1,6-addition is proposed. This mechanism features the activation of a dimeric precatalyst by an equivalent of Grignard reagent, active catalyst coordination to the internal olefin of the substrate in a Cu^I-π-complex, followed by coordination of the catalyst to the remote olefin forming another Cu^I-π-complex. From the latter Cu^I-complex, an oxidative addition gives a Cu^{III}-σ-complex at the δ-carbon, followed by transfer of the alkyl moiety to the δ-position. This reductive elimination yields the product and reforms the active Cu^I catalyst via transmetalation with another molecule of Grignard reagent.



KEYWORDS: *asymmetric catalysis, mechanism, copper, Grignard reagent, extended conjugate addition*

INTRODUCTION

Methods for the Cu-catalyzed enantioselective formation of C−C bonds using organometallic reagents are among the key transformations of high importance for the synthesis of complex molecules.[1,2] Among them, enantioselective 1,4-addition (1,4-ECA, Scheme 1a) using Grignard reagents[3−5] has proven to be valuable in numerous syntheses in recent years.[6] A special case of ECA is the enantioselective 1,6-addition (1,6-ECA, Scheme 1b) in which substrates **3** bearing two olefins in conjugation with an electron-withdrawing group are selectively converted into valuable products **4**.[7−10] The 1,6-ECA not only yields enantioenriched multifunctional building blocks,[11−13] but this reaction is also an intriguing example of the high chemo-, regio-, and enantioselectivity one can obtain using enantioselective Cu catalysis.

Although many synthetic methods have been designed for the enantioselective construction of C−C bonds using organometallic reagents employing Cu catalysis,[1−5] only a limited number of mechanistic studies toward these reactions has been conducted.[14,15] With respect to the use of organometallic reagents for extended conjugate additions, the mechanistic investigations on the stoichiometric addition of Gilman reagents to 2-en-4-ynoates by Krause[16] and Nakamura[17,18] are the most extensive studies reported to date. The proposed mechanism by Nakamura and co-workers[17] shown in Scheme 2, based on experimental data and computational studies, comprises the following: (1) formation of a Cu^I-π-complex by coordination of Me_2CuLi to substrate **5**, (2) an oxidative addition to give the Cu^{III}-σ-complex **7** (Cu-coordination to the β-position), (3) copper migration to yield σ/π-allenyl-Cu^{III}-complex **8** (Cu-coordination to the δ-position), and (4) a reductive elimination forming a Cu^I-species and the product **9**.

In this paper, we describe the results of a largely structural study toward the mechanism of the Cu-catalyzed enantioselective 1,6-addition of Grignard reagents to dienoates using the "reversed JosiPhos" ligand **L2**.[7b,c] Furthermore, we have compared the observed parameters and trends for 1,6-ECA

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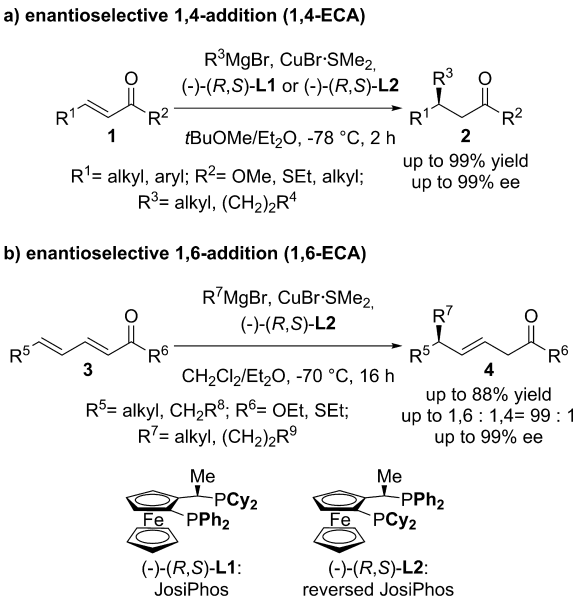
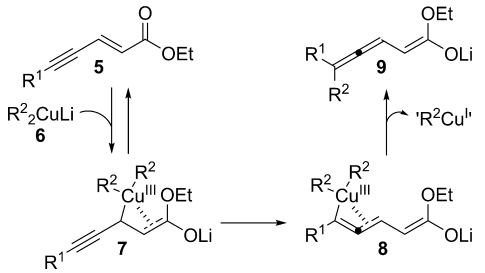
Scheme 1. Cu-Catalyzed Enantioselective 1,4-[3b−d] and 1,6-ECA[7b,c] of Grignard Reagents



Scheme 2. Proposed Mechanism by Nakamura et al.[17] for Cuprate 1,6-Addition to an Enynoate



with those obtained for the corresponding enantioselective 1,4-addition.[3a−d,15a]

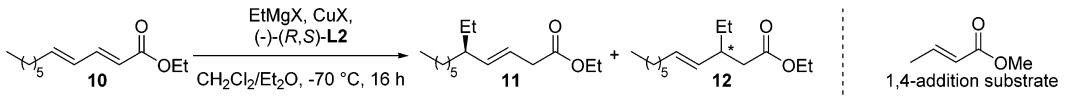
RESULTS

Halide Dependency. First, the halide dependency of the 1,6-ECA was studied using the same conditions that we identified[7b] as optimal for the addition of ethyl Grignard reagents to bisunsaturated ester substrates (**3**, R^5 = alkyl, Scheme 1). The 1,6-ECA of EtMgBr to substrate **10** using CuBr·SMe_2 and **L2** (Table 1, entry 1) yielded product **11** in excellent regioselectivity (ratio of 1,6-:1,4-addition = 99:1) and enantioselectivity (96% ee). When CuCl was used as Cu source instead of CuBr·SMe_2, **11** was obtained in lower regioselectivity and the same enantioselectivity (entry 2). When CuI replaced CuBr·SMe_2, **11** was obtained with similar regioselectivity and higher enantioselectivity (98% ee, entry 3). The use of EtMgCl, instead of EtMgBr, gave a low conversion when CuCl was used as Cu source (entry 4). When a combination of EtMgCl and CuBr·SMe_2 was used, **11** was obtained in lower regio- and enantioselectivity (entry 5 vs entry 1). The use of EtMgI in combination with either CuBr·SMe_2 or CuI (entry 6 and 7) gave lower conversion, lower regioselectivity and slightly lower (CuBr·SMe_2) or the same (CuI) enantioselectivity compared to the use of EtMgBr and CuBr·SMe_2. In conclusion, a combination of EtMgBr with either CuBr·SMe_2 or CuI gives the best results in terms of conversion, regio- and enantioselectivity. Furthermore, the use of the Grignard reagent derived from the organobromide is important to obtain high conversion and selectivity to product **11**.

When the regioselectivity of the reaction was lower, we were able to identify the ee of the obtained 1,4-addition product **12** (entries 2, and 5 to 7). Interestingly, in all cases the 1,4-addition product was obtained with low ee compared to the 1,6-addition product (**12** in all cases <26% ee vs **11** consistently ≥90% ee). Finally, a comparison of the halide dependency for the 1,4-ECA[15a] (to enoates) and 1,6-ECA (to dienoates) reveals similar trends, even when these studies were conducted using different catalysts (**L1** for 1,4-ECA, **L2** for 1,6-ECA); with a bromide in either the Cu source or the Grignard reagent high conversions and selectivities are obtained, while the use of EtMgI, or the combination of EtMgCl and CuCl, gives lower conversions and selectivities. The enantioselectivity for the 1,6-addition seems to be less dependent on the nature of the halide than for the 1,4-addition.

Ester Size Dependency. In a previous study, we found that the size of the ester has a profound influence on the 1,4-ECA to crotonates[3c] (Table 2, far right columns). Therefore, we studied the influence of the different esters on the 1,6-ECA (Table 2). Using methyl sorbate (**13a**), the 1,6-addition product **14a** was obtained with high regioselectivity and 75% ee (entry 1). The enantioselectivity of the 1,6-ECA increased progressively when bulkier esters were used (entry 2 to 4), yielding the 1,6-addition

Table 1. Halide Dependency of the 1,6-ECA



	1,6-addition[a]					1,4-addition[a−c]	
entry	EtMgX	CuX	conv. (%)[d]	**11**:**12**[e]	ee **11** {ee 1,4 (**12**)} (%)[e]	conv. (%)	ee (%)
1	EtMgBr	CuBr·SMe_2	>95%	99:1	96%	92%	94%
2	EtMgBr	CuCl	>95%	83:17	96% {20%}	90%	95%
3	EtMgBr	CuI	>95%	98:2	98%	90%	95%
4	EtMgCl	CuCl	<5%	n. d.	n. d.	80%	70%
5	EtMgCl	CuBr·SMe_2	>95%	80:20	94% {26%}	96%	80%
6	EtMgI	CuBr·SMe_2	57%	79:21	90% {13%}	40%	40%
7	EtMgI	CuI	51%	82:18	96% {9%}	50%	88%

[a]Conditions: see Supporting Information (SI), 5% Cu, 5.25% **L2**. [b]Data can also be found in SI Table S6 of ref 15a. [c]Substrate: methyl crotonate; product: methyl 3-methylpentanoate. [d]Conversion was determined by GC-MS. [e]Ratio of 1,6:1,4 and ee's were determined by chiral GC.

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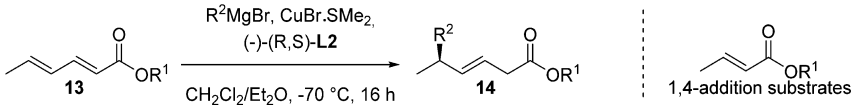
Table 2. Dependency on the Size of the Ester in 1,6-ECA



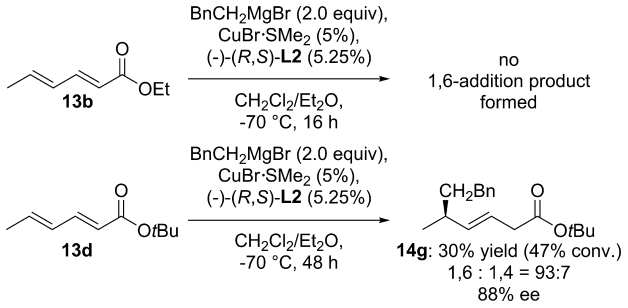
	1,6-addition[a]							1,4-addition[a,b]	
entry	R^1	13	R^2	14	isolated yield (%)	1,6:1,4[c]	ee 1,6 (%)[c]	conv. (%)	ee (%)
1	Me	**13a**	Et	**14a**	64%	>99:1	75%	>95%[d]	92%[d]
2	Et	**13b**	Et	**14b**	84%[e]	98:2[e]	95%[e]	>95%[d]	78%[d]
3	*i*Pr	**13c**	Et	**14c**	82%	99:1	97%	>95%[d]	54%[d]
4	*t*Bu	**13d**	Et	**14d**	88%	98:2	98%	<5%[f]	n. d.
5	*t*Bu	**13d**	*n*hexyl	**14e**	72%	98:2	98%		
6	*t*Bu	**13d**	*i*pentyl	**14f**	77%	99:1	99%		

[a]Conditions: see SI, 5% Cu, 5.25% **L2**. [b]Substrates: methyl, ethyl, *iso*-propyl or *tert*-butyl crotonate; products: methyl, ethyl, *iso*-propyl or *tert*-butyl 3-methylpentanoate. [c]Ratio of 1,6:1,4 and ee's were determined by chiral GC. [d]Data can also be found in Scheme 1 of ref 3c (in parentheses). [e]Data can also be found in Table 3 of ref 7b [enantiomer of ligand was used and enantiomer of product was obtained]. [f]Unreported data.

products in 95% ee (R^1= Et, **14b**), 97% ee (R^1= *i*Pr, **14c**), and 98% ee (R^1= *t*Bu, **14d**), respectively, while the regioselectivity remained constant. The addition of several other alkyl Grignard reagents to **13d** (R^1= *t*Bu) gives the corresponding 1,6-addition products with high enantioselectivity as well (entries 5 and 6). The observed trend is in sharp contrast to the one found for 1,4-ECA to crotonates.[3c] In the 1,4-ECA the highest enantioselectivity is obtained using methyl crotonate, bearing a small methyl ester, while the *iso*-propyl ester gives low ee, and the bulkier *tert*-butyl crotonate gives very low conversion to the 1,4-addition product.[3c]

It is especially interesting that the 1,6-addition of phenethyl magnesium bromide to *tert*-butyl sorbate **13d** proceeds with low conversion and high regio- and stereoselectivity, while the addition of this Grignard reagent to ethyl sorbate **13b** gave no conversion (Scheme 3).

Scheme 3. Enantioselective 1,6-Addition of Phenethyl Magnesium Bromide to Sorbates[a]



[a]Conditions: a solution of **13** in CH_2Cl_2 was added in 2 h to a solution of EtMgBr (solution in Et_2O, 2.0 equiv), (−)-(*R*,*S*)-**L2** (5.25 mol %) and CuBr·SMe_2 (5 mol %) in CH_2Cl_2 (0.2 M final concentration in **13**) at −70 °C, 16 or 48 h total reaction time.

Michael Acceptor Dependency. Next, we studied the 1,6-ECA to several substrates bearing various electron-withdrawing groups (Table 3). As reported earlier,[7b] the use of ethyl ester **15a** gave the 1,6-addition product in 80% yield, 99:1 regioselectivity, and 93% ee (entry 1). The 1,6-ECA of EtMgBr to the more electron-poor Michael acceptor **15b**, incorporating an ethyl thioester as electron-withdrawing group (EWG), gave the 1,6-addition product **16b** in high regioselectivity, modest yield and low enantioselectivity (entry 2). When EtMgBr was reacted with the even more electron-poor Michael acceptor methyl ketone **15c**, the 1,6-ECA proceeded with low regio- and enantioselectivity (entry 3). In contrast, the 1,4-ECA to either monounsaturated thioesters[3d] or ketones[3b] gives the 1,4-addition products in high yield, regio- and enantioselectivity.

Substrates with an EWG group featuring a possible second coordination site for Mg were tested as well. Addition of EtMgBr to sulphone[3f,19] **15d** gave the 1,6-addition product **16d** in low yield, high regioselectivity, and negligible enantioselectivity (entry 4). Use of dienoyloxazolidinone **15e** gave the 1,6-addition product **16e** in modest yield and regioselectivity as well as negligible ee (entry 5). The use of imidazolyldienone substrate **15f** gave the 1,4-addition product **17f** in low yield, high regioselectivity, and negligible ee (entry 6).

Finally, we studied the 1,6-addition of the less reactive MeMgBr to substrates bearing an ester, thioester, and ketone as EWG. As reported in our previous studies, use of ester **15a** gave low conversion to the 1,6-addition product **16g** (entry 7).[7b] However, the use of thioester **15g** or **15b** allowed the isolation of 1,6-addition products, **16h** and **16i**, respectively, in high yield, regio- and enantioselectivity (entry 8, 9), emphasizing the remarkable difference between ester and thioester EWG in these transformations.[7c] Addition of MeMgBr to ketone **15c** gave 1,6-addition product **16j** in modest yield, regioselectivity, and ee (entry 10).

In conclusion, a fine-tuning of the Michael acceptor properties of the substrate, with respect to the reactivity of the Grignard reagent, is required to obtain the 1,6-addition products in high yield with excellent regio- and enantioselectivities. Furthermore, when the substrate possesses two heteroatom coordination sites for Mg, the 1,6-ECA (or 1,4-ECA to bisunsaturated Michael acceptors) proceeds with negligible enantioselectivity.

Influence of the Olefin Substitution Pattern. Methyl substitution of the olefins has a major impact on the 1,4-ECA of Grignard reagents to α,β-unsaturated ketone,[20] ester, and thioester substrates. Using standard reaction conditions for the 1,4-ECA using **L2**, the addition of EtMgBr to the α-Me substituted ester ethyl tiglate (Table 4, entry 1, far right columns), the β-Me substituted ester ethyl 3-methyl-2-butenoate (Table 4, entry 2, far right columns), and β-Me substituted thioester substrate (*S*)-ethyl (*E*)-3-phenylbut-2-enethioate **18** (Scheme 4) gave low conversion. The EtMgBr 1,4-ECA to the α-Me substituted thioester substrate (*S*)-ethyl (*E*)-2-methylbut-2-enethioate **19** gives full conversion to 1,4-addition product **20**, although the ee of **20** is negligible. The impact of α-Me substitution on the 1,4-ECA to ketone substrates is even more

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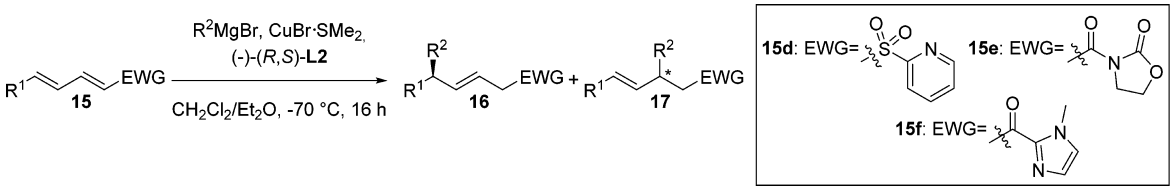
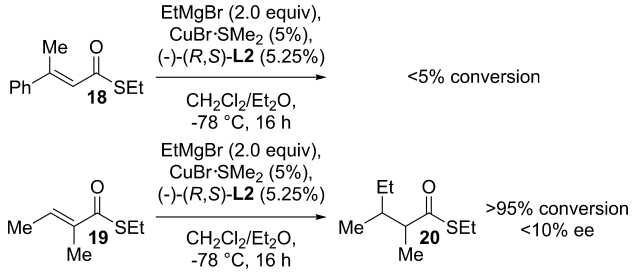
Table 3. Michael Acceptor Dependency of the 1,6-ECA



	1,6-addition[a]							
entry	R^1	EWG	15	R^2	16/17	yield (%)	1,6:1,4[b]	ee 1,6 (%)[b]
1[c]	*n*Bu	CO_2Et	**15a**	Et	**16a**	80%	99:1	93%
2	*n*Bu	COSEt	**15b**	Et	**16b**	58%	>95:5	≈ 40%[d]
3	*n*Bu	COMe	**15c**	Et	**16c**	≈ 60%[d]	63:37	≈ 30%[d]
4	*n*Bu	sulphone	**15d**	Et	**16d**	26%	98:2	2%
5	Me	(CO)oxazolidinone	**15e**	Et	**16e**	64%	75:25[e]	3%
6	Me	(CO)imidazole	**15f**	$BnCH_2$	**17f**	34%	<5:95[e]	2%
7[f]	Et	CO_2Et	**15a**	Me	**16g**	<10%	n. d.	n. d.
8[f]	Et	COSEt	**15g**	Me	**16h**	85%	99:1	93%
9[g]	*n*Bu	COSEt	**15b**	Me	**16i**	83%	99:1	89%
10	*n*Bu	COMe	**15c**	Me	**16j**	54%	63:37	66%

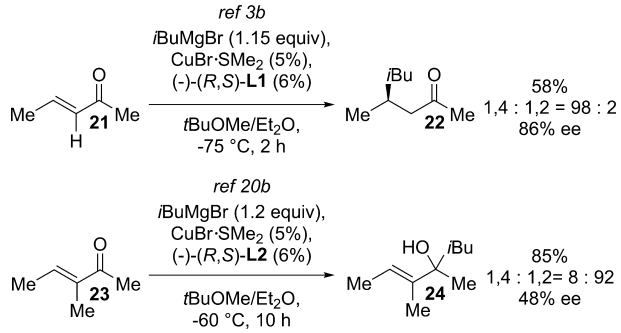
[a]Conditions: see SI, 5% Cu, 5.25% **L2**. [b]Ratio 1,6:1,4 and ee's were determined by chiral GC. [c]Data can also be found in Table 4 of ref 7b [the enantiomer of the ligand was used and the enantiomer of the product was obtained]. [d]Signals corresponding to the two enantiomers on chiral GC were partly overlapping. [e]Ratio of 1,6:1,4 was determined by NMR. [f]Data can also be found in Scheme 3 of ref 7b. [g]Data can also be found in Table 2 of ref 7c.

Scheme 4. Influence of Methyl Substituted Olefins on the Enantioselective 1,4-Addition to Unsaturated Thioesters[a]



[a]Conditions: 1,4-addition to **18**: a solution of **18** in CH_2Cl_2 was added in 2 h to a solution of EtMgBr (solution in Et_2O, 2.0 equiv), (−)-(*R*,*S*)-**L2** (5.25 mol %) and CuBr·SMe_2 (5 mol %) in CH_2Cl_2 (0.2 M final concentration in **18**) at −78 °C, 16 h total reaction time. 1,4-addition to **19**: a solution of **19** in CH_2Cl_2 was added in 2 h to a solution of EtMgBr (solution in Et_2O, 2.0 equiv), (−)-(*R*,*S*)-**L2** (5.25 mol %) and CuBr·SMe_2 (5 mol %) in CH_2Cl_2 (0.2 M final concentration in **19**) at −78 °C, 16 h total reaction time.

Scheme 5. Influence of Methyl Substituted Olefins on the Enantioselective 1,4-Addition to Unsaturated Ketones[a]



[a]Conditions: 1,4-addition to **21**: a solution of *i*BuMgBr (solution in Et_2O, 1.15 equiv) was added to a solution of **21**, (−)-(*R*,*S*)-**L1** (6 mol %) and CuBr·SMe_2 (5 mol %) in *t*BuOMe (0.1 M final concentration in **21**) at −75 °C, 2 h total reaction time. 1,4-addition to **23**: a solution of *i*BuMgBr (solution in Et_2O, 1.2 equiv) in *t*BuOMe was added over 15 min to a solution of **23**, (+)-(*S*,*R*)-**L2** (6 mol %) and CuBr·SMe_2 (5 mol %) in *t*BuOMe (0.075 M final concentration in **23**) at −60 °C, 10 h total reaction time.

dramatic (for an example, see Scheme 5). When α,β-unsaturated α-Me substituted ketone substrates are treated with alkyl Grignard reagents at low temperature in the presence of a catalytic amount of Cu-**L2**, instead of 1,4-addition products, the 1,2-addition products are obtained in high yield, regio- and stereoselectivity in most cases.[20]

We were interested in the effect that methyl substitution at various positions of the diene moiety in the sorbates **25** would have on the 1,6-ECA (Table 4). The 1,6-ECA of EtMgBr to α-Me substituted substrate **25a** gave the corresponding 1,6-addition product **26a** in similar yield, regioselectivity, and even higher enantioselectivity (entry 1) than the corresponding 1,6-ECA to α-H substituted substrate **15a** (Table 3, entry 1). With respect to the α-stereogenic center, 1,6-addition product **26a** was obtained as a mixture of *anti*- and *syn*-isomers; this suggests that the stereogenic center at the δ-position does not induce any diastereoselectivity in the trapping of the vinyl enolate intermediate at the α-position by a proton. Addition of EtMgBr to the β-Me substituted substrate **25b** gave a low conversion and low yield of a mixture of 1,4- and 1,6-addition products (Table 4, entry 2). The conversion was low for the 1,6-ECA to the γ-Me substituted substrate **25c** at −70 °C (entry 3, for a corresponding experiment at −60 °C see SI footnote F1). This is reminiscent of the 1,4-ECA to the α-Me substituted thioester substrate (entry 1, far right columns). Finally, at −70 °C the 1,6-ECA to the δ-Me substituted substrate **25d** gave low conversion to the 1,4-addition product **27d** (entry 4, for a corresponding experiment at −60 °C see SI, footnote F2). In conclusion, while β-, γ-, and δ-Me substitution of sorbates give worse results for the 1,6-ECA, the use of the α-Me substituted substrate gives even better results than the α-H substrate.

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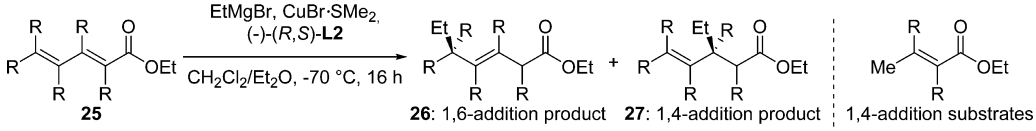
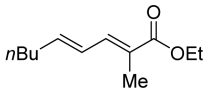
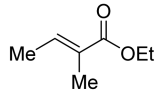
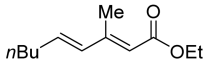
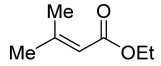
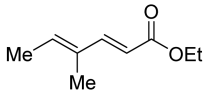
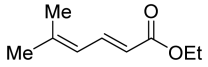
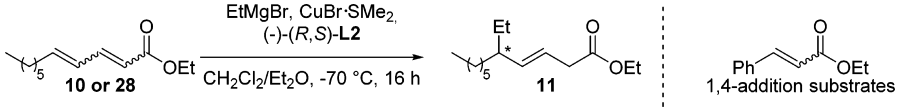
Table 4. Influence of Methyl-Substituted Olefins on the Enantioselective 1,6-Addition

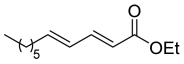
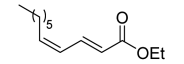
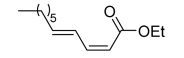
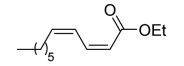


	1,6-addition[a]						1,4-addition[a]	
entry	25		conv. (%)[b]	yield (%)	1,6:1,4[c]	ee 1,6 (%)[c]	substrate	conv. (%)[b]
1		**25a**	94%	83%	> 99:1	97% {1:1}[d]		<5%
2		**25b**	<25%[e]	19%[f]	n. d.[f]	n. d.		<5%
3		**25c**	≈15%[g]	n. d.	n. d.[h]	n. d.[i]		
4		**25d**	≈25%[j]	n. d.	5 : 95	n. d. {27%}[k]		

[a]Conditions: see SI, 5% Cu, 5.25% **L2**. [b]Conversion was determined by GC-MS. [c]Ratio of 1,6:1,4 and ee's were determined by chiral GC. [d]A mixture of *syn*- and *anti*-products was obtained. [e]≈ 55% of substrate **25b** was recovered. [f]Mixture of products with MS fragmentation patterns corresponding to 1,6- and 1,4-addition products was found. [g]≈ 55% of substrate **25c** was recovered. [h]A mixture of 1,6- and 1,4-products was obtained; overlap of the peaks corresponding to substrate and 1,4-addition product on chiral GC did not allow determination of these ratios. [i]ee for the 3*Z*-1,6-addition product was 5%. [j]≈ 60% of substrate **25d** was recovered. [k]Value between brackets corresponds to ee of 1,4-addition product.

Table 5. Dependency of the Enantioselective 1,6-Addition on the Olefin Geometry of the Sorbates



	1,6-addition[a]						1,4-addition[a,c]		
entry	substrate		conv. (%)[d]	1,6:1,4[e]	ee 1,6 (%)[e]	recovered **10** or **21**	substrate	conv. (%)[d]	ee (%)
1		**10**	>95% {77%}[f]	99:1	96% (*R*)		*E*[g]	>95%[g]	98% (*S*)[h]
2		**28a**	>95%	98:2	96% (*S*)		*Z*[i]	>95%[i]	53% (*R*)[h]
3		**28b**	>95%	94:6	12% (*S*)				
4		**28c**	>95%	99:1	66% (*R*)				
5[j]	**10**		95%	99:1	96% (*R*)	**10**[k]			
6[j]	**28a**		26%	98:2	n. d.[l]	**28a**[k]	*Z*[i]	10%[i,m,n]	59% (*R*)[h]
7[j]	**28b**		40%	99:1	19% (*S*)	**28b**[k]			
8[j]	**28c**		55%	99:1	60% (*R*)	**28c**[k]			

[a]Conditions: see SI, 5% Cu, 5.25% **L2**. [b]Data can also be found in Table 4 of ref 15a. [c]For footnote F3 see SI. [d]Conversion was determined by GC-MS. [e]Ratio of 1,6:1,4 and ee's were determined by chiral GC. [f]Isolated yield. [g]Substrate: *E*-methyl cinnamate; product: methyl 3-phenylpentanoate. [h]Please note: enantiomer of catalyst was used. [i]Substrate: *Z*-methyl cinnamate; product: methyl 3-phenylpentanoate. [j]Total reaction time: 2 h 10 min to 3 h. [k]Remaining starting material was recovered without isomerization. [l]Overlap of the peaks corresponding to substrate and 1,6-addition product on chiral GC did not allow determination of this ee. [m]Reaction was quenched after 10% conversion. [n]Recovered starting material *Z*-: *E*-methyl cinnamate= 94:6.

Olefin Geometry Dependency. We also studied the influence of the geometry of the two olefinic moieties in the dienoates on the 1,6-ECA (Table 5). Enantioselective 1,6-addition of EtMgBr to all-*E* substrate **10** affords the *R*-enantiomer of the corresponding product **11** in high yield, regioselectivity and 96% ee (entry 1). As expected, the opposite enantiomer of the 1,6-addition product, *S*-**11**, is obtained when the 2*E*,4*Z*-substrate **28a** is used in the 1,6-ECA in high yield, regioselectivity and 96% ee (entry 2). This result contrasts to the 1,4-ECA of *E*- and *Z*-cinnamates (entry 1 and 2, far right columns, for footnote F3 see SI). For the 1,4-ECA, the opposite enantiomer of the 1,4-addition product is obtained with lower enantioselectivity due to isomerization of the *Z*-substrate under the reaction conditions (vide infra).[15a] The 1,6-ECA to the 2*Z*,4*E*-substrate **28b** gave *S*-**11** but with low ee (entry 3). Using the 2*Z*,4*Z*-substrate **28c**, compared to the use of **28b**, the

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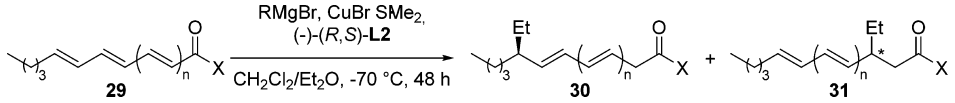
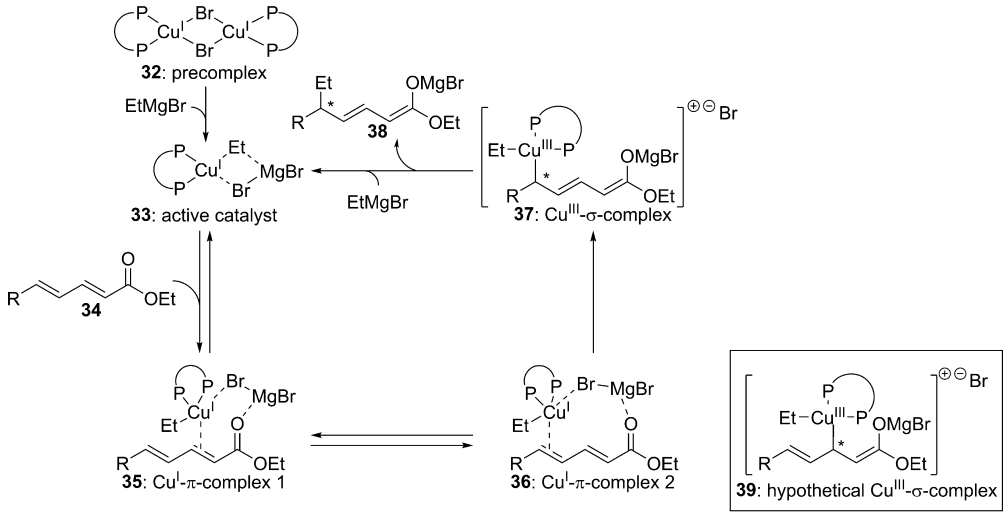
Table 6. Enantioselective 1,8- and 1,10-Addition



1,8-addition[a]									
entry	*n*	X	**29**	R	cat (%)	conv. (%)[b]	yield	1,8:1,6:1,4[c]	ee 1,8-product (%)[c]
1	1	OEt	**29a**	Et	5%	>95%	47%	63:8:29	7%
2	1	SEt	**29b**	Me	7.5%	92%	63%	86:0:14	72%
1,10-addition[a]									
entry	*n*	X	**29**	R	cat (%)	conv. (%)[b]	yield	1,10:1,8 + 1,6:1,4[c]	ee 1,10-product (%)[c]
3	2	OEt	**29c**	Et	5%	85%	22%	49:8:43	12%
4	2	SEt	**29d**	Me	10%	82%	44%	59:0:41	45%

[a]Conditions: see SI. [b]Conversion was determined by GC-MS. [c]Ratio of 1,6:1,4 and ee's were determined by chiral GC.

Scheme 6. Mechanism of the Enantioselective 1,6-Addition[a]



[a]For footnotes F4, F10, and F12, see SI.

opposite enantiomer *R*-**11** was obtained, however, with a higher enantioselectivity (entry 4).

The difference in the ee's obtained using **28b** and **28c** could possibly arise from isomerization of the substrate under the reaction conditions.[15a,21] Therefore, we performed several 1,6-ECA reactions where we did not allow the reaction to proceed until completion, in order to study the integrity of the olefins. For none of the substrates **28a**, **28b**, or **28c**, olefin isomerization was observed under the reaction conditions (entries 5 to 8). This is again in contrast to the 1,4-ECA to cinnamates,[15a] where isomerization of the *Z*-cinnamate to the *E*-cinnamate was observed under the reaction conditions (entry 6, far right columns). The relatively high stereoselectivity observed for the 1,6-ECA to **28c**, compared to the 1,6-ECA to **28b**, is thus most likely the result of a different coordination mode of the Cu-**L2** catalyst to this less space-requiring substrate.

Enantioselective 1,8- and 1,10-Addition. Finally, we explored the enantioselective extended conjugate additions to substrates that either possess three conjugated olefins in conjugation with the EWG being a substrate for an enantioselective 1,8-addition[22] (Table 6, 1,8-ECA) or four conjugated olefins, a substrate for an enantioselective 1,10-addition (1,10-ECA). The Cu-catalyzed addition of EtMgBr to the 1,8-ECA substrate **29a** mainly gave rise to the 1,8-addition product **30a**, although in modest yield and low ee (entry 1). In conjunction with the 1,8-addition product also 1,4-addition product **31a**, and only traces of the 1,6-addition product were obtained. The 1,8-addition product **30b** was the main product when the 1,8-ECA of MeMgBr to thioester substrate **29b** was performed (entry 2). The product **30b** was obtained in reasonable yield, regio- and enantioselectivity; however, a higher catalyst loading (7.5 mol %) was required to achieve high conversion. Again, the main side-product was the 1,4-addition product **31b**, although in this case the 1,6-addition product was absent.

For 1,10-ECA to ester substrate **29c**, a mixture of 1,4- and 1,10-addition product was obtained, in combination with traces of 1,6- and 1,8-addition products (entry 3). The 1,10-addition product **30c** was obtained in a comparable ee with the 1,8-addition product (entry 1). The use of MeMgBr and thioester substrate **29d** gave the 1,10-addition product **30d** as the main product in reasonable yield and modest ee using 10 mol % of Cu-**L2** (entry 4). The 1,4-addition product was obtained as well, while the 1,6- and 1,8-addition products were absent.

In conclusion, the 1,6-, 1,8- and 1,10-ECA to their corresponding thioester substrates (**15b**, **29b** and **29d**, respectively) give the products in decreasing regio- and stereoselectivity the more remote the olefin (and thus the newly formed stereogenic center) is from the thioester functionality. Furthermore, 1,8- and 1,10-ECA gives a low

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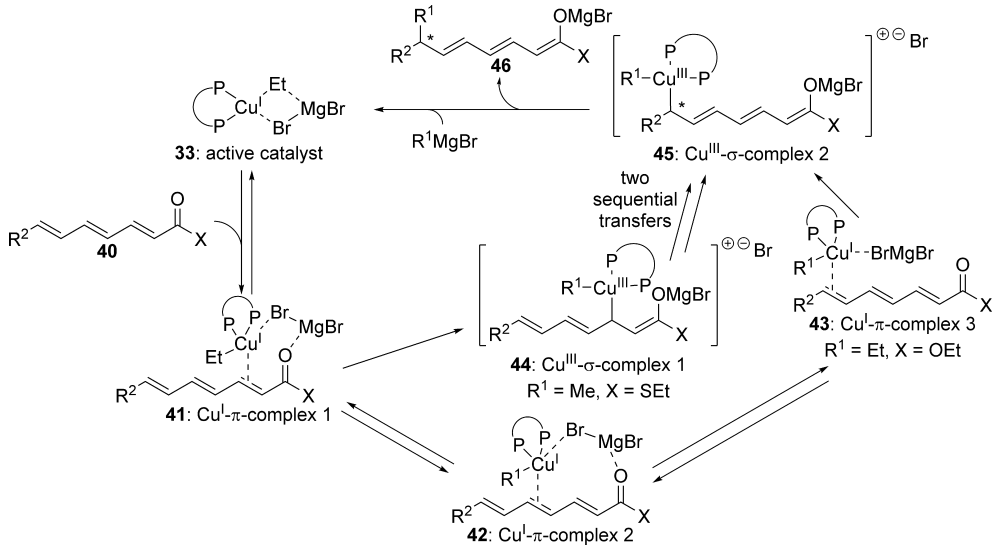
Scheme 7. Mechanism for Enantioselective 1,8-Additions[a]



[a]For footnotes F12 and F14, see SI.

stereodiscrimination when ester substrates are used. It is striking that in all the cases of 1,8- and 1,10-ECA studied, the 1,4-addition products or the addition product, for which the alkyl is transferred to the most remote olefinic carbon of the π-system, are exclusively formed.

DISCUSSION

Mechanism of the Enantioselective 1,6-Addition. A mechanism that is consistent with our results is depicted in Scheme 6 (for footnote F4, see SI). In our proposed mechanism, the precomplex **32**[15a] is converted by the Grignard reagent (alkyl transfer) to form the active binuclear Cu,Mg-catalyst **33**. Such an activation was observed during the studies toward the mechanism of the 1,4-addition of Grignard reagents.[15a] Analogous to the first Cu^I-π-intermediate in the 1,4-addition mechanism,[15a] this precomplex **33** coordinates to the internal olefin of substrate **34**, forming Cu^I-π-intermediate **35**.[16b,c,f,23] The low conversion observed for the β-Me substituted substrate **25b** under the standard reaction conditions (−70 °C, Table 4, entry 2) supports the involvement of the internal olefin in the 1,6-addition mechanism (for footnote F5, see SI).

After formation of the initial Cu^I-π-intermediate **35**, the Cu catalyst coordinates to the remote olefin giving a second Cu^I-π-intermediate **36**; this step is most likely reversible. This intermediate **36** is, for several reasons, more likely than a first Cu^{III}-σ-complex **39** (for footnote F6, see SI), a hypothetical intermediate that would be analogous to **7** in the mechanism for 1,6-addition of Me_2CuLi to 2-en-4-ynoates proposed[17] by Nakamura et al. (Scheme 2). First of all, the lower enantiomeric excess observed for the 1,4-addition products compared to the 1,6-addition products using the same reagents and substrates (Table 1, entries 2, 5−7) supports the involvement of a second Cu^I-π-intermediate **36**, since we assume that from the hypothetical Cu^{III}-σ-complex **39** at the β-position the stereochemical information is transferred to the δ-position, and subsequently to the 1,6-addition product (for footnote F7 and for Figure S1; for a graphical depiction of this transfer, see SI). This would mean that the 1,4-addition product (e.g., **12**, Table 1) and the 1,6-addition product (e.g., **11**) would be formed with similar enantiomeric excess if intermediate **39** would be involved in the mechanism as the stereochemistry is already established at this stage (also see SI, footnotes F8 and F9). Second, the opposite trends on stereoselectivity as a function of the ester size (Table 2) for the 1,4- (for enoates) and 1,6-addition (for dienoates), as well as the high stereoselectivity obtained for the α-Me substrate (Table 4, entry 1) similarly argue against hypothetical intermediate **39**. Third, for strong Michael acceptors, for which the formation of Cu^{III}-σ-intermediate **39** should be more facile, the observed low regio- and stereoselectivity for the formation of the 1,6-addition product (e.g., for thioester substrate **15b** and ketone substrate **15c**, Table 3, entries 2 and 3) is an indication that intermediate **39** is unlikely to be involved in the formation of the 1,6-addition product for ester substrates (for footnote F10, see SI). Finally, the fact that no isomerization of any of the *Z*-olefins was observed under the reaction conditions for the 2*Z*,4*E*-substrate **28b**, and the 2*Z*,4*Z*-substrate **28c** (Table 5, entries 6 and 7) makes it unlikely that a Cu^{III}-σ-intermediate on the β-position is involved in the mechanism of the 1,6-addition (for footnote F11, see SI).

From the second Cu^I-π-intermediate **36**, an oxidative addition gives Cu^{III}-σ-intermediate **37** at the δ-position. A subsequent reductive elimination, transferring the alkyl group from the Cu^{III}-σ-intermediate to the δ-position of the dienoate yields the 1,6-addition product **38**. Alkyl transfer to the resulting Cu^I-intermediate by a new equivalent of the Grignard reagent then allows the reformation of the active catalyst **33**.

For the β-Me substituted substrate **25b**, the low conversion that is observed (Table 4, entry 2) can be explained by the steric repulsion in an intermediate similar to **35**. However, the low conversion for γ-Me-substituted substrate **25c** and δ-Me-substituted substrate **25d** (Table 4, entries 3 and 4, respectively) is caused by the steric hindrance in the corresponding intermediates **36** or **37**.

Stereochemical Course of the 1,6-Addition. The results we have obtained with our structural study toward the 1,6-addition mechanism give some insight in the requirements for the formation of the δ-substituted product with high stereoselectivity. The 1,6-addition products are obtained with high enantiomeric excess when the Mg, which we propose is coordinating to the carbonyl in the stereodiscriminating step, is forced toward the Cu in any of the intermediates involving Cu

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coordination to the olefins (**35** or **36**). This is achieved either by the use of a bulky *t*Bu-ester (Table 2, entry 4) or by the use of the α-Me-substituted dienoate (Table 4, entry 1). In contrast, when there is a possibility for the Mg to be doubly coordinated to the electron-withdrawing group (e.g., in the CO-oxazolidinone, Table 3, entry 5 and the pyridine sulphone, Table 3, entry 4) and is thus not in the vicinity of the Cu, the 1,6-addition proceeds without any stereodivergence (for footnote F13, see SI).

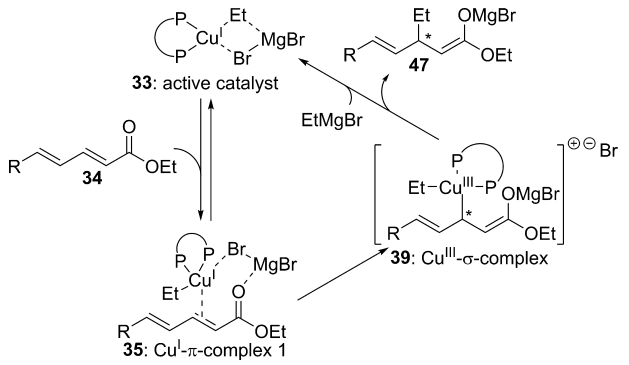
Furthermore, our study of the use of the various halides in both catalyst and Grignard reagent shows that the choice of halide influences the stereoselectivity of the 1,6-addition, as well as the conversion (Table 1). The dependency on the halide can be explained in two possible ways. First of all, a coordination of the Cu-(halide)-Mg-halide to both the carbonyl and the olefin in a pseudo 8-membered ring in Cu^{I}-π-complex **36**, in which the halide is required to have the right size, might furnish the high stereodiscrimination. Alternatively, the bulky P-substituents of the ligand (two phenyl and two cyclohexyl groups) might force a (rigid) conformer in the stereodiscriminating step, especially when the Mg-halide coordinated to the carbonyl has the right size. A nine-membered intermediate in the Cu^{III}-σ-complex **37** is unlikely, due to the investigation of similar Cu^{III}-σ-complexes at low temperatures by NMR spectroscopy.[24] These Cu^{III}-σ-complexes have been identified to possess a square planar geometry.[24] Unfortunately, the aforementioned studies of Cu^{III}-σ-complexes do not include any bidentate ligands coordinating the Cu.

Mechanism of the 1,8- and 1,10-Addition. A plausible mechanism for the formation of 1,8- and 1,10-addition products using the appropriate substrate (**29a**,**b** or **29c**,**d**, Table 6) involves, analogous to the 1,6-addition mechanism, active catalyst **33**, Cu^{I}-π-complex 1 **41**, and Cu^{I}-π-complex 2 **42** (Scheme 7). When an oxoester is used as electron-withdrawing group, from intermediate **42**, Cu^{I}-π-complexes with the third olefin (**43**, 1,8-addition), or, subsequently, the third and the fourth olefin (1,10-addition) are accessible. These intermediates with the Cu^{I}-π-complex coordinated to the remote olefin (e.g., **43**), then form a Cu^{III}-σ-complex at the remote C atom of the π-system (the ζ-position for 1,8-addition (**45**), the θ-position for 1,10-addition). Analogous to the 1,6-addition from this Cu^{III}-σ-intermediate, the alkyl group is transferred to the ζ- or the θ-position to yield the product, while simultaneously, complexation of another Grignard reagent allows the reformation of the active catalyst.

The low stereoselectivity observed for the 1,8- and 1,10-addition to oxoester substrates strengthens our proposal that in the stereodiscriminating step the distance between the Cu and the Mg, coordinated to the enolate, is highly important for high enantioselectivity in extended conjugate additions. It is striking that for the 1,8- and 1,10-addition using the oxoester substrates the reaction proceeds with low stereoselectivity, while for the thioester substrates the 1,8- and 1,10-addition products are obtained with high and modest enantioselectivity, respectively. This difference points at a different mechanism for 1,8- and 1,10-addition when a thioester (vs the oxoester) is used as electron-withdrawing group, although further studies are necessary. In this alternative mechanism after the first Cu^{I}-π-intermediate **41** an oxidative addition gives the Cu^{III}-σ-complex at the β-position (**44**), due to the better Michael acceptor properties of the thioester functionality (for footnote F14 and F15 see SI). From intermediate **44** the Cu^{III} is then transferred from the β- to consecutively, the δ- and the ζ-position (for 1,8-ECA, **45**), or subsequently to the δ-, ζ- and θ-position (for 1,10-ECA). In this mechanism the enantioselectivity will have been predetermined at the formation of the Cu^{III}-σ-intermediate at the δ-position (i.e., addition of the Cu at either the *re*- or *si*-face of the olefin). The stereochemical information would then be transferred along the carbon-chain, with some racemization, explaining the decreasing enantioselectivity for 1,6- > 1,8- > 1,10-addition.

Formation of 1,4-Addition Products by the Reaction of a Grignard Reagent with Dienoates. A mechanism for the formation of the 1,4-addition products (Scheme 8) involves the

Scheme 8. Mechanism for the Catalytic Formation of the 1,4-Addition Product in Dienoates[a]



[a]For footnote F12 see SI.

active catalyst **33** and Cu^{I}-π-complex **35**, both present in the proposed 1,6-addition mechanism. The increased formation of 1,4-addition product vs 1,6- < 1,8- < 1,10-addition product, the more extended the conjugation is, most probably indicates that these reactions share common intermediates. From Cu^{I}-π-complex **35**, oxidative addition gives Cu^{III}-σ-complex **39**, in which the Cu is coordinated to the β-position. Subsequently, a reductive elimination, transferring the alkyl group from the Cu^{III}-σ-intermediate to the β-position of the dienoate, gives the 1,4-addition product. From our results showing dramatic differences in the ee of the 1,4- and 1,6-adducts of the dienoates (see Table 1) it is evident that the 1,6-ECA and 1,4-ECA have a diverging stereodefining step.

The low regioselectivity for the 1,6-ECA of EtMgBr to thioester and ketone substrates (**15b** and **15c**, Table 3, entries 2 and 3, respectively) can be explained by a higher rate for the oxidative addition at the β-position, in comparison with the rate for isomerization to the δ-position.

CONCLUSIONS

The structure-based mechanistic studies that we have conducted for this research have allowed us to identify substrates (α,β,γ,δ-bisunsaturated *tert*-butyl esters and α-Me substituted α,β,γ,δ-bisunsaturated ethyl esters) for which the stereodiscrimination of the 1,6-addition to dienoates using Grignard reagents is even better (up to 99% ee) than for previously reported substrates. Furthermore, use of the α,β,γ,δ-bisunsaturated *tert*-butyl esters in the 1,6-ECA allows the addition of a Grignard reagent that did not display the desired reactivity[7b] before. Additionally, we show that 1,8-addition products can be obtained in reasonable yield, regio- and stereoselectivity. With the combined studies described here, we have obtained further insight in the mechanism of the 1,6-addition. This has led to an adapted proposal for the 1,6-addition mechanism (Scheme 6). Finally, our results make it likely that there is a different mechanism for the 1,8- and 1,10-

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addition to either oxoester or thioester substrates (Scheme 7). Further research, including extensive kinetic studies (combining in situ and quenching experiments) and high level quantum chemical calculations (for which the exact description of the Grignard reagent in solution[25] remains a big challenge), will shed more light on the mechanism for 1,6-addition using Grignard reagents.

EXPERIMENTAL SECTION

The general procedure for the enantioselective 1,6-conjugate addition is as follows. In a dried Schlenk tube equipped with a septum and a stir bar under a N_2 atmosphere, CuBr·SMe_2 (5.0 mol %) and (*R*,*S*)-reversed JosiPhos (**L2**, 5.25 mol %) were dissolved in anhydrous CH_2Cl_2 (4 mL/mmol substrate). After the mixture was stirred for 5 min at room temperature, it was cooled to −70 °C, and the Grignard reagent (solution in Et_2O, 2.0 equiv) was added. After it was stirred for an additional 10 min, a solution of the substrate (1.0 equiv) in anhydrous CH_2Cl_2 (additional 1.0 mL/mmol substrate) was added with syringe pump over 2 h. The reaction mixture was stirred overnight (16 h including addition) at −70 °C, and subsequently, EtOH (0.2 mL/mmol substrate) and an aq. NH_4Cl-solution (1 M, 1.0 mL/mmol substrate) were added. The mixture was warmed to room temperature, and an additional 10 mL/mmol substrate of the NH_4Cl-solution and 10 mL/mmol substrate of CH_2Cl_2 were added, and the layers were separated. After extraction with CH_2Cl_2 (2 × 10 mL/mmol substrate), the combined organic extracts were dried, and in view of the volatility, they were carefully concentrated to a yellow oil. Flash column chromatography (3:97 Et_2O/pentane) yielded the product as a colorless oil. (Occasionally the product was polluted by traces of a yellow colored side product undetectable by GC/MS or NMR.)

Halide Dependency. (*R*,*E*)-Ethyl 5-ethylundec-3-enoate (**11**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*)-ethyl undeca-2,4-dienoate (**10**) and EtMgBr. In the experiments using EtMgCl (2.0 equiv) or EtMgI (2.0 equiv), these reagents replaced EtMgBr (2.0 equiv). In the experiments using CuI (5 mol %) or CuCl (5 mol %), these reagents replaced CuBr·SMe_2 (5 mol %). Results: [Using EtMgCl and CuCl, 0.25 mmol scale, no conversion]; [Using EtMgCl and CuBr·SMe_2, 0.25 mmol scale, full conversion, 94% ee (*R*-enantiomer), 1,6:1,4 = 80:20, (ee 1,4-addition product: 26%)]; [Using EtMgBr and CuCl, 0.25 mmol scale, full conversion, 96% ee (*R*-enantiomer), 1,6:1,4 = 83:17, (ee 1,4-addition product: 20%)]; [Using EtMgBr and CuBr·SMe_2, 0.25 mmol scale, full conversion, 96% ee (*R*-enantiomer), 1,6:1,4 = 99:1]; [Using EtMgBr and CuI, 0.25 mmol scale, full conversion, 98% ee (*R*-enantiomer), 1,6:1,4 = 98:2]; [Using EtMgI and CuBr·SMe_2, 0.25 mmol scale, 57% conversion, 90% ee (*R*-enantiomer), 1,6:1,4 = 79:21, (ee 1,4-addition product: 13%)]; [Using EtMgI and CuI, 0.25 mmol scale, 51% conversion, 96% ee (*R*-enantiomer), 1,6:1,4 = 82:18, (ee 1,4-addition product: 9%)]. Data: $[\alpha]_D^{20}$ = −2.4 (*R*-enantiomer, *c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.45 (dt, *J* = 15.3, 6.9 Hz, 1H), 5.26 (dd, *J* = 15.3, 8.8 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.01 (d, *J* = 6.9 Hz, 2H), 1.89−1.80 (m, 1H), 1.43−1.15 (m, 15H), 0.86 (t, *J* = 6.8 Hz, 3H), 0.82 ppm (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ 172.2 (C), 139.0 (CH), 121.4 (CH), 60.4 (CH_2), 44.4 (CH), 38.2 (CH_2), 34.8 (CH_2), 31.8 (CH_2), 29.4 (CH_2) 27.8 (CH_2), 27.1 (CH_2), 22.6 (CH_2), 14.2 (CH_3), 14.1 (CH_3), 11.6 ppm (CH_3); MS (*m*/*z*) 240 (7) [M^+], 124 (100) [$C_8H_{12}O^+$], 81 (79) [$C_5H_5O^+$], 67 (56) [$C_4H_3O^+$], 55 (57) [$C_3H_3O^+$]; HRMS calcd for $C_{15}H_{29}O_2^+$ 241.2162; found, 241.2160; ee and regioselectivity were determined by chiral GC analysis, column: Chiraldex-B-PM, 40 to 110 °C in 7 min, 110 °C for 90 min; retention times (min): 68.1 (an enantiomer of the 1,4-addition product), 69.0 (other enantiomer of the 1,4-addition product), 75.0 (*S*-**11**), 75.9 (*R*-**11**).

Ester Size Dependency. (*S*,*E*)-methyl 5-methylhept-3-enoate (**14a**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*)-methyl hexa-2,4-dienoate (**13a**) and EtMgBr. Results: [0.5 mmol scale, 64% yield, (The low yield can be explained either by volatility of the products or by a substantial degradation of methyl sorbate under the reaction conditions) 75% ee, 1,6:1,4 = >99:1, colorless oil]. Data: $[\alpha]_D^{20}$ = +14.9 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.55−5.34 (m, 2H), 3.66 (s, 3H), 3.02 (d, *J* = 5.9 Hz, 2H), 2.02 (dt, *J* = 13.5, 6.8 Hz, 1H), 1.28 (p, *J* = 7.3 Hz, 2H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.83 ppm (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ 172.8 (C), 140.6 (CH), 120.0 (CH), 51.8 (CH_3), 38.4 (CH), 38.1 (CH_2), 29.7 (CH_2), 20.0 (CH_2), 11.8 ppm (CH_3); MS (*m*/*z*) 156 (5) [M^+], 85 (100) [$C_4H_5O_2^+$], 82 (80) [$C_5H_6O^+$], 67 (45) [$C_4H_3O^+$], 59 (44) [$C_2H_3O_2^+$], 55 (95) [$C_3H_3O^+$]; HRMS calcd for $C_9H_{16}O_2Na^+$ 179.1043; found, 179.1039; ee was determined by chiral GC analysis for 2-methylbutanoic acid,[26,27] column: Chiraldex-B-PM, 50 to 60 °C in 1 min, 60 °C for 70 min, 60 to 160 °C in 10 min, 160 °C for 4 min, retention times (min): 81.5 (major), 82.0 (minor). Regioselectivity was determined by chiral GC analysis, column: Chiraldex-B-PM, 50 to 60 °C in 1 min, 60 °C for 140 min, retention times (min): 112.6 (1,4-product), 119.6 (**14a**).

(*S*,*E*)-*iso*-propyl 5-methylhept-3-enoate (**14c**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*)-*iso*-propyl hexa-2,4-dienoate (**13c**) and EtMgBr. Results: [0.5 mmol scale, 82% yield, 97% ee, 1,6:1,4 = 99:1, colorless oil]. Data: $[\alpha]_D^{20}$ = +13.7 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.52−5.34 (m, 2H), 5.05−4.93 (m, 1H), 2.96 (d, *J* = 6.6 Hz, 2H), 2.01 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.34−1.15 (m, 8H), 0.95 (dd, *J* = 6.7, 1.6 Hz, 3H), 0.83 ppm (td, *J* = 7.3, 1.4 Hz, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.9 (C), 140.3 (CH), 120.3 (CH), 67.8 (CH), 38.6 (CH_2), 38.5 (CH), 29.7 (CH_2), 21.9 (CH_3), 20.2 (CH_3), 11.8 ppm (CH_3); MS (*m*/*z*) 184 (2) [M^+], 142 (21) [M^+ − *i*Pr+H], 124 (31) [$C_8H_{12}O^+$], 113 (22), 97 (44) [M^+ − CO_2*i*Pr], 82 (52) [$C_6H_{10}^+$], 67 (22) [$C_4H_3O^+$], 55 (100) [$C_3H_3O^+$]; HRMS calcd for $C_{11}H_{20}O_2Na^+$ 207.1356; found, 207.1351; ee was determined by chiral GC analysis for 2-methylbutanoic acid,[26,27] column: Chiraldex-B-PM, 50 to 60 °C in 1 min, 60 °C for 70 min, 60 to 160 °C in 10 min, 160 °C for 4 min; retention times (min): 81.3 (major), 82.1 (minor). Regioselectivity was determined by chiral GC analysis, column: Chiraldex-B-PM, 50 to 60 °C in 1 min, 60 °C for 140 min, 60 to 160 °C in 10 min, retention times (min): 149.0 (1,4-product, minor), 149.1 (1,4-product, major), 149.9 (**14c**).

(*S*,*E*)-*tert*-butyl 5-methylhept-3-enoate (**14d**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*)-*tert*-butyl hexa-2,4-dienoate (**13d**) and EtMgBr. Results: [0.5 mmol scale, 88% yield, 98% ee, 1,6:1,4 = 98:2, colorless oil]. Data: $[\alpha]_D^{20}$ = +15.3 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.56−5.30 (m, 2H), 2.90 (d, *J* = 6.4 Hz, 2H), 2.01 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.43 (s, 9H), 1.37−1.20 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.83 ppm (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.7 (C), 140.0 (CH), 120.7 (CH), 80.4 (C), 39.5 (CH_2),

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38.5 (CH), 29.7 (CH_2), 28.2 (CH_3), 20.2 (CH_3), 11.8 ppm (CH_3); MS (*m*/*z*) 198 (1) [M^+], 142 (15) [$M^+ - t$Bu + H], 97 (17) [M^+-CO_2tBu], 57 (100) [$C_4H_9^+$]; HRMS (APCI+) calcd for $C_{12}H_{22}O_2Na^+$ 221.1512; found, 251.1503; ee was determined by chiral GC analysis for 2-methylbutanoic acid,[26,27] column: Chiraldex-B-PM, 50 to 60 °C in 1 min, 60 °C for 70 min, 60 to 160 °C in 10 min, 160 °C for 4 min, retention times (min): 81.6 (major), 82.1 (minor). Regioselectivity was determined by chiral GC analysis, column: Chiraldex-B-PM, 50 to 60 °C in 1 min, 60 °C for 140 min, 60 to 160 °C in 10 min, 160 °C for 4 min, retention times (min): 150.6 (1,4-product, minor), 150.7 (1,4-product, major), 151.2 (**14d**).

(*S*,*E*)-*tert*-butyl 5-methylundec-3-enoate (**14e**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*)-*tert*-butyl hexa-2,4-dienoate (**13d**) and hexylMgBr. Results: [0.5 mmol, 72% yield, 98% ee, 1,6:1,4 = 98:2, colorless oil]. Data: $[\alpha]_D^{20}$ = +9.6 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.50−5.33 (m, 2H), 2.91 (d, *J* = 6.1 Hz, 2H), 2.15−2.04 (m, 1H), 1.44 (s, 9H), 1.32−1.19 (m, 10H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.87 ppm (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.8 (C), 140.4 (CH), 120.5 (CH), 80.4 (C), 39.6 (CH_2), 37.1 (CH_2), 36.8 (CH), 32.0 (CH_2), 29.6 (CH_2), 28.2 (CH_3), 27.4 (CH_2), 22.8 (CH_2), 20.7 (CH_3), 14.3 ppm (CH_3); MS (*m*/*z*) 254 (1) [M^+], 128 (30) [$C_7H_{12}O_2^+$], 57 (100) [$C_4H_9^+$]; HRMS calcd for $C_{16}H_{31}O_2^+$ 255.2318; found, 255.2318. Regio- and enantioselectivity were determined by conversion into the ethyl ester[28] and subsequent chiral GC analysis, column: Chiraldex-B-PM, 80 °C, retention times (min): 118.4 (1,4-product, minor), 122.4 (1,4-product, major), 132.6 (**14e**, major), 139.3 (**14e**, minor).

(*S*,*E*)-*tert*-butyl 5,8-dimethylnon-3-enoate (**14f**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*)-*tert*-butyl hexa-2,4-dienoate (**13d**) and *iso*-pentylMgBr. Results: [0.5 mmol, 77% yield, 99% ee, 1,6:1,4 = 99:1, colorless oil]. Data: $[\alpha]_D^{20}$ = +7.0 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.52−5.32 (m, 2H), 2.91 (d, *J* = 6.0 Hz, 2H), 2.14−1.99 (m, 1H), 1.56−1.39 (m, 10H), 1.25 (dd, *J* = 12.6, 7.1 Hz, 2H), 1.19−1.07 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.85 ppm (dd, *J* = 6.6, 0.6 Hz, 6H); ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.8 (C), 140.4 (CH), 120.5 (CH), 80.4 (C), 39.6 (CH_2), 37.1 (CH), 36.7 (CH_2), 34.8 (CH_2), 28.3 (CH), 28.2 (CH_3), 22.9 (CH_3), 22.8 (CH_3), 20.7 ppm (CH_3); MS (*m*/*z*) 240 (1) [M^+], 128 (35) [$C_7H_{12}O_2^+$], 57 (100) [$C_4H_9^+$]; HRMS calcd for $C_{15}H_{29}O_2^+$ 241.2162; found, 241.2162. Regio- and enantioselectivity were determined by conversion into the ethyl ester[28] and subsequent chiral GC analysis, column: Chiraldex-B-PM, 90 °C, retention times (min): 117.6 (1,4-product, minor), 123.5 (1,4-product, major), 131.5 (**14f**, major), 139.8 (**14f**, minor).

(*S*,*E*)-*tert*-butyl 5-methyl-7-phenylhept-3-enoate (**14g**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*)-*tert*-butyl hexa-2,4-dienoate (**13d**) and phenethylMgBr; reaction time: 48 h. Results: [47% conversion, 30% yield, 88% ee, 1,6:1,4 = 93:7, colorless oil]. Data: $[\alpha]_D^{20}$ = +6.3 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.31−7.13 (m, 5H), 5.58−5.41 (m, 2H), 2.97 (d, *J* = 6.6 Hz, 2H), 2.63−2.53 (m, 2H), 2.24−2.14 (m, 1H), 1.67−1.58 (m, 2H), 1.47 (s, 9H), 1.04 ppm (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.7 (C), 142.9 (C), 139.8 (CH), 128.5 (CH), 128.4 (CH), 125.7 (CH), 121.3 (CH), 80.5 (C), 39.6 (CH_2), 38.8 (CH_2), 36.5 (CH), 33.7 (CH_2), 28.2 (CH_3), 20.8 ppm (CH_3); MS (*m*/*z*) 274 (1) [M^+], 218 (32) [$M^+ - t$Bu+H], 131 (43) [$C_{10}H_{11}^+$], 104 (33) [$C_8H_8^+$], 191 (51) [$C_7H_7^+$], 57 (100) [$C_4H_9^+$]; HRMS calcd for $C_{18}H_{26}O_2Na^+$ 297.1825; found, 297.1827; ee was determined by chiral HPLC analysis, column: (*R*,*R*)-Whelk-01, (99.9:0.1 heptane:*i*PrOH); retention times (min): 17.3 (major peak, 1,4-addition product), 16.8 (minor peak, 1,4-addition product), 19.1 (*S*-**14g**), 19.1 (*R*-**14g**).

Michael Acceptor Dependency. *E*-2-(4-ethyloct-2-enylsulfonyl)pyridine (**16d**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 2-([1*E*,3*E*]-octa-1,3-dienylsulfonyl)pyridine (**15d**) and EtMgBr; upon addition of the substrate the solution turns bright red, upon quenching the solution becomes orange. Results: [0.25 mmol scale, 26% yield, 2% ee, 1,6:1,4 = 98:2, colorless oil]. Data: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.81−8.73 (m, 1H), 8.04 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.92 (td, *J* = 7.7, 1.7 Hz, 1H), 7.52 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 5.31 (dd, *J* = 5.1, 2.1 Hz, 2H), 4.11 (dd, *J* = 4.1, 2.0 Hz, 2H), 1.83−1.69 (m, 1H), 1.33−0.89 (m, 8H), 0.81 (t, *J* = 7.3 Hz, 3H), 0.63 ppm (t, *J* = 7.4 Hz, 3H); GCOSY ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): Coupling between the NMR signals at δ = 5.31 and 4.11 ppm indicate 1,6-addition product; ee and regioselectivity were determined by chiral HPLC analysis, column: chiralcel OD-H, (98:2 heptane/*i*PrOH); retention times (min): 33.0 (1,4-addition product), 34.3 (1,4-addition product), 37.2 (**16d**), 39.4 (**16d**).

E-3-(5-methylhept-3-enoyl)oxazolidin-2-one (**16e**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using 3-(2*E*,4*E*)-hexa-2,4-dienoyloxazolidin-2-one (**15e**) and EtMgBr. Results: [0.25 mmol scale, 64% yield, 3% ee for 1,6-product, 1,6:1,4 = 75:25, colorless oil]. Data: $[\alpha]_D^{20}$ = +0.9 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.62−5.41 (m, 2H), 4.45−4.34 (m, 3H), 4.07−3.94 (m, 3H), 3.64 (d, *J* = 5.8 Hz, 2H), 2.04 (dt, *J* = 13.5, 6.8 Hz, 1H), 1.37−1.22 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.84 ppm (t, *J* = 7.4 Hz, 3H). Residual absorptions 1,4-addition product: δ = 5.40−5.20 (m, 2H), 4.45−4.34 (m, 3H), 4.07−3.94 (m, 3H), 3.70 (dt, *J* = 7.0, 1.7 Hz, 1H), 2.93 (qd, *J* = 15.7, 7.1 Hz, 2H), 2.50−2.41 (m, 1H), 1.63 ppm (dd, *J* = 6.3, 1.5 Hz, 2H); GCOSY ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): Coupling between the NMR signals at δ = 5.30 and 3.64 ppm indicate 1,6-addition product; ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.2 (C), 153.6 (C), 141.2 (CH), 119.4 (CH), 62.2 (CH_2), 42.7 (CH_2), 38.9 (CH_2), 38.5 (CH), 29.7 (CH_2), 20.1 (CH_3), 11.8 ppm (CH_3); MS (*m*/*z*) 211 (8) [M^+], 182 (35) [M^+ − Et], 96 (36) [$C_6H_8O^+$], 95 (100) [$C_6H_7O^+$], 55 (24) [$C_3H_3O^+$]; HRMS calcd for $C_{11}H_{17}NO_3Na^+$ 234.1101; found, 234.1097; regioselectivity was determined by ^{1}H NMR with d1= 10 s; ee was determined by chiral GC analysis for 2-methylbutanoic acid,[26,27] column: Chiraldex-B-PM, 50 to 60 °C in 1 min, 60 °C for 70 min, 60 to 160 °C in 10 min, 160 °C for 4 min; retention times (min): 81.6 (major), 82.0 (minor).

E-1-(1-methyl-1H-imidazol-2-yl)-3-phenethylhex-4-en-1-one (**17f**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*)-1-(1-methyl-1H-imidazol-2-yl)hexa-2,4-dien-1-one (**15f**) and phenethylMgBr. Results: [0.5 mmol scale, 98% conversion, 34% yield, 2% ee, 1,6:1,4 = <5:95, colorless oil]. Data: $[\alpha]_D^{20}$ = +0.5 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.34−7.13 (m, 5H), 7.11 (s, 1H), 6.98 (s, 1H), 5.47 (dq, *J* = 15.2, 6.2 Hz, 1H), 5.34 (ddd, *J* = 15.2, 8.4, 1.4 Hz, 1H), 3.95 (s, 3H), 3.16 (ddd, *J* = 21.8, 15.8, 7.1 Hz, 2H), 2.77 (dt, *J* = 8.5, 5.5 Hz, 1H), 2.62 (dddd, *J* = 19.9, 13.8, 10.7, 5.7 Hz, 2H), 1.83−1.72 (m, 1H), 1.70−1.58 (m, 1H), 1.70−1.58 ppm (m, 2H). Residual

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absorptions phenethyl alcohol: δ = 7.34−7.13 (m, 5H), 3.85 (t, J = 6.7 Hz, 2H), 2.87 ppm (t, J = 6.7 Hz, 2H); GCOSY ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): Coupling between the NMR signals at δ = 3.85 and 1.65 ppm and the coupling between the NMR signals at δ = 3.16 and 2.77 ppm indicate 1,4-addition product; ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 192.3 (C), 142.7 (C), 134.0 (CH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 126.9 (C), 125.8 (CH), 125.7 (CH), 44.7 (CH_2), 38.8 (CH_3), 37.1 (CH_2), 36.2 (CH), 33.6 (CH_2), 18.0 ppm (CH_3). Residual absorptions phenethyl alcohol: δ = 138.65 (C), 128.9 (CH), 128.3 (CH), 126.5 (CH), 63.7 (CH_2), 39.3 ppm (CH_2); MS (m/z) 282 (1) [M^+], 254 (52) [M^+-MeCH], 191 (61) [M^+-Bn], 163 (69) [M^+-MeCH-Bn], 150 (58) [$C_9H_{11}N_2O^+$], 149 (62) [$C_9H_{10}N_2O^+$], 109 (93) [$C_5H_5N_2O$], 91 (100) [Bn^+], 83 (60) [$C_5H_7O^+$], 82 (81) [$C_5H_6O^+$]; HRMS calcd. for $C_{18}H_{23}N_2O^+$ 283.1805, found 283.1805; regioselectivity was determined by ^{1}H NMR with d1= 10 s; ee was determined by chiral HPLC analysis, column: chiralcel OJ-H, (95:5 heptane:*i*PrOH); retention times (min): 17.0 (minor), 18.4 (major).

(*S*,*E*)-*S*-ethyl 5-methylnon-3-enethioate (**16i**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*)-*S*-ethyl nona-2,4-dienethioate (**15b**) and MeMgBr. Results: [0.5 mmol scale, 83% yield, 89% ee, 1,6:1,4 = 99:1, colorless oil]. Data: $[\alpha]_D^{20}$ = +9.0 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.50−5.39 (m, 2H), 3.19 (d, J = 5.7 Hz, 2H), 2.84 (q, J = 7.4 Hz, 2H), 2.18−2.04 (m, 1H), 1.31−1.16 (m, 9H), 0.96 (d, J = 6.7 Hz, 3H), 0.86 ppm (t, J = 6.7 Hz, 3H); ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 198.7 (C), 142.6 (CH), 119.6 (CH), 47.9 (CH_2), 36.9 (CH), 36.7 (CH_2), 29.7 (CH_2), 23.5 (CH_2), 23.0 (CH_2), 20.6 (CH_3), 14.9 (CH_3), 14.3 ppm (CH_3); MS (m/z) 214 (10) [M^+], 124 (34) [M^+-SEt-Et], 83 (46) [$C_6H_{11}^+$], 69 (100) [$C_5H_9^+$]; HRMS calcd for $C_{12}H_{22}OS^+$ 214.1391; found, 214.1401; ee and regioselectivity were determined by chiral GC analysis, column: Chiraldex-B-PM, 50 to 98 °C in 4.8 min, 98 °C for 200 min; retention times (min): 163.8 (an enantiomer of the 1,4-addition product), 191.1 (*R*-**16i**), 192.3 (*S*-**16i**).

Influence of the Olefin Substitution Pattern. (5*R*,*E*)-ethyl 5-ethyl-2-methylnon-3-enoate (**26a**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*)-ethyl 2-methylnona-2,4-dienoate (**25a**) and EtMgBr. Results: [0.5 mmol scale, 94% conversion, 83% yield, 1:1 mixture of *cis* and *trans* diastereomers, 97% ee, 1,6:1,4 = >99:1, colorless oil]. Data: $[\alpha]_D^{20}$ = +2.9 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.42 (dd, J = 15.3, 7.8 Hz, 1H), 5.23 (dd, J = 15.3, 8.8 Hz, 1H), 4.23−3.99 (m, 2H), 3.22−2.89 (m, 1H), 1.88−1.72 (m, 1H), 1.53−1.02 (m, 13H), 0.99−0.64 ppm (m, 6H); ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 175.3 (C), 136.6 (CH), 129.0 (CH), 60.5 (CH_2), 44.5 (CH), 43.1 (CH), 34.8 (first diastereomer CH_2), 34.7 (second diastereomer CH_2), 29.6 (CH_2), 28.1 (CH_2), 22.9 (CH_2), 17.7 (CH_3), 14.3 (CH_3), 14.2 (CH_3), 11.8 ppm (CH_3); MS (m/z) first diastereomer: 226 (10) [M^+], 102 (100) [$C_5H_{10}O_2^+$], 95 (44) [$C_6H_7O^+$], 69 (47) [$C_5H_9^+$], 55 (69) [$C_3H_3O^+$], second diastereomer: 226 (10) [M^+], 102 (100) [$C_5H_{10}O_2^+$], 95 (45) [$C_6H_7O^+$], 69 (47) [$C_5H_9^+$], 55 (70) [$C_3H_3O^+$]; HRMS calcd for $C_{14}H_{26}O_2Na^+$ 249.1825; found, 249.1822; ee and regioselectivity were determined by chiral GC analysis, column: Chiraldex-B-PM, 50 to 110 °C in 6 min, 110 °C for 90 min; retention times (min): 38.4 (an enantiomer of the 1,4-addition product), 51.3 (major enantiomer of the first 1,6-addition diastereomer), 52.0 (minor enantiomer of the first 1,6-addition diastereomer)), 52.9 (minor enantiomer of the second 1,6-addition diastereomer), 54.1 (major enantiomer of the second 1,6-addition diastereomer)).

A mixture of 27% *Z*-ethyl 4,5-dimethylhept-3-enoate (*Z*-**26c**) and 73% *E*-ethyl 4,5-dimethylhept-3-enoate (*E*-**26c**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*)-ethyl 4-methylnona-2,4-dienoate (**25c**) and EtMgBr; reaction time 40 h, reaction temperature −60 °C. Results: [0.5 mmol scale, 94% conversion, 59% yield, 0% ee, > 92% 1,6-addition product, colorless oil]. Data: $[\alpha]_D^{20}$ = +1.3 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.38−5.28 (m, 1H), 4.12 (qd, J = 7.1, 1.6 Hz, 2H), 3.09−2.98 (m, 2H), 2.45 (*E*-**26c**, dt, J = 13.9, 7.0 Hz, 1H), 2.03 (*Z*-**26c**, dd, J = 14.1, 7.0 Hz, 1H), 1.60 (*E*-**26c**, d, J = 1.3 Hz, 3H), 1.52 (*Z*-**26c**, s, 5H), 1.49 (**27c**, s, 1H), 1.38−1.27 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 0.96 (*E*-**26c**, t, J = 7.3 Hz, 3H), 0.87 (*Z*-**26c**, t, J = 7.0 Hz, 3H), 0.79 ppm (td, J = 7.4, 1.6 Hz, 3H); GCOSY ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): Coupling of the overlapping NMR signals for both the *E*- and *Z*-product at δ = 5.38−5.28 and 3.09−2.98 ppm indicate *Z*- and *E*-1,6-addition product;^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.64 (C), 143.0 (C), 116.4 (*E*-**26c**, CH), 115.4 (*Z*-**26c**, CH), 60.6 (*E*-**26c**, CH_2), 60.5 (*Z*-**26c**, CH_2), 44.5 (*Z*-**26c**, CH), 36.2 (*E*-**26c**, CH), 33.8 (*Z*-**26c**, CH_2), 33.3 (*E*-**26c**, CH_2), 27.8 (*Z*-**26c**, CH_2), 27.6 (*E*-**26c**, CH_2), 19.3 (*Z*-**26c**, CH_3), 18.9 (*E*-**26c**, CH_3), 18.0 (*Z*-**26c**, CH_3), 14.3 (*E*-**26c**, CH_3), 12.3 (*E*-**26c**, CH_3), 12.1 ppm (*Z*-**26c**, CH_3); MS (m/z) 184 (27) [M^+], 110 (40) [$C_7H_{10}O^+$], 97 (43) [$C_5H_5O_2^+$], 96 (68) [$C_6H_8O^+$], 81 (47) [$C_5H_5O^+$], 69 (93) [$C_5H_9^+$], 55 (100) [$C_3H_3O^+$]; HRMS calcd for $C_{11}H_{21}O_2^+$ 185.1536; found, 185.1535; Ratio *E*- and *Z*-product was determined by ^{1}H NMR with d1= 10 s; ee and regioselectivity were determined by chiral GC analysis, column: Chiraldex-B-PM, 50 to 110 °C in 6 min, 110 °C for 90 min; retention times (min): 84.2 (an enantiomer of *E*-**26c**), 95.1 (an enantiomer of *E*-**26c**), 100.1 (an enantiomer of *Z*-**26c**) 102.4 (an enantiomer of *Z*-**26c**).

Olefin Geometry Dependency. *E*-Ethyl 5-ethylundec-3-enoate (**11**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using EtMgBr and (2*E*,4*E*)-ethyl undeca-2,4-dienoate (**10**), or EtMgBr and (2*E*,4*Z*)-ethyl undeca-2,4-dienoate (**28a**), or EtMgBr and (2*Z*,4*E*)-ethyl undeca-2,4-dienoate (**28b**), or EtMgBr and (2*Z*,4*Z*)-ethyl undeca-2,4-dienoate (**28c**) (including 8% ((2*Z*,4*E*)-ethyl undeca-2,4-dienoate). Results: [Using the (2*E*,4*E*)-enantiomer, 0.25 mmol scale, 77% yield, full conversion, 96% ee (*R*-enantiomer), 1,6:1,4 = 99:1]; [Using the (2*E*,4*Z*)-enantiomer, 0.25 mmol scale, full conversion, 96% ee (*S*-enantiomer), 1,6:1,4 = 98:2]; [Using the (2*Z*,4*E*)-enantiomer, 0.25 mmol scale, full conversion, 12% ee (*S*-enantiomer), 1,6:1,4 = 94:6]; [Using the (2*Z*,4*Z*)-enantiomer, 0.25 mmol scale, full conversion, 66% ee (*R*-enantiomer), 1,6:1,4 = 99:1]. Data: see Halide dependency section.

Isomerization study: To observe possible isomerization under reaction conditions the general procedure for the enantioselective 1,6-conjugate addition using EtMgBr and (2*E*,4*E*)-ethyl undeca-2,4-dienoate (**10**), or EtMgBr and (2*E*,4*Z*)-ethyl undeca-2,4-dienoate (**28a**), or EtMgBr and (2*Z*,4*E*)-ethyl undeca-2,4-dienoate (**28b**), or EtMgBr and (2*Z*,4*Z*)-ethyl undeca-2,4-dienoate (**28c**) was followed. Before completion (after 2 h addition and an additional 10 min-1 h stirring) the reaction mixture was quenched at −70 °C using EtOH (0.2 mL/mmol substrate) and an aq. NH_4Cl-solution (1 M, 1.0 mL/mmol substrate). The olefin geometry was established using ^{1}H NMR,

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GC (column: Chiraldex-B-PM, 40 to 110 °C in 7 min, 110 °C for 90 min; retention times (min): 2*E*,4*E* = 65.4; 2*Z*,4*E* = 72.1; 2*E*,4*Z* = 75.1; 2*Z*,4*Z* = 83.2, and GC-MS. Results: [Using the (2*E*,4*E*)-enantiomer, 0.25 mmol scale, 95% conversion, 96% ee (*R*-enantiomer), 1,6:1,4 = 99:1, no isomerization of the starting material]; [Using the (2*E*,4*Z*)-enantiomer, 0.20 mmol scale, 26% conversion, ee not determined (overlap of GC peaks with starting material), 1,6:1,4 = 98:2, no isomerization of the starting material]; [Using the (2*Z*,4*E*)-enantiomer, 0.20 mmol scale, 40% conversion, 19% ee (*S*-enantiomer), 1,6:1,4 = 99:1, no isomerization of the starting material]; [Using the (2*Z*,4*Z*)-enantiomer, 0.25 mmol scale, 55% conversion, 60% ee (*R*-enantiomer), 1,6:1,4 = 99:1, no isomerization of the starting material]

Enantioselective 1,8- and 1,10-Addition. (*R*,3*E*,5*E*)-ethyl 7-ethylundeca-3,5-dienoate (**30a**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*,6*E*)-ethyl undeca-2,4,6-trienoate (**29a**) and EtMgBr, 48 h reaction time. Results: [0.5 mmol scale, 47% yield (combined yield 1,8-, 1,6- and 1,4-addition products), 7% ee, 1,8:1,6:1,4 = 63:8:29, colorless oil]. Data: $[\alpha]_D^{20}$ = +1.5 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.10 (dd, *J* = 15.1, 10.3 Hz, 1H), 6.02−5.94 (m, 1H), 5.63 (dt, *J* = 22.5, 7.3 Hz, 1H), 5.38 (dd, *J* = 14.8, 8.9 Hz, 1H), 4.20−4.05 (m, 3H), 3.08 (dd, *J* = 7.2, 1.0 Hz, 2H), 1.92−1.80 (m, 1H), 1.48−1.12 (m, 11H), 0.91−0.78 ppm (m, 6H). Residual absorptions side-products: δ = 3.24−3.19 (1,6-add. product, m, 2H), 2.43 (1,6-add. product, dd, *J* = 8.3, 5.4 Hz, 1H), 2.30 (**31a**, ddd, *J* = 22.7, 14.5, 7.2 Hz, 2H), 2.04 ppm (**31a**, q, *J* = 7.0 Hz, 1H); GCOSY ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): Coupling between the NMR signals at δ = 2.25 and 2.05 ppm and the coupling between the NMR signals at δ = 5.58 and 2.05 ppm indicate 1,4-addition product, Coupling between the NMR signals at δ = 5.63 and 3.08 ppm and the coupling between the NMR signals at δ = 5.39 and 1.85 ppm indicate 1,8-addition product; ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.0 (C), 139.5 (CH), 134.2 (CH), 129.5 (CH), 122.4 (CH), 60.8 (CH_2), 44.7 (CH), 38.3 (CH_2), 34.8 (CH_2), 29.7 (CH_2), 28.2 (CH_2), 23.0 (CH_2), 14.3 (CH_3), 14.2 (CH_3), 11.9 ppm (CH_3); Residual absorptions side-product **31a**: δ = 172.8 (C), 133.8 (CH), 133.6 (CH), 131.2 (CH), 130.2 (CH), 60.3 (CH_2), 41.2 (CH), 40.3 (CH_2), 32.4 (CH_2), 31.6 (CH_2), 27.9 (CH_2), 22.4 (CH_2), 14.4 (CH_3), 14.1 (CH_3), 11.7 ppm (CH_3); MS (*m*/*z*) 238 (25) [M^+], 135 (68) [$C_9H_{11}O^+$], 121 (48) [$C_8H_9O^+$], 107 (100) [$C_7H_7O^+$], 93 (85) [$C_7H_9^+$], 79 (91) [$C_6H_7^+$], 67 (64) [$C_4H_3O^+$]; HRMS calcd for $C_{15}H_{26}O_2Na^+$ 261.1825; found, 261.1820; Regioselectivity was determined by ^{1}H NMR with d1=10 s; ee was determined by chiral GC analysis for 2-ethylhexanoic acid,[27] column: Chiraldex-B-PM, 50 to 120 °C in 7 min, 120 °C for 70 min; retention times (min): 41.2 (major), 43.2 (minor).

(*R*,3*E*,5*E*)-*S*-ethyl 7-methylundeca-3,5-dienethioate (**30b**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*,6*E*)-*S*-ethyl undeca-2,4,6-trienethioate (**29b**) and MeMgBr, 48 h reaction time, 7.5% catalyst. Results: [0.5 mmol scale, 91% conversion, 63% yield (combined yield 1,8- and 1,4- product), 72% ee, 1,8:1,6:1,4 = 86:0:14, colorless oil]. Data: $[\alpha]_D^{20}$ = −13.4 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.13 (dd, *J* = 15.0, 10.4 Hz, 1H), 5.99 (dd, *J* = 15.2, 10.3 Hz, 1H), 5.69−5.52 (m, 2H), 3.28 (dd, *J* = 7.3, 0.9 Hz, 2H), 2.87 (q, *J* = 7.4 Hz, 2H), 2.19−2.08 (m, 1H), 1.36−1.18 (m, 9H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.91−0.84 ppm (m, 3H); Residual absorptions **31b**: δ = 2.80−2.71 (m, 1H), 2.52 (ddd, *J* = 22.1, 14.5, 7.2 Hz, 2H), 2.08−2.01 (m, 1H), 1.05 ppm (d, *J* = 6.7 Hz, 3H); GCOSY ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): Coupling between the NMR signals at δ = 2.75 and 2.53 ppm and the coupling between the NMR signals at δ = 5.48 and 2.75 ppm indicate 1,4-addition product, coupling between the NMR signals at δ = 5.60 and 3.27 ppm and the coupling between the NMR signals at δ = 5.56 and 2.12 ppm indicate 1,8-addition product; ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 198.0 (C), 141.6 (CH), 135.5 (CH), 127.7 (CH), 122.0 (CH), 47.7 (CH_2), 36.9 (CH), 36.8 (CH_2), 29.7 (CH_2), 23.5 (CH_2), 23.0 (CH_2), 20.6 (CH_3), 14.8 (CH_3), 14.2 ppm (CH_3); Residual absorptions side-product **31b**: δ = 135.1 (CH), 133.9 (CH), 130.1 (CH), 129.7 (CH), 51.1 (CH_2), 34.3 (CH), 32.4 (CH_2), 31.6 (CH_2), 23.5 (CH_2), 22.4 (CH_2), 20.0 (CH_3), 14.9 (CH_3), 14.1 ppm (CH_3); MS (*m*/*z*) 240 (11) [M^+], 95 (64) [$C_6H_7O^+$], 81 (69) [$C_5H_5O^+$], 79 (39) [$C_6H_7^+$], 67 (100) [$C_4H_3O^+$]; HRMS calcd for $C_{14}H_{25}OS^+$ 241.1621; found, 214.1621; Regioselectivity was determined by ^{1}H NMR with d1=10 s; ee was determined by chiral GC analysis for 2-methylhexanoic acid,[27] column: Chiraldex-B-PM, 50 to 130 °C in 8 min, 130 °C for 70 min; retention times (min): 22.6 (minor), 23.8 (major).

(*R*,3*E*,5*E*,7*E*)-ethyl 9-ethyltrideca-3,5,7-trienoate (**30c**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*,6*E*,8*E*)-ethyl trideca-2,4,6,8-tetraenoate (**29c**) and EtMgBr, 48 h reaction time. Results: [0.5 mmol scale, 85% conversion, 22% yield (combined yield 1,10-, 1,8-/1,6- and 1,4-addition products), 1,10-product 12% ee, 1,10:1,8/1,6:1,4 = 49:8:43, colorless oil]. Data: $[\alpha]_D^{20}$ = +1.4 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.24−5.94 (m, 4H), 5.69 (qd, *J* = 14.0, 6.7 Hz, 1H), 5.44 (dd, *J* = 15.0, 9.0 Hz, 1H), 4.20−4.05 (m, 2H), 3.11 (d, *J* = 7.2 Hz, 2H), 1.96−1.83 (m, 1H), 1.52−1.12 (m, 11H), 0.96−0.77 ppm (m, 6H). Residual absorptions side-products: δ = 3.22 (1,6- or 1,8-addition, dd, *J* = 7.5, 1.6 Hz, 2H), 2.54−2.43 (**31c**, m, 1H), 2.43−2.22 (**31c**, m, 2H), 2.08 ppm (**31c**, q, *J* = 6.8 Hz, 2H); GCOSY ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): Coupling between the NMR signals at δ = 2.52 and 2.30 ppm and the coupling between the NMR signals at δ = 5.43 and 2.52 ppm indicate 1,4-addition product, Coupling between the NMR signals at δ = 5.55 and 3.21 ppm indicate either 1,6- or 1,8-addition product, Coupling between the NMR signals at δ = 5.44 and 1.80 ppm and the coupling between the NMR signals at δ = 5.77 and 3.10 ppm indicate 1,10-addition product; ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.6 (C), 140.4 (CH), 133.9 (CH), 133.0 (CH), 130.0 (CH), 129.5 (CH), 124.1 (CH), 60.7 (CH_2), 44.8 (CH), 38.3 (CH_2), 34.7 (CH_2), 29.5 (CH_2), 28.1 (CH_2), 22.8 (CH_2), 14.2 (CH_3), 14.1 (CH_3), 11.7 ppm (CH_3); Residual absorptions side-product **31c**: δ = 172.5 (C), 135.7 (CH), 135.0 (CH), 131.8 (CH), 131.1 (CH), 130.3 (CH), 130.3 (CH), 60.2 (CH_2), 41.2 (CH), 40.1 (CH_2), 32.5 (CH_2), 31.5 (CH_2), 27.7 (CH_2), 22.2 (CH_2), 14.3 (CH_3), 13.9 (CH_3), 11.5 ppm (CH_3); MS (*m*/*z*) 264 (40) [M^+], 133 (82) [$C_{10}H_{13}^+$], 119 (77) [$C_9H_{11}^+$], 105 (67) [$C_8H_9^+$], 93 (50) [$C_7H_9^+$], 91 (100) [$C_7H_7^+$]; HRMS calcd for $C_{17}H_{29}O_2^+$ 265.2162; found, 265.2163; ee was determined by chiral GC analysis for 2-ethylhexanoic acid,[27] column: Chiraldex-B-PM, 50 to 120 °C in 7 min, 120 °C for 70 min; retention times (min): 42.0 (major), 44.0 (minor).

(*R*,3*E*,5*E*,7*E*)-*S*-ethyl 9-methyltrideca-3,5,7-trienethioate (**30d**) was prepared via the general procedure for the enantioselective 1,6-conjugate addition using (2*E*,4*E*,6*E*,8*E*)-*S*-ethyl trideca-2,4,6,8-tetraenethioate (**29d**) and MeMgBr, 48 h reaction time, 10% catalyst. Results: [0.5 mmol scale, 82%

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conversion, 44% yield (combined yield 1,10- and 1,4-addition products), 1,10-product 45% ee, 1,10:1,8/1,6:1,4 = 59:0:41, colorless oil]. Data: $[\alpha]_D^{20} = -13.4$ (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.23−5.96 (m, 4H), 5.76−5.51 (m, 2H), 3.30 (d, J = 7.3 Hz, 1H), 2.91−2.82 (m, 2H), 2.21−2.12 (m, 1H), 1.41−1.17 (m, 9H), 0.99 (d, J = 6.7 Hz, 3H), 0.93−0.84 ppm (m, 3H), Residual absorptions **31d**: δ = 2.82−2.74 (m, 1H), 2.53 (ddd, J = 36.9, 14.5, 7.2 Hz, 2H), 2.12−2.04 (m, 2H), 1.06 (d, J = 6.7 Hz, 1H); GCOSY ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): Coupling between the NMR signals at δ = 2.78 and 2.52 ppm and the coupling between the NMR signals at δ = 5.54 and 2.78 ppm indicate 1,4-addition product, coupling between the NMR signals at δ = 5.61 and 2.16 ppm and the coupling between the NMR signals at δ = 5.65 and 3.30 ppm indicate 1,10-addition product; ^{13}C NMR (100.59 MHz, $CDCl_3$, 25 °C, TMS): δ = 197.7 (C), 142.1 (CH), 135.2 (CH), 133.6 (CH), 129.5 (CH), 128.3 (CH), 123.4 (CH), 47.7 (CH_2), 36.9 (CH), 36.7 (CH_2), 29.5 (CH_2), 23.4 (CH_2), 22.8 (CH_2), 19.9 (CH_3), 14.6 (CH_3), 14.1 ppm (CH_3); Residual absorptions side-product **31d**: δ = 198.3 (C), 136.8 (CH), 135.1 (CH), 132.0 (CH), 130.3 (CH), 130.2 (CH), 129.6 (CH), 50.9 (CH_2), 34.3 (CH), 32.5 (CH_2), 31.4 (CH_2), 23.3 (CH_2), 22.2 (CH_2), 20.5 (CH_3), 14.8 (CH_3), 13.9 ppm (CH_3); Residual absorption: δ = 22.3 ppm; MS (m/z) 266 (22) [M^+], 93 (100) [$C_7H_9^+$], 91 (53) [$C_7H_7^+$], 79 (44) [$C_6H_7^+$], 77 (33) [$C_6H_5^+$]; HRMS calcd for $C_{16}H_{27}OS^+$ 267.1777; found, 267.1779; Regioselectivity was determined by ^{1}H NMR with d1=10 s; ee was determined by chiral GC analysis for 2-methylhexanoic acid,[27] column: Chiraldex-B-PM, 50 to 130 °C in 8 min, 130 °C for 70 min; retention times (min): 22.6 (minor), 23.8 (major).

■ ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs501297s.

Footnotes, experimental protocols for the synthesis of substrates, and spectral data (PDF)

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Notes

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