Copper-Catalyzed Enantioselective Conjugate Addition of Grignard Reagents to α,β-Unsaturated Esters**

*Fernando López, Syuzanna R. Harutyunyan, Auke Meetsma, Adriaan J. Minnaard, and Ben L. Feringa**

The development of catalyst systems for the enantioselective conjugate addition of organometallic reagents to α,β-unsaturated compounds has been the subject of intensive research over the past few decades.[1] Whereas extraordinary advances have been made in asymmetric 1,4-additions to enones, lactones, and nitroalkenes,[1–5] in the case of acyclic α,β-unsaturated esters the progress has been limited,[6] despite the enormous synthetic potential of the resulting enantiopure β-substituted esters as building blocks for natural product synthesis.[7,8]

The lower intrinsic reactivity of α,β-unsaturated esters relative to that of enones,[9] and the challenge to control the different conformers present in acyclic unsaturated systems, may account for this paucity of versatile methodologies. To address these issues, several alternatives based on the use of different ester surrogates (i.e. oxazolidinones, pyrrolidinones, pyrazolidinones, acyl phosphonates, and imides), were developed successfully, with highly enantioselective Michael additions of soft nucleophiles resulting.[10] However, for alkyl metal compounds only an enantioselective conjugate addition of dialkyl zinc reagents to unsaturated *N*-acyl oxazolidinones has been reported to date.[11] Very recently, our research group described an alternative strategy based on a conjugate addition to alkylidene malonates that yields β-substituted esters after a decarboxylation step, but the method is restricted to the addition of dimethylzinc.[12,13] Therefore, despite these important achievements, general and efficient enantioselective conjugate additions of organometallic reagents to α,β-unsaturated esters remain a major challenge.

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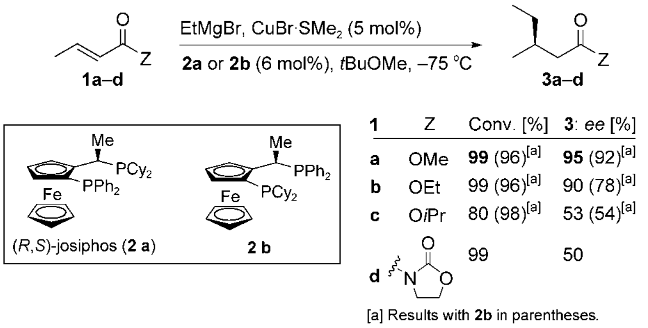
Encouraged by the recent successful developments in the asymmetric addition of Grignard reagents to enones,[14] we decided to explore the conjugate addition to α,β-unsaturated acid derivatives and report herein the first highly enantioselective catalytic conjugate addition of organomagnesium reagents to this class of substrates.[15] The reactions are easy to execute, rigorously inert conditions are not required, and an air-stable (pre)catalyst has been identified that can be recycled and reused without any deterioration in yield or enantioselectivity.

Preliminary screening involved the crotonic acid derivatives **1a–d** (Scheme 1). The data obtained indicated that the catalyst complexes prepared from the ligands josiphos (**2a**) or **2b**,[14,16] CuBr·SMe$_2$, and EtMgBr were the most efficient. These complexes led to higher stereoselectivities than the other combinations of diphosphines, Cu sources, and ethylmagnesium halides tested. Remarkably, the use of sterically hindered esters (e.g. **1c**) to avoid the undesired 1,2-addition, or more reactive ester surrogates, such as the oxazolidinone **1d**, is not required. Indeed, the highest conversions and stereoselectivities were observed with methyl crotonate (**1a**).

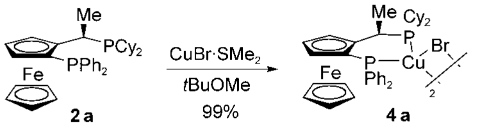


1	Z	Conv. [%]	3: *ee* [%]
a	OMe	**99** (96)[a]	**95** (92)[a]
b	OEt	99 (96)[a]	90 (78)[a]
c	O*i*Pr	80 (98)[a]	53 (54)[a]
d		99	50

[a] Results with **2b** in parentheses.

Scheme 1. Initial screening of catalysts and crotonic acid derivatives. Cy = cyclohexyl.

The influence of the catalyst loading was investigated for the addition of EtMgBr to **1a**. The addition was equally effective with 1 mol% of the catalyst **2a**/CuBr·SMe$_2$, and even with 0.2 mol% (substrate-to-catalyst ratio (S/C) of 500:1); the same conversion and enantioselectivity were observed (99% conversion, 95% *ee*).[17] No less significantly, the reaction proved to be very robust; reagent grade solvents were tolerated without the need for the rigorous exclusion of moisture and oxygen. This robustness led us to believe that a relatively air-stable catalyst could be participating in the process. After completion of the reaction, the addition of pentane to the crude residue led to the recovery, following filtration, of the dinuclear Cu complex **4a**.[18] The participation of this complex in the catalytic cycle is evident, as the reaction of **1a** with recovered **4a** (0.5 mol%) and EtMgBr afforded **3a** with the same yield and enantioselectivity. Furthermore, **4a** could be prepared independently as shown in Scheme 2 and proved to be air-stable, which significantly increased the simplicity of the procedure. Interestingly, the slow evaporation of a solution of **4a** in acetonitrile provided single crystals of the related mononuclear trigonal-planar Cu complex **4a′**. The X-ray crystal structure obtained for this complex is shown in Figure 1.[19,20]



Scheme 2. Preparation of the copper catalyst **4a**.

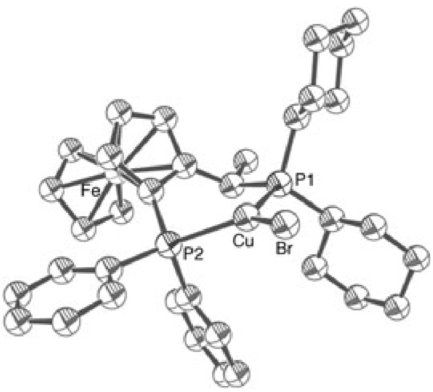
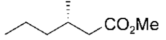
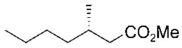
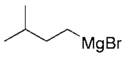
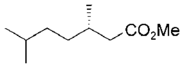
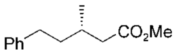
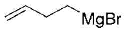
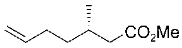


Figure 1. X-ray structure of **4a′**. Hydrogen atoms have been omitted for clarity.

Next, we analyzed the scope of the asymmetric conjugate addition to methyl crotonate **1a** with respect to the Grignard reagent. Reactions were typically carried out with 0.5 mol% of the copper catalyst **4a**, and conversion was complete within 2 h at −75 °C. As shown in Table 1, the method is suitable for the addition of several different Grignard reagents and provides exclusively the product of 1,4-addition (regioselectivity > 99:1) with high to excellent enantioselectivity.[21]

To determine the scope of the reaction with respect to the β substituent on the electrophile, a series of α,β-unsaturated esters were prepared in a single step by a Horner–Emmons

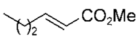
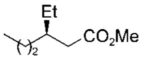
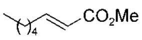
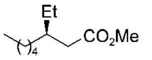
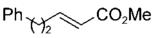
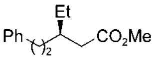
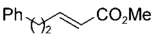
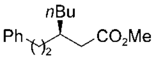
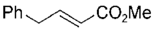
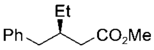
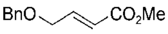
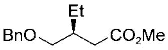
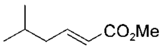
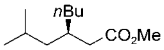
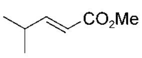
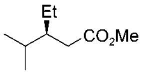
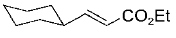
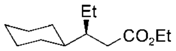
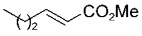
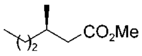
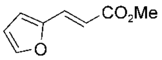
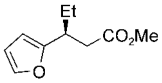
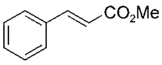
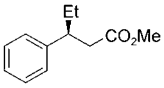
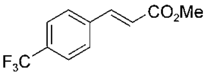
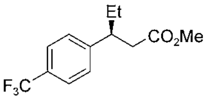
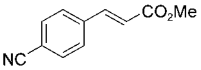
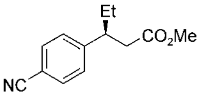
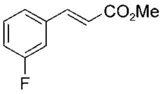
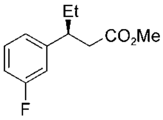
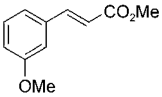
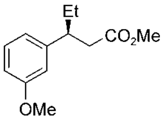
Table 1: Enantioselective conjugate addition of Grignard reagents RMgBr to methyl crotonate (**1a**).[a]

Entry	RMgBr	Product	Yield [%][b,c]	*ee* [%][d,e]
1	*n*PrMgBr	 CO$_2$Me	86	95 (*S*)
2	*n*BuMgBr	 CO$_2$Me	92	95 (*S*)
3	 MgBr	 CO$_2$Me	90	96
4	 Ph MgBr	 Ph CO$_2$Me	84	87
5	 MgBr	 CO$_2$Me	67	85 (*S*)

[a] Conditions: **1a** was added dropwise over 1 h to a solution of RMgBr (1.15–1.25 equiv) and **4a** (0.5 mol%) in *t*BuOMe. [b] Conversion > 98% (GC-MS) after 2 h in all cases. [c] Yield of isolated product. [d] Determined by GC on a chiral phase (G-TA for entries 1, 2, and 5; dex-CB for entry 3) or HPLC (chiralcel OD-H for entry 4).[22] [e] Absolute configurations were established by comparison with known compounds.

reaction or through olefin cross-metathesis.[23] The results, summarized in Table 2, indicate that a broad range of unsaturated esters with different groups at the β position participate successfully in the enantioselective conjugate addition. As a general trend, less hindered α,β-unsaturated esters, without branching at the γ position (Table 2, entries 1–8), afforded better results with the complex **4a**, derived from josiphos (**2a**); the corresponding products were formed with complete regioselectivity and enantioselectivities in the range 86–95 % *ee*. However, for substrates with bulky groups at the double bond (e.g. **5g** and **5h**), superior efficiency was observed when the ligand **2b**, in which the positions of the alkyl and aryl phosphine groups have been interchanged, was used instead of **2a** (Table 2, entries 9, 10).[24] Thus, the addition of EtMgBr to **5g** and **5h** (Table 2, entries 10, 12) proceeded smoothly at −75 °C to afford the desired products with nearly complete stereoselectivity (98–99 % *ee*) and in excellent yields. To further demonstrate the potential of this method, the conjugate addition to **5g** was carried out on a 1-g scale (0.5 mol % catalyst); **6g** was afforded in 88 % yield and with an excellent 98 % *ee* (Table 2, entry 11). Interestingly, the study of the addition of MeMgBr to **5a** led us to find a practical limitation of the method: Although the product was formed with high enantioselectivity (93 % *ee*), the reaction rate was prohibitively slow (19 % conversion after 24 h; 37 % conversion in the presence of TMSCl; Table 2, entries 13, 14).

Table 2: Scope of the enantioselective conjugate addition of Grignard reagents to α,β-unsaturated esters.[a]

Entry		5	RMgBr	Product (6)	Catalyst (mol %)	Yield [%][b]	*ee* [%][c]
1	a		EtMgBr		**4a** (0.5)	99[d]	93
2	b		EtMgBr		**4a** (0.5)	89	88
3	c		EtMgBr		**4a** (0.5)	91	91
4	c		*n*BuMgBr		**4a** (0.5)	94	92
5	d		EtMgBr		**4a** (0.5)	75	95
6	e		EtMgBr		**4a** (2.5)	85	86
7	f		*n*BuMgBr		**4a** (0.5)	87	88
8					**4a** (2.5)	99[d]	92
9	g		EtMgBr		**4a** (2.5)	93[d,e]	87 (*S*)
10					**4b** (2.5)	99[d,e]	99 (*S*)
11					**4b** (0.5)	88[e]	98 (*S*)
12	h		EtMgBr		**4b** (2.5)	86[e]	98 (*S*)
13	a		MeMgBr		**4a** (2.5)	19[d]	93
14					**4a** (2.5)	37[d,g]	90
15	i		EtMgBr		**4a** (2.5)	62[d,e]	86
16					**4b** (0.5)	90[e]	95
17	j		EtMgBr		**4a** (2.5)	42[d–f]	75 (*S*)
18					**4b** (1.5)	94[e,f]	98 (*S*)
19	k		EtMgBr		**4b** (1.5)	99[e,f]	96
20	l		EtMgBr		**4b** (5)	80[e,f]	88
21	m		EtMgBr		**4b** (1.5)	92[e,f]	97
22	n		EtMgBr		**4b** (1.5)	91[e,f]	97

[a] Conditions: **4** (see table), RMgBr (1.15 equiv), 0.35 M in *t*BuOMe, −75 °C, unless otherwise noted. [b] Yield of isolated product unless otherwise noted. [c] Determined by GC on a chiral phase (G-TA or dex-CB) or HPLC (chiralcel OD-H).[22] [d] Conversion (GC).[22] [e] RMgBr: 2.5 equivalents. [f] Reaction carried out in CH_2Cl_2, 0.25 M. [g] TMSCl (5.0 equiv) used. Bn = benzyl, TMS = trimethylsilyl.

Finally, we studied the addition to aryl-substituted α,β-unsaturated esters (Table 2, entries 15–22). As in the case of β-substituted hindered substrates, higher enantioselectivities were observed in these reactions when the Cu complex **4b** was used as the catalyst (e.g. Table 2, entries 15, 16 and 17, 18). The poor solubility at low temperature in aliphatic ethers of most of these substrates (**5j**–**n**) required the use of CH_2Cl_2

as the solvent to achieve complete conversions and to avoid undesired 1,2-addition products. Although slightly longer reaction times (3–5 h) were needed than for aliphatic substrates, the method proved to be highly effective and afforded exclusively the desired 1,4-addition products with enantioselectivities ranging from 88–98 % *ee*. Finally, preliminary results indicate that aryl moieties that bear donor and acceptor substituents are tolerated, even those with potentially competitive groups, such as nitrile groups.

In conclusion, we have demonstrated that inexpensive and readily available Grignard reagents and stable dinuclear Cu complexes can be used for the first time in catalytic enantioselective conjugate addition reations to simple acyclic α,β-unsaturated methyl esters. These reactions provide access to highly valuable β-substituted chiral esters in good yields and with excellent enantioselectivities (up to 99 % *ee*). Studies are underway to establish the full scope of this methodology, as well as to elucidate the reaction mechanism.

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Keywords: asymmetric catalysis · conjugate addition · copper · enantioselectivity · Grignard reaction

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[19] Alternatively, **4a′** can be prepared by mixing **2a** and $CuBr{\cdot}SMe_2$ in acetonitrile and converted into the dimeric complex **4a** by treatment with halogenated solvents. See Supporting Information for the characterization of **4a** and **4a′** and further information.

[20] CCDC 261573 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[21] Sterically hindered Grignard reagents, such as *i*PrMgBr, and aryl Grignard reagents, such as PhMgBr, have provided poor results so far. (*i*PrMgBr: 26 % conversion, 12 % *ee*; PhMgBr: 55 % conversion, 1 % *ee*.)

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