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Catalytic Enantioselective 1,6-Conjugate Addition of Grignard Reagents to Linear Dienoates**

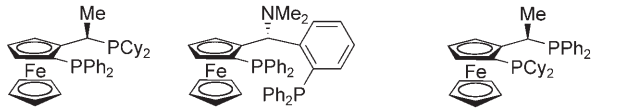
Tim den Hartog, Syuzanna R. Harutyunyan, Daniel Font, Adriaan J. Minnaard, and Ben L. Feringa**

Dedicated to Prof. Dr. Hans Wynberg on the occasion of his 85th birthday.

Achieving selectivity (chemo- and regio- as well as stereoselectivity) has always been a major challenge in organic synthesis.[1] This is particularly evident for conjugate addition (CA).[2] In asymmetric conjugate addition[3] (ACA), besides high regioselectivity (1,4- vs. 1,2-addition), excellent control of stereoselectivity has been achieved.

Compared to 1,4-ACA, conjugate addition to extended Michael acceptors[4] requires additional control of regioselectivity. For α,β,γ,δ-unsaturated Michael acceptors, tuning of the electron density on the Cu reagent allows regioselective 1,4-[5] or 1,6-addition[6–8] as shown in pioneering work by Yamamoto et al. (for dienoates) and Krause et al. (for enynes). Only modest progress has been made in enantioselective conjugate additions to extended dienones and dienoates.[9] In 2005 Hayashi et al.[10] succeeded in the arylation of selected (β-substituted)[11] dienones in an asymmetric fashion (up to 98% *ee*) employing Rh catalysis. In 2006 Fillion et al.[12] reported the 1,6-ACA of dialkylzinc reagents to Meldrum's acids with good selectivity (up to 84% *ee*). Recently, Jørgensen et al.[13] disclosed the ACA of different nucleophiles (β-ketoesters and glycine imine) to a variety of δ-unsubstituted dienones and dienoates employing an organocatalyst (up to 99% *ee*). In all of these methodologies the excellent regioselectivity is associated with specific structural features of the substrate. Enantioselective conjugate addition to particularly challenging acyclic dienones or dienoates monosubstituted at the β and δ position has not been reported yet. In particular the addition of simple alkyl groups to dienoates is highly warranted owing to the synthetic versatility of the chiral multifunctional building blocks obtained. Herein, we report the first Cu-catalyzed ACA of simple alkyl Grignard reagents to linear δ-substituted 2,4-dienoates.[14]

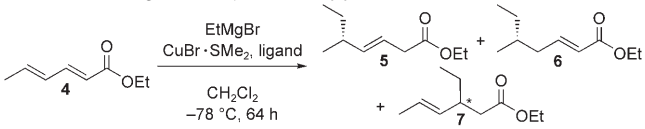
Recently, an extensive study on the mechanism of the 1,4-ACA of Grignard reagents was reported from our laboratory.[15] Noting the proposed mechanistic similarities between the 1,4-ACA and 1,6-CA,[16] we decided to further expand our catalytic system[17] towards 1,6-ACA. As an initial model reaction we chose the addition of EtMgBr to ethyl sorbate (**4**).[18] The reversed josiphos ligand (+)-**3** (Scheme 1, (−)-**3** shown) was employed at −78 °C, and the β,γ-unsaturated 1,6-addition product **5** was obtained with excellent regio- and enantioselectivity (Table 1, entries 4 and 5). Remarkably, only a trace (<2%) of the 1,4-addition product **7** and no 1,2-addition product were detected by GC analysis. Furthermore, we did not obtain any of the α,β-unsaturated 1,6-addition



(*R*,*S*)-(−)-**1**, josiphos (*R*,*S*)-(−)-**2**, taniaphos (*R*,*S*)-(−)-**3**, reversed josiphos

Scheme 1. Chiral ferrocenyl-based phosphines used in ACA of Grignard reagents. Cy = cyclohexyl.

Table 1: Results of initial catalyst screening for the enantioselective 1,6-addition of EtMgBr to ethyl sorbate (**4**).[a]



Entry	Ligand	Conv. [%]	**5**/**7**[b]	*ee* [%][b,c]
1	–	>99	34:66	0
2	(−)-**1**	≈80	–	–
3	(−)-**2**	≈35	–	–
4	(+)-**3**	>99	98:2	95 (*R*)
5[d]	(−)-**3**	>99	99:1	95 (*S*)

[a] Conditions: **4** was added to a solution of EtMgBr (3.0 M in Et_2O, 2.0 equiv), ligand (5.25 mol%), and CuBr·SMe_2 (5 mol%) in CH_2Cl_2 (0.2 M in **4**). [b] The product ratio **5**/**7** and *ee* values were determined by GC on a chiral phase. [c] The absolute configuration of **5** was determined by conversion into a known compound (see the Supporting Information). [d] The reaction was performed at −70 °C for 16 h.

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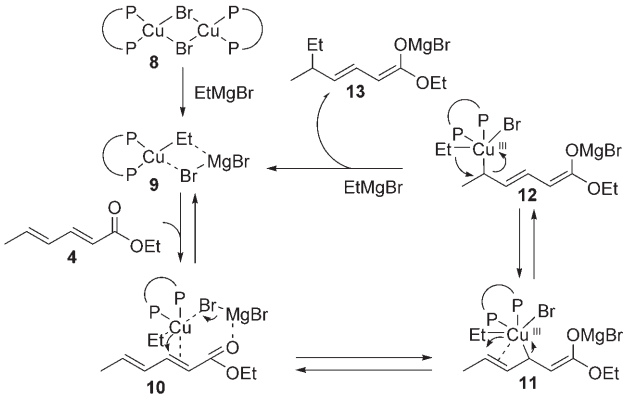
product **6**; in situ quenching of the magnesium bromide dienolate by ethanol gives the kinetic product **5**.

The asymmetric 1,6-addition is remarkably sensitive to the structure of the catalyst. The use of either josiphos (−)-**1** or taniaphos (−)-**2** at −78 °C led to less than 5% yield[19] in 64 h (Table 1, entries 2 and 3). In contrast, the use of a catalytic amount of a simple copper salt at −78 °C led to formation of a mixture of regioisomers with a preference for the 1,4-addition product **7** (Table 1, entry 1).

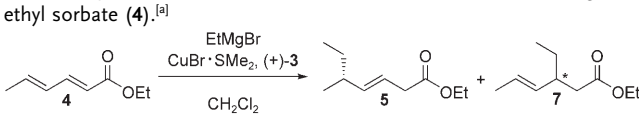
Since the reaction is slow at −78 °C we investigated the influence of the temperature. Increasing the temperature of the reaction mixture up to −60 °C allowed shorter reaction times (4 h) without loss of regio- or stereoselectivity (Table 2, entry 2). However, the use of higher temperatures led to gradual loss of both regio- and stereoselectivity (Table 2, entries 3 and 4). To demonstrate the synthetic potential of this methodology we performed the reaction on a 0.5-g scale with only 2% catalyst; product **5** was obtained in good yield with excellent regio- (99:1) and enantioselectivity (95% *ee*; Table 2, entry 5).

Based on our recent mechanistic studies on CA of Grignard reagents[15] and the mechanism proposed by Krause and Nakamura for 1,6-CA,[16] we propose the catalytic cycle depicted in Scheme 2 for our system. The cycle starts with formation of reactive complex **9** from the dimeric resting state **8** of the catalyst. Presumably, **9** forms a π complex **10** with substrate **4**, followed by formation of the copper(III)[20] σ complex **11**.[21] Next, **11** undergoes sequential copper migration via σ/π-allylcopper(III) complex **12** to the remote position.[22] The catalytic cycle ends by reductive elimination to form product **13** and reformation of complex **9**. Preference for the formation of the 1,6-addition product over the 1,4-product in view of the proposed mechanism can be explained by a lower activation energy for migration of the Cu complex compared to that of alkyl addition at the 4-position, since this addition would disturb the conjugation system.[16b]



Scheme 2. Proposed catalytic cycle for the 1,6-ACA of EtMgBr to ethyl sorbate (**4**).

Table 2: Optimization for the enantioselective 1,6-addition of EtMgBr to ethyl sorbate (**4**).[a]

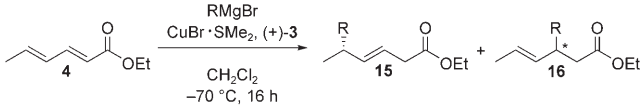


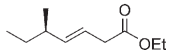
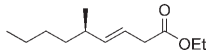
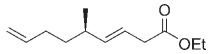
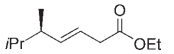
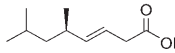
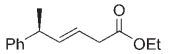
Entry	*T* [°C]	*t* [h]	Conv. [%]	**5**/**7**[b]	*ee* [%][b,c]
1	−78	64	>99	98:2	95 (*R*)
2	−60	4	>99	99:1	95 (*R*)
3	−55	3	>99	98:2	92 (*R*)
4	−40	2.5	>99	77:23	67 (*R*)
5[d]	−70	24	98 (77)[e]	99:1	95 (*R*)

[a] Conditions: **4** was added to a solution of EtMgBr (3.0 M in Et_2O, 2.0 equiv), (+)**3** (5.25 mol%), and CuBr·SMe_2 (5 mol%) in CH_2Cl_2 (0.2 M in **4**). [b] The product ratio **5**/**7** and *ee* values were determined by GC on a chiral phase. [c] The absolute configuration was determined by conversion into known compound (see the Supporting Information). [d] The reaction was performed with 2 mol% CuBr·SMe_2, 2.1 mol% (+)-**3**, and 1.5 equiv EtMgBr. [e] Yield of isolated product.

Following optimization of the reaction conditions and having achieved excellent regio- and enantioselectivity, we examined the scope of 1,6-ACA with respect to addition of different Grignard reagents.[23] Grignard reagents possessing longer alkyl chains (Table 3, entry 2) and a homoallylic Grignard (Table 3, entry 3) also gave excellent enantio- and regioselectivity. Addition of the hindered Grignard *i*PrMgBr yields a respectable stereoselectivity (72% *ee*) (Table 3, entry 4). However, addition of other hindered and aromatic Grignard reagents resulted in very low conversion even at −60 °C in 16 h (Table 3, entries 5 and 6).

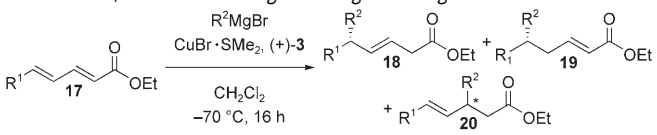
Table 3: Enantioselective 1,6-addition of several Grignard reagents RMgBr to ethyl sorbate (**4**).[a]

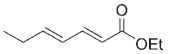
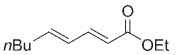
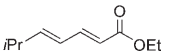
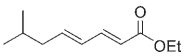
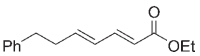
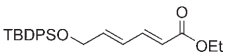
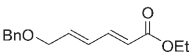


Entry	R		Product	Yield [%]	**15**/**16**[b]	*ee* [%][b,c]
1	Et	**5**		84	98:2	95 (*R*)
2	Bu	**15a**		85	99:1	97 (−)
3	but-3-enyl	**15b**		57	97:3	92 (−)
4	*i*Pr	**15c**		54	99:1	72 (−)
5	*i*Bu	**15d**		<5[d]	–	–
6	Ph	**15e**		<5[d]	–	–

[a] Conditions: **4** was added to a solution of RMgBr (1.5–3.0 M in Et_2O, 2.0 equiv), (+)-**3** (5.25 mol%), and CuBr·SMe_2 (5 mol%) in CH_2Cl_2 (0.2 M in **4**). [b] The product ratio **15**/**16** and *ee* values were determined by GC on a chiral phase. [c] The absolute configuration was determined by conversion into a known compound (see the Supporting Information). [d] Conversion (degradation) was ca. 35%.

Table 4: Enantioselective 1,6-addition of Grignard reagents RMgBr to dienoates **17**.[a]



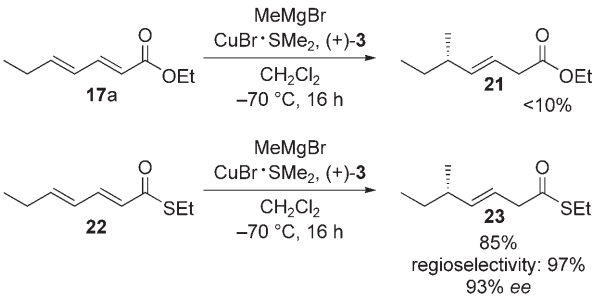
Entry		Substrate	R^2	Product	Yield [%]	**18**/**20**[b]	*ee* [%][b]
1	**17a**		Bu	**18a**	88	99:1	96 (−)
2	**17b**		Et	**18a**	80	99:1	93 (+)
3	**17c**		Et	**18c** + **19c**	82	96:4	79 (−)
4	**17d**		Et	**18d**	77	98:2	93 (+)
5	**17e**		Et	**18e**	73	98:2	90 (+)
6	**17f**		Et	**18f**	82	96:4	73 (−)
7	**17g**		Et	**18g**	69	>95:5[c]	90 (−)

[a] Conditions: **17** was added to a solution of RMgBr (3.0 M in Et_2O, 2.0 equiv), (+)-**3** (5.25 mol%), and CuBr·SMe_2 (5 mol%) in CH_2Cl_2 (0.2 M in **17**). [b] The product ratio **18**/**20** and *ee* values were determined by GC on a chiral phase. [c] Ratio **18g**/**20g** was determined by NMR spectroscopy.

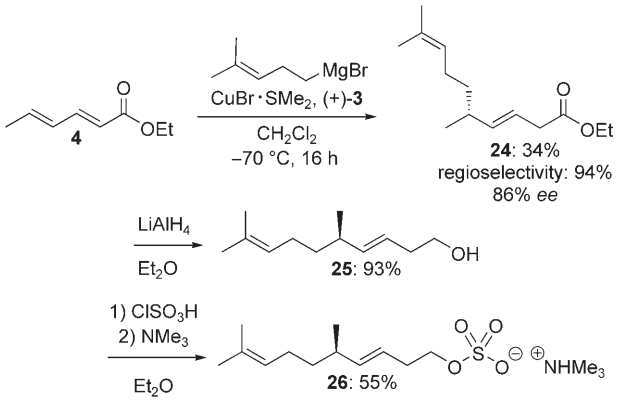
To further examine the scope of the 1,6-ACA with respect to δ substitution in the substrate, we applied our optimized conditions to the reactions of several extended dienoates. Substrates with linear aliphatic chains at the δ position provided similar high levels of selectivity (Table 4, entries 1 and 2). Bulky substituents at the ε position (Table 4, entry 3) caused a drop in regio- and enantioselectivity. In addition to the anticipated β,γ-unsaturated product **18c,** the α,β-unsaturated product **19c** was obtained.[24] Excellent control of regio- and stereoselectivity was also achieved when bulky substituents are separated by an additional CH_2 spacer (Table 4, entry 4). High enantiomeric excess was obtained as well for the substrate functionalized with a phenyl moiety (Table 4, entry 5). However, functionalization by a bulky TBDPS-protected hydroxy group at the ε position caused a drop in regio- and enantioselectivity (Table 4, entry 6). Replacing the TBDPS protectng group by a Bn group provided high regio- and stereocontrol again (Table 4, entry 7).

Since chiral methyl-substituted alkyl chains are abundant in natural products[25] the ACA of MeMgBr comprises particularly important synthetic methodology.[17d,26] In our earlier work we used α,β-unsaturated thioesters to overcome the intrinsically low reactivity of ester substrates to MeMgBr.[27] In this context ester substrate **17a** gave, as expected, a low yield (Scheme 3); however, the use of thioester **22** instead yielded the anticipated product **23** in high yield and excellent regio- and enantioselectivity.

To illustrate the potential of this new method we performed a short total synthesis of the sulfated alkene **26**, which was isolated from the Echinus *Temnopleurus hardwickii*.[28] As shown in Scheme 4 this synthesis features a 0.5-g scale asymmetric 1,6-addition of a functionalized Grignard reagent to ethyl sorbate with high enantioselectivity, followed by $LiAlH_4$ reduction of the ester and sulfation of the alcohol to obtain **26** in good yield and stereoselectivity (three steps, 17% overall yield, 86% *ee*).



Scheme 3. Enantioselective 1,6-addition of MeMgBr to dienoate **17a** and thioester **22**.



Scheme 4. A short total synthesis of a the sulfated alkene **26**, which was isolated from the Echinus *Temnopleurus hardwickii*.

In conclusion, we have developed a highly enantioselective 1,6-ACA (with up to 97% *ee*) to α,β,γ,δ-unsaturated esters, providing valuable multifunctional building blocks. This is also the first example of a 1,6-ACA for which regioselectivity is primarily dictated by the catalyst.

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Keywords: 1,6-conjugate addition · asymmetric catalysis · copper · enantioselectivity · Grignard reaction

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[11] For β-unsubstituted dienones regioselectivity drops to 70%.

[12] E. Fillion, A. Wilsily, E-T. Liao, *Tetrahedron: Asymmetry* **2006**, *17*, 2957 – 2959.

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[14] The Cu-catalyzed 1,6-ACA to 2,4-dienones has been studied and gave a mixture of 1,2- and 1,6-addition products. Studies to optimize these results are underway.

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[19] Mainly degradation of starting material was observed.

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[22] Theoretical calculations of Nakamura et al.[16b] and experimental data of Krause et al.[16a] identified this step as rate determining. For the 1,4-ACA of Grignard reagents we found that the rate-determining step is the reductive elimination (to form **13**).[15] Further research is needed to identify the rate-determining step for this catalytic cycle.

[23] Freshly prepared Grignard reagents should be used to obtain good yields.

[24] In entry 3 of Table 4 **19c** is present in varying amounts (35–50%).

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