Catalytic Enantioselective Conjugate Addition with Grignard Reagents

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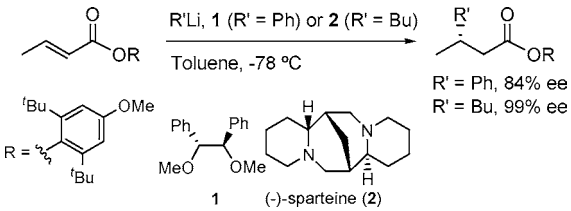
ABSTRACT
In this Account, recent advances in catalytic asymmetric conjugate addition of Grignard reagents are discussed. Synthetic methodology to perform highly enantioselective Cu-catalyzed conjugate addition of Grignard reagents to cyclic enones with ee's up to 96% was reported in 2004 from our laboratories. Excellent levels of stereocontrol were achieved with Cu(I) halides, alkylmagnesium bromides, and commercially available chiral ferrocenyl diphosphines. Studies carried out during the last 2 years demonstrated that these Cu-catalysts are very effective for the enantioselective conjugate addition of Grignard reagents to acyclic enones, α,β-unsaturated esters, and thioesters. On the basis of this methodology, a diastereo- and enantioselective iterative route to deoxypropionate units was developed and applied to the synthesis of natural products. Finally, we summarize our recently conducted mechanistic investigations and the application of this catalytic system to the enantioselective S_N2' substitution reactions of allylic bromides with Grignard reagents.

Introduction

The conjugate addition (CA) of organometallic reagents to α,β-unsaturated compounds is one of the basic methods in our repertoire for the construction of C−C bonds.[1] These addition reactions have been used as key steps in the synthesis of numerous biologically active compounds and show a broad scope because of the large variety of donor and acceptor compounds that can be employed. It is evident that a tremendous effort was devoted over the last three decades to develop asymmetric variants of this reaction.[2]

The first successful approaches were based on the Cu-mediated CA of organolithium and Grignard reagents to α,β-unsaturated systems covalently modified with chiral auxiliaries.[3] Other strategies made use of organocopper compounds with chiral nontransferable groups, such as chiral alkoxycuprates and amidocuprates.[2,3] For instance, Corey et al. reported in 1986 enantioselectivities of over 90% by using a chiral ephedrine-derived alkoxycuprate.[4] The use of organolithium reagents in the presence of stoichiometric amounts of chiral ether **1** or amine **2** ligands was also explored, providing high enantioselectivities in the CAs to α,β-unsaturated *N*-cyclohexylimines and sterically crowded esters (Scheme 1).[5]

Scheme 1. Asymmetric CA of Organolithium Reagents with Stoichiometric Chiral Ligands



Although some of these strategies provide high enantioselectivities with several substrates, the development of catalytic rather than stoichiometric processes is the main challenge to provide truly efficient synthetic methods.

It was not until the late 1980s that the feasibility of a catalytic (≤10 mol % chiral catalyst) and enantioselective CA was demonstrated. Lippard and co-workers reported the first enantioselective CA of a Grignard reagent to an enone, using catalytic amounts of Cu-amide complex **3**.[6] Subsequently, a variety of catalytic systems, on the basis of, for example, Cu thiolates **4**−**7**[7] and phosphine-oxazoline ligand **8**,[8] were introduced for the CA of Grignard reagents. Although the scope remained limited and ee's infrequently reached the 90% level. (Figure 1), high enantioselectivity (ee 92%) was observed in two examples (**8**). Despite the fact that the parameters governing the stereocontrol were less clear, these excellent contributions

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Fernando López was born in 1975; he studied chemistry at the University of Santiago de Compostela where he obtained his degree in 1998. During his PhD at the same university, under the supervision of Professor José L. Mascareñas, he carried out two predoctoral stays at the ETH-Zürich (Erick M. Carreira) and at Yale University (John F. Hartwig). After receiving his PhD in 2003, he was awarded with a Marie Curie Postdoctoral fellowship, and he joined the group of Professor Feringa at the University of Groningen, where his work was focused on enantioselective catalysis. In 2005, he was awarded with a Ramón y Cajal contract from the Spanish Ministry of Education and Science and joined the University of Santiago de Compostela in 2006.

Adriaan J. Minnaard received his PhD degree from Wageningen Agricultural University, The Netherlands, in 1997 with Prof. Dr. Ae. de Groot and Dr. J.B.P.A. Wijnberg. He has been a scientist at DSM-Research in Geleen, The Netherlands, from 1997 to 1999. Subsequently, he joined the University of Groningen in 1999 as an Assistant Professor in the department of Prof. Ben L. Feringa. In 2005, he was appointed Associate Professor in Bio-Organic Chemistry. His work focuses on asymmetric catalysis and natural product synthesis. Currently, he is a guest researcher in the group of Prof. H. Waldmann at the Max Planck Institute for Molecular Physiology in Dortmund, Germany.

Ben L. Feringa received his PhD degree from the University of Groningen in 1978 with Professor Hans Wynberg. He was a research scientist with Royal Dutch Shell, both at the Shell Research Center in Amsterdam and at the Shell Biosciences Laboratories in Sittingbourne, United Kingdom, from 1978 to 1984. He joined the University of Groningen in 1984 as a lecturer and was appointed Professor at the same University in 1988 and in 2003 the Jacobus van't Hoff distinguished Professor in Molecular Sciences. He was the recipient of several international awards. In 2004, he was elected foreign honory member of the American Academy of Arts and Sciences and in 2006 became a member of the Royal Netherlands Academy of Sciences. He has recently received the Spinoza award from The Netherlands Organization of Scientific Research and the Prelog Medal of the ETH Zurich. Professor Feringa is the scientific editor of the RSC journal Organic and Biomolecular Chemistry.

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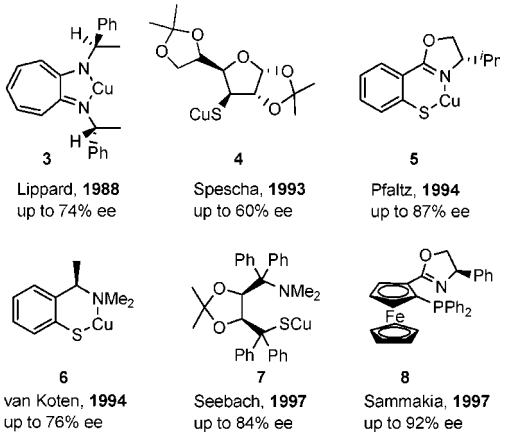


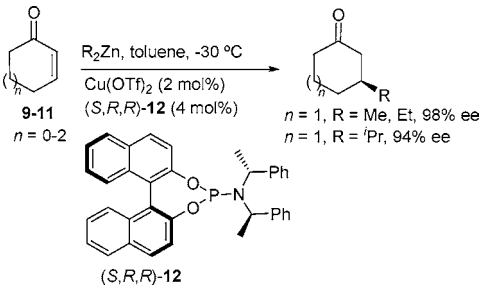
FIGURE 1. Selected catalytic systems developed for the CA of Grignard reagents to enones.[6–8]

provided an important basis to allow the development of the catalytic methodology described here.

The difficulties encountered in the development of an effective enantioselective method (i.e., the fast uncatalyzed reaction and the high sensitivity toward various reaction parameters)[1,2,9] encouraged the synthetic community to explore less reactive organometallic species, such as organo-zinc, copper, aluminum, silicon, or boron reagents, in combination with different metal sources (Cu, Rh, Pd, Ni, Co).

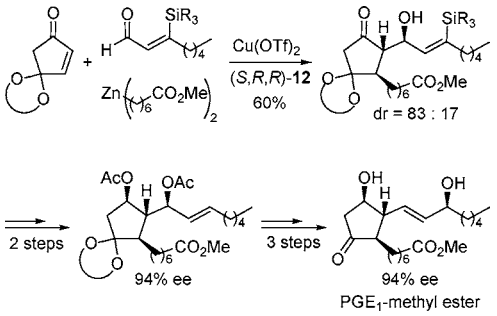
Early work by Soai et al. showed the viability of performing the CA of dialkylzinc reagents to enones with modest enantioselectivities using substoichiometric amounts of chiral complexes of Ni and Co.[10] A Cu-catalyzed CA of Et_2Zn to cyclohexenone (**9**) with 32% ee was subsequently reported.[11] The discovery in 1996 that chiral monodentate phosphoramidites are excellent ligands for the asymmetric Cu-catalyzed CA of R_2Zn reagents[12] led to the first highly enantioselective Cu-catalyzed CA of dialkylzinc reagents to enones.[13] Thus, binaphthol-based phosphoramidite **12** and $Cu(OTf)_2$ provided for the first time enantioselectivities up to 98% with cyclic enones **9**−**11** and a synthetically useful protocol for this asymmetric C−C bond formation (Scheme 2).

Scheme 2. Cu-Catalyzed Enantioselective CA of Dialkylzinc Reagents to Cyclic Enones



Notably, tandem catalytic enantioselective CA-aldol reactions of dialkylzinc reagents to cyclic enones, in the presence of aldehydes, were developed. The potential of this three-component coupling protocol is demonstrated in the short total synthesis of prostaglandin E_1 methyl ester (Scheme 3).[14]

Scheme 3. Tandem Enantioselective CA-Aldol Reaction. Synthesis of PGE_1-methyl Ester



These discoveries stimulated numerous modifications to our original catalytic system as well as the introduction of a broad range of new efficient phosphorus-based catalysts (>350 new chiral ligands reported) for the Cu-catalyzed CA of dialkylzinc reagents. Several reviews are testimony of the impressive progress in this field over recent years.[15–19]

In contrast, for the introduction of aryl and vinyl groups, the Rh-catalyzed CA of boron reagents developed by Miyaura, Hayashi et al., and our group among others is still the method of choice.[20]

The efficiency of dialkylzinc and boron reagents in the catalytic enantioselective CA clearly displaced in the past decade the use of Grignard reagents in this transformation.[21] Dialkylzinc reagents have distinct advantages compared to Grignard reagents, because they show low reactivity in the uncatalyzed reaction and high tolerance for functional groups, both in the substrate and zinc reagent. The enantioselective version of the 1,4-addition with Grignard reagents continues to offer us a major challenge, since it is not only essential to obtain high enantioselectivities but also to avoid the fast noncatalyzed addition of the organomagnesium reagent to the carbonyl group (1,2-addition). Nevertheless, we anticipate that there are significant incentives to use common Grignard reagents as opposed to dialkylzinc compounds, including their ready availability, the transfer of all the alkyl groups of the organometallic compound, and the higher reactivity of the magnesium enolates obtained. These features, and the scarceness of synthetically useful catalytic CAs of RMgX reagents to enones and enoates, stimulated us to search for effective catalysts for this enantioselective transformation. Encouraged by the promising enantioselectivities reached so far with a wide variety of chiral ligands (and in a few cases high ee of 92%),[2,6–8] the notion that possibly competing chiral Cu complexes are present and the apparent lack of a unique catalyst led us to refocus our efforts toward the discovery of a highly active catalyst system.

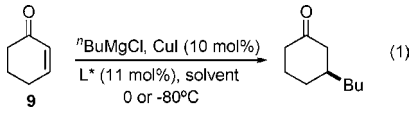
In this Account, we summarize the recent breakthroughs in CA of Grignard reagents from our laboratory. We discuss the actual scope of the new methodology and present a mechanistic proposal of the catalytic process. Moreover, the application of these catalysts to a related enantioselective Cu-catalyzed process, that is, S_N2' dis-

placement reactions of allylic electrophiles (allylic substitutions), is described.

Highly Enantioselective Cu-Catalyzed CA of Grignard Reagents

Enantioselective CAs to Cyclic Enones. Most ligands used so far in the field of Cu-catalyzed 1,4-addition of Grignard reagents fulfill the criteria of combining P, S, or Se with N or O donor atoms in their structure, to coordinate selectively with Cu and Mg of the organometallic species, respectively.[7−8,22] In a systematic search for the optimal ligand and Cu source, we initially tested several types of phosphoramidites,[23] but the enantioselectivities were consistently poor. The fact that free Cu-salts show high activity in the CA of Grignard reagents, even at −80 °C, led to the realization that tight binding of Cu ions by bidentate ligands might be essential. Interestingly, albeit chiral diphosphine ligands have dominated the field of asymmetric catalysis in the last 30 years,[24] none of these ligands were reported to be effective in the CA of Grignard reagents. A priori, diphosphines would not match with the metal-differentiating coordination concept, although in several of these diphosphine ligands, the two phosphorus atoms have very different electronic and steric properties.

In our hands, privileged bidentate phosphines such as BINAP, Trost ligand, and DuPhos led to poor enantioselectivities in the model reaction (5−28% ee) (eq 1, Figure



(1)

2). On the contrary, promising enantioselectivities (45−70% ee) were obtained with ferrocenyl-based diphosphine ligands, including Mandyphos, Walphos, and Josiphos.[25] Among these ferrocenyl ligands, Taniaphos[26] provided in the preliminary screening the highest enantioselectivity (95% ee), although with modest regioselectivity (1,4:1,2 = 60:40) (Figure 2).

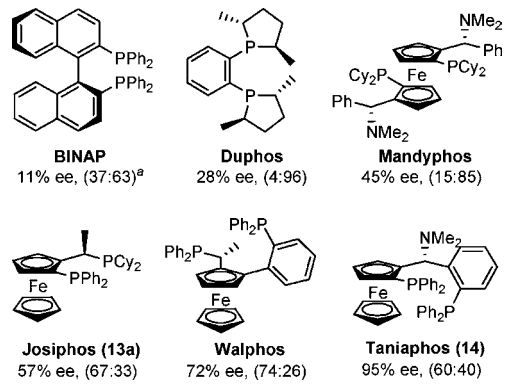
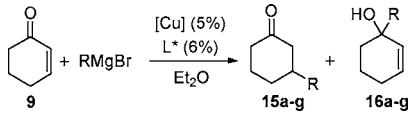
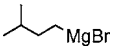


FIGURE 2. Selectivity of several diphosphine ligands in the model reaction; in parentheses regioselectivity: (1,4:1,2 ratio).

Optimization of the reaction parameters led to conditions using 5 mol % of CuCl, 6 mol % of Taniaphos (**14**), and 1.15 equiv of EtMgBr in Et_2O at 0 °C, which afforded full conversion in 15 min with a regioselectivity of 95% (1,4- vs 1,2-addition product) and an excellent 96% ee.[27] The results with a variety of Grignard reagents using these optimal conditions are shown in Table 1.

Table 1. Enantioselective Cu-Catalyzed CA of Grignard Reagents to Cyclohexenone (9)[a]



RMgBr	L*	15:16	ee (%)	15
EtMgBr	**14**	95:5	96	**15a**
MeMgBr	**14**	83:17	90	**15b**
^{n}PrMgBr	**14**	81:19	94	**15c**
^{n}BuMgBr	**14**	88:12	96	**15d**
^{i}PrMgBr	**14**	78:22	1	**15e**
^{i}BuMgBr	**14**	62:38	33	**15f**
	**14**	76:24	95	**15g**
^{i}PrMgBr[b]	**13a**	99:1	54	**15e**
^{i}BuMgBr[b]	**13a**	99:1	92	**15f**
EtMgBr[b]	**13a**	99:1	56	**15a**

[a] >98% conversion after 15 min at 0 °C using CuCl. [b] >98% conversion after 2 h at −60 °C using CuBr·SMe_2.

Thus, the products **15b**−**d** were obtained with 90−96% ee using RMgBr reagents with linear alkyl chains (R = Me, ^{n}Pr, ^{n}Bu). Employing Grignard reagents with branched alkyl chains, a strong influence of the substitution pattern on the enantioselectivity was observed. In particular, the incorporation of isopropyl and isobutyl fragments resulted in poor ee's, although isoamylmagnesium bromide afforded the 1,4-addition product **15g** with 95% ee. When we tested other ferrocenyl diphosphine ligands (Figure 2) with the α- and β-branched Grignard reagents ^{i}PrMgBr and ^{i}BuMgBr, we found that Josiphos (**13a**) provides excellent regiocontrol (99%) with moderate (**15e**, 54% ee) to high (**15f**, 92% ee) enantioselectivities. Contrary to Taniaphos, the Josiphos ligand is more effective at low temperatures (e.g., −60 °C vs 0 °C) and in combination with CuBr·SMe_2 instead of CuCl.

Therefore, the proper selection of Taniphos or Josiphos in a complementary way allows the use of a broad range of inexpensive and readily available Grignard reagents. Moreover, this enantioselective Cu-catalyzed CA is not only limited to cyclohexenone as other cyclic enones as well as lactones provide high levels of regio- and enantioselectivity (Figure 3).[27]

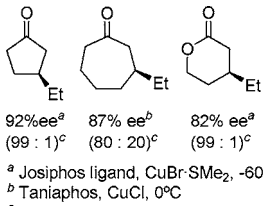


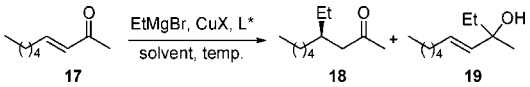
FIGURE 3. Representative examples of CA products to cyclic systems.

Enantioselective CA to Acyclic Enones. Having established that highly enantioselective CAs of Grignard reagents to cyclic enones can be easily accomplished with

Cu-complexes of commercially available ferrocenyl-based diphosphines, we turned our attention to the challenging class of acyclic enones.[28] The β-substituted linear ketones resulting from the CA to acyclic enones are common subunits in biologically active molecules and are important building blocks for natural product synthesis. Some procedures for their enantioselective preparation have been reported to date although the enantioselectivities are usually substrate- and ligand-dependent.[29]

We initially investigated the CA of EtMgBr to the model substrate (*E*)-3-nonen-2-one (**17**), catalyzed by CuCl and Taniaphos (**14**) (Table 2). The product was obtained with good regioselectivity at 0 °C, but much to our surprise, a complete lack of enantioselectivity was observed. Performing the CA at low temperatures and in particular using Josiphos (**13a**) dramatically enhanced the selectivity up to 86% ee. Further improvement could be obtained by using the less coordinating solvent ^{t}BuOMe instead of Et_2O.

Table 2. Enantioselective CA of EtMgBr to (*E*)-3-Nonen-2-one (17)[a,b]

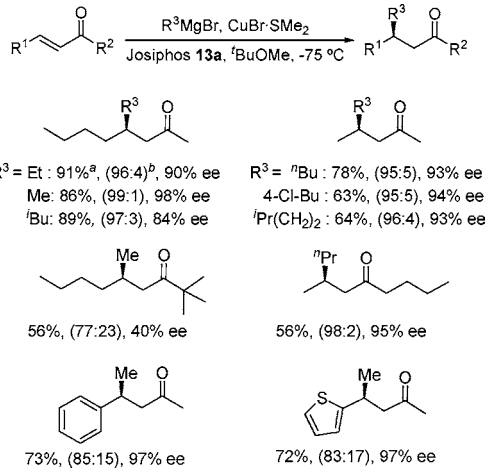


L*	CuX	solvent	T (°C)	**18**:**19**	ee (%)
14	CuCl	Et_2O	0	84:16	1
14	CuCl	Et_2O	−75	70:30	48
13a	CuBr·SMe_2	Et_2O	−75	91:9	86
13a	CuBr·SMe_2	^{t}BuOMe	−75	99:1	90

[a] EtMgBr added to a solution **17**, 5% CuX and 6% ligand. [b] All conversions >98%.

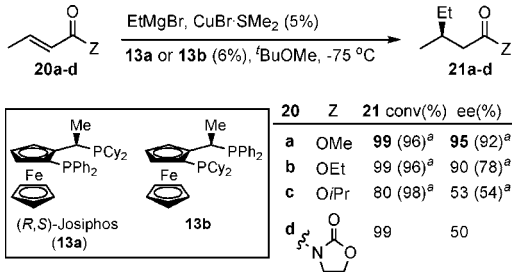
Gratifyingly, these conditions resulted also in high selectivities when Grignard reagents with different linear alkyl chains were used, whereas the substrate scope included a variety of aliphatic linear enones (Scheme 4). Particularly noteworthy is the addition of MeMgBr (e.g., to octenone), which provides the corresponding products with 97−98% ee, even when only 1 mol % of catalyst is employed.[30]

Scheme 4. Enantioselective CA of RMgBr Reagents to Linear Enones



[a] Isolated yield. [b] 1,4:1,2 ratio.

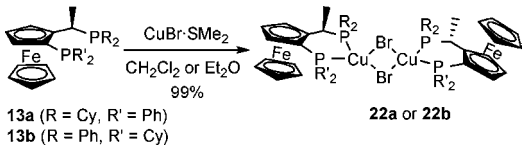
Scheme 5. Screening of Catalysts and Crotonic Acid Derivatives



20	Z	**21** conv(%)	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 **13b** between parenthesis.

Scheme 6. Preparation of Cu-complexes 22a and 22b[34]



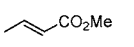
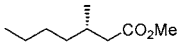
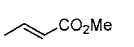
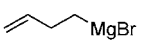
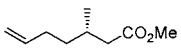
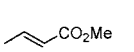
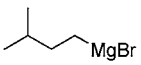
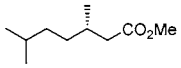
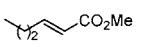
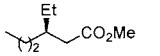
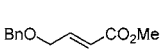
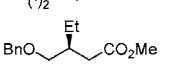
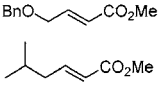
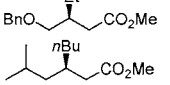
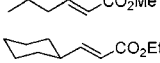
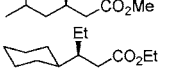
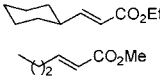
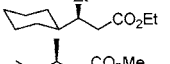
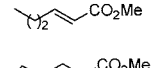
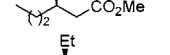
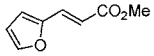
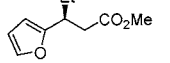
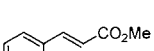
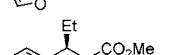
Both β-substituted aliphatic and aromatic enones can be used. For instance, benzylideneacetone and β-thienyl- and β-furyl-substituted enones reacted smoothly in ^{t}BuOMe at −75 °C with RMgBr reagents to give the corresponding enones with high yields, regioselectivities, and excellent enantioselectivities of 90−97% (Scheme 4). In contrast, the CA of α-branched and aryl Grignard reagents or the use of sterically hindered enones provides only moderate enantioselectivities.[28]

Enantioselective CA of Grignard Reagents to α,β-Unsaturated Esters and Thioesters. The CA of Grignard reagents to α,β-unsaturated acid derivatives and, in particular, to α,β-unsaturated esters is highly attractive. Despite the enormous synthetic potential of the resulting β-substituted esters as chiral building blocks for natural product synthesis, the progress during recent decades in the enantioselective CA of organometallic reagents to these unsaturated systems has been limited.[31] The lower intrinsic reactivity of α,β-unsaturated esters compared to that of enones may account for this paucity of methodologies. Indeed, to the best of our knowledge, no combinations of catalysts and alkyl organometallic reagents had previously shown to be successful for these CAs, and only an enantioselective CA of dialkylzinc reagents to the more reactive α,β-unsaturated *N*-acyloxazolidinones has been reported by Hird and Hoveyda.[32,33]

An initial screening demonstrated that Josiphos ligands **13a** and **13b** were very effective in promoting the Cu-catalyzed CA of EtMgBr to unsaturated crotonates **20a**−**d** (Scheme 5). The use of sterically hindered esters (e.g., **20c**), which usually help to avoid undesired 1,2-additions, or more reactive ester surrogates such as the oxazolidinone **20d** is not required. Indeed, the highest conversions and stereoselectivities are obtained with methyl crotonate **20a** (Scheme 5).[34]

Interestingly, the dinuclear Cu-complexes **22a** and **22b** (Scheme 6) could be recovered from the crude reaction mixtures or, alternatively, prepared independently by mixing equimolar amounts of ligands (**13a** or **13b**) and CuBr·SMe_2 in an appropriate solvent. It was established that these Cu-complexes participate in the catalytic cycle,

Table 3. Enantioselective CA to α,β-Unsaturated Esters[a]

Substrate	20	RMgBr	Product (21)	Cat (mol %)	Yield (%)[b]	ee (%)
	**a**	^{n}BuMgBr		**22a** (0.5)	92	95
	**a**			**22a** (0.5)	67	85
	**a**			**22a** (0.5)	90	96
	**e**	EtMgBr		**22a** (0.5)	99[c]	93
	**f**	EtMgBr		**22a** (2.5)	85	86
	**g**	^{n}BuMgBr		**22a** (2.5)	99[c]	92
	**h**	EtMgBr		**22b** (2.5)	86[d]	98
	**e**	MeMgBr		**22a** (2.5)	19[c]	93
	**i**	EtMgBr		**22b** (0.5)	90[d]	95
	**j**	EtMgBr		**22b** (1.5)	94[d,e]	98 (*S*)
	**j**	EtMgBr		**22b** (1.5)	100[c-e]	53 (*R*)

[a] Cu-complex **22** (see table), 1.15 equiv. of RMgBr, ^{t}BuOMe, −75 °C. [b] Isolated yield. [c] Conversion (GC). [d] 2.5 equiv of RMgBr employed. [e] Carried out in CH_2Cl_2.

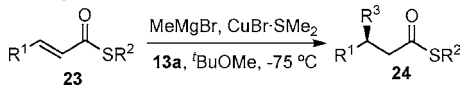
as the reaction of **20a** and EtMgBr with the independently prepared (or recovered) complexes **22a** and **22b** (0.5 mol %) afforded **21a** with the same yields and enantioselectivities as previously obtained with the complexes prepared in situ.

Table 3 summarizes the broad scope of the new asymmetric catalytic process. As a general trend, linear aliphatic Grignard reagents provided excellent results in the CA to methyl crotonate, affording the products with excellent regio- and enantioselectivities and complete conversions using only 0.5 mol % of catalyst. With regard to the electrophiles, less hindered α,β-unsaturated esters, without branching at the γ position, afford better results with the Cu-complex **22a**. However, for substrates with bulky groups (**20h**) or aromatic rings (**20i**−**j**) at the double bond, a superior efficiency is observed when catalyst **22b** is used instead of **22a**.

The CA of RMgBr reagents can also be performed with the *Z*-enoates, leading to the products with opposite absolute configurations. However, lower ee's were consistently obtained in these reactions. Analysis at different times of the reaction mixtures performed with *Z*-methyl cinnamate revealed that an isomerization of the *Z*-enoate to their *E*-enoate occurred during the CA reaction, therefore causing the decrease in the ee.[35]

From the perspective of potential applications to the synthesis of biologically active compounds, the introduction of methyl groups via the CA of MeMgBr to α,β-unsaturated esters is a particularly relevant goal. Unfortunately, the addition of MeMgBr to **20e** showed the limitation of the methodology. Although the product was formed with high enantioselectivity (93% ee), the reaction rate was prohibitively low because of the decreased reactivity of MeMgBr. To address this issue, we focus our attention on the more reactive but equally readily accessible α,β-unsaturated thioesters.[36]

Table 4. Enantioselective CA of MeMgBr to α,β-Unsaturated Thioesters (23)[a]



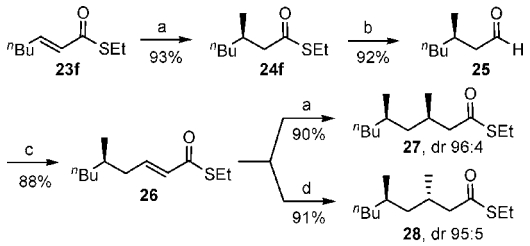
23	R^1	R^2	yield (%)	24	ee (%)
a	^{n}pent	Et	90	**a**	96
b	^{n}pent	Me	93	**b**	96
c	^{n}Pr	Et	92	**c**	96
d	$BnO(CH_2)_3$	Et	94	**d**	95
e	Ph	Et	88	**e**	95

[a] **23**, MeMgBr, $CuBr{\cdot}SMe_2$ (1.0 mol %), **13a** (1.2 mol %), ^{t}BuOMe, −75 °C.

Gratifyingly, the additions of MeMgBr to unsaturated thioesters **23a-e** revealed the success of the approach.[37] The complex prepared in situ from $CuBr{\cdot}SMe_2$ (1.0 mol %) and Josiphos (**13a**, 1.1 mol %) catalyzed the CA of MeMgBr providing the corresponding β-methyl-substituted thioester (**24a**−**e**) with complete regioselectivity and excellent enantioselectivities (95−96% ee) (Table 4).

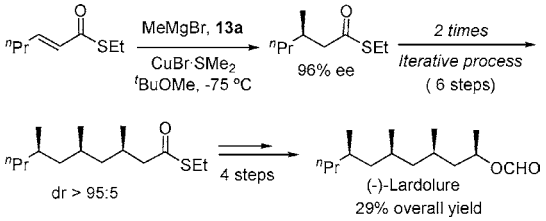
The drastically higher yields obtained for the methyl adducts from α,β-unsaturated thioesters, compared to the oxoester analogs,[34] are most probably because of their

Scheme 7. An Iterative Catalytic Route to Enantiopure syn- and anti-1,3-Dimethyl Arrays[a]



[a] (a) MeMgBr, **13a** (1.2 mol %), CuBr·SMe_2 (1 mol %), ^{t}BuOMe, −75 °C; (b) 10% Pd/C (5%), Et_3SiH; (c) $Ph_3PCHCOSEt$, CH_2Cl_2; (d) MeMgBr, *ent*-**13a** (1.2 mol %), CuBr·SMe_2 (1 mol %), ^{t}BuOMe, −75 °C.

Scheme 8. Application of the Iterative CA in the Synthesis of (-)-Lardolure



inherent electronic properties which are closer to those of enones. However, a possible positive effect arising from coordination of the active catalyst to the sulfur atom may not be ruled out.

Application to the Synthesis of syn- and anti-1,3-Dimethyl Arrays and Deoxypropionate Subunits. Total Synthesis of (-)-Lardolure. With this new procedure in hand, an iterative method to provide access to optically active syn- and anti-1,3-dimethyl arrays and deoxypropionate subunits was devised.[38,39] The approach relies on sequential enantioselective CAs to unsaturated thioesters (Scheme 7). The first stereogenic center is created by the addition of MeMgBr to **23f**, using Josiphos **13a** (95% ee). The resulting thioester **24f** can be efficiently converted in one step into the corresponding aldehyde **25**, which subsequently undergoes a Wittig reaction to give the desired Michael acceptor **26**. A second catalytic (1 mol %) CA using Josiphos **13a** or its enantiomer *ent*-**13a** affords with excellent selectivities the syn- or anti-1,3-dimethyl derivatives **27** (90% yield, dr 96:4) and **28** (91% yield, dr 95:5).

The synthetic utility of this iterative catalytic protocol and the versatility of β-methyl-substituted thioesters was further demonstrated in the asymmetric total synthesis of (-)-lardolure, a multi-methyl-branched insect pheromone (Scheme 8).

Mechanistic Studies. Recently, we conducted an extensive spectroscopic and mechanistic study on these enantioselective Cu-catalyzed reactions.[35] We have identified several parameters such as solvent, nature of the halide (present in the Grignard reagent and Cu (I) source), and additives (i.e., dioxane and crown ethers) which directly affect the formation and nature of the intermediate active species and, therefore, the selectivity, rate, and overall outcome of the catalytic CA reaction. Importantly,

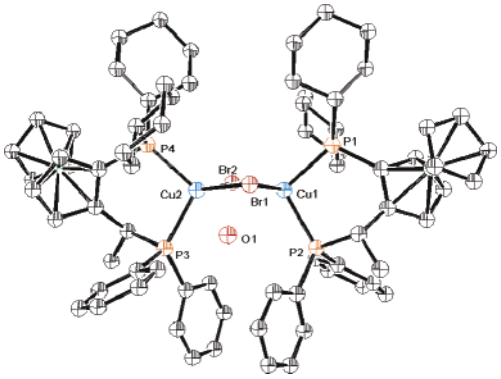
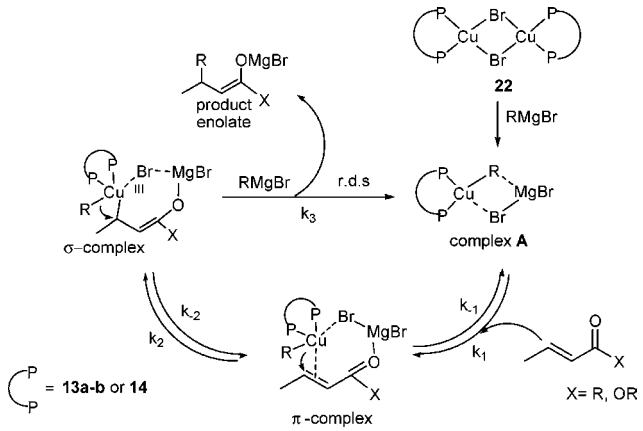


FIGURE 4. X-ray structure of **22b** (hydrogen atoms are omitted for clarity).

Scheme 9. Proposed Catalytic Cycle



we have shown, and rationalized, that the presence of Mg^{2+} and Br^- ions in this intermediate are essential to achieve high selectivity and efficiency in the present catalytic system.

Kinetic studies carried out on a model reaction (addition of EtMgBr to methyl crotonate catalyzed by **13a**) indicate that the rate of the CA reaction is dependent on catalyst, Grignard reagent, and substrate. Although the determination of the reaction order in methyl crotonate and Grignard reagent was impeded because of side reactions and inhomogeneity,[35] the observation that the reaction rate increases with their concentrations suggests that both reactants are involved in the rate-limiting step. On the other hand, the order of the reaction (1.10) with respect to the catalyst suggests that a mononuclear species is involved. This was also supported by the observation that the ee of the product shows linear dependency on the ee of the catalyst. The structure of the initial dinuclear Cu-Josiphos complex **22b** was established by X-ray analysis (Scheme 6, Figure 4).

A reaction pathway which is consistent with the experimental, kinetic, and spectroscopic results is proposed in Scheme 9.

Alkyl transfer from the Grignard reagent to the chiral Cu complexes **22** generates the Cu-complex **A**, as deduced from NMR experiments. Very likely, this complex functions in a similar manner as previously postulated for organocuprate additions.[40]

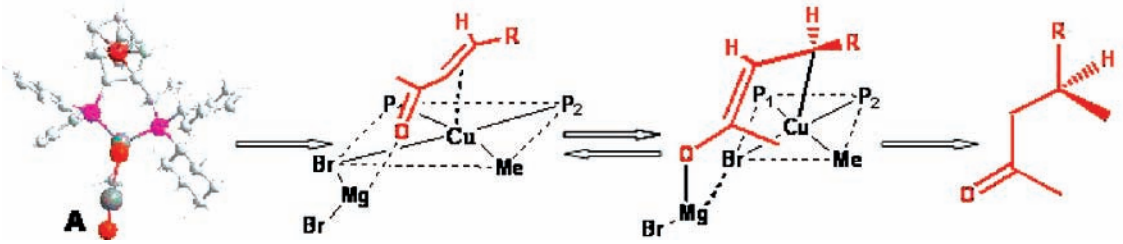


FIGURE 5. Working model for the enantioselective CA of Grignard reagents (P_1:PPh_2 moiety P_2-:PCy_2).

The second intermediate proposed is a Cu-olefin π-complex with an additional interaction of Mg^{2+} with the carbonyl oxygen of the enone (enoate). The formation of a π-complex is presumably followed by intramolecular rearrangement to a Cu(III)-intermediate, where Cu forms a σ-bond with the β-carbon of the enone (enoate), in fast equilibrium with the π-complex.

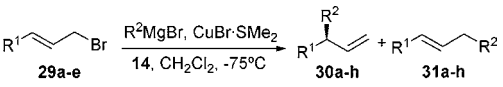
This catalytic cycle can explain the observed isomerization of *Z*-enoates to their *E*-isomers, which occurs within the time scale of the reaction. Indeed, these isomerization experiments provide evidence for the presence of a fast equilibrium between a π-complex and a Cu(III) species (σ-complex), which should be followed by the rate-limiting, reductive elimination step and the formation of complex **A** again.

The proposed catalytic cycle is in accordance with the results of the kinetic studies. The dependence of the reaction rate on the substrate and Grignard reagent indicates that both reactants are involved in the rate-limiting step. This step is preceded by fast equilibria between complexes, for example, substrate-bound sigma-complex and pi-complex and substrate-unbound complex **A** (Scheme 9).

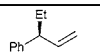
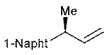
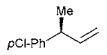
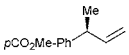
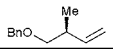
Tentative Model for Stereocontrol. Optimized semiempirical [PM3(tm)] calculations indicate that Cu-complex **A** adopts a distorted tetrahedral structure with the positioning of the Grignard reagent at the bottom face of the complex (Figure 5).[35]

In the proposed model, it can be envisioned that the enone approaches the alkylcopper complex **A** from the least hindered side and binds to the top apical position. This forces the complex to adopt a square pyramidal geometry, which is stabilized via π-complexation of the alkene moiety to the Cu and, importantly, through the interactions between Mg and the carbonyl moiety of the skewed enone. Formation of a transition structure with the chairlike seven-membered ring conformation is proposed in the next step, where Cu forms a σ-bond approaching from the bottom side of the β-carbon leading to the Cu(III) intermediate with the absolute configuration shown (Figure 5). Up to this stage in the catalytic cycle, complex formation is reversible, but in the subsequent rate-determining step, the methyl transfer step, the product stereochemistry is established. To avoid steric interactions with the dicyclohexyl moieties at the nearby phosphorus, the final transfer of methyl group occurs as shown in Figure 5. Although this model predicts the correct sense of asymmetric induction, it is nevertheless a hypothetical model and further mechanistic studies and DFT (Density Functional Theory) calculations need to be performed to shed light on the factors that determine the origin of the enantioselectivity.

Table 5. Cu-Catalyzed Enantioselective Allylic Alkylation with Grignard Reagents[a]



29a R^1 = Ph **d** R^1 = *p*-CO_2Me-Ph
b R^1 = 1-Napht. **e** R^1 = $BnOCH_2$
c R^1 = *p*-Cl-Ph

29	R^2	**30:31**	**30**		Yield[b]	ee(%)
a	Et	82:18		**b**	99[c,d]	96
a	Et	81:19		**b**	92	95
a	^{n}Bu	87:13		**c**	92	94
a		91:9		**d**	93	95
a	Me	97:3		**a**	91	98
b	Me	100:0		**e**	87	96
c	Me	99:1		**f**	95	97
d	Me	98:2		**g**	94	97
e	Me	100:0		**h**	93	92

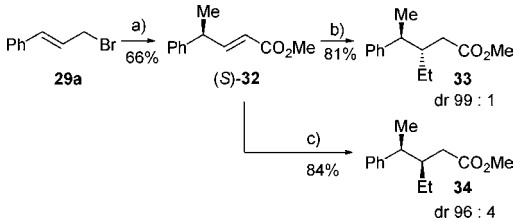
[a] RMgBr (1.15 equiv), **14** (1.1 mol %), $CuBr{\cdot}SMe_2$ (1.0 mol %), CH_2Cl_2, −78 °C. [b] Isolated yield. [c] Conversion (GC). [d] **14** (6 mol %), $CuBr{\cdot}SMe_2$ (5 mol %).

Enantioselective Allylic Alkylation with Grignard Reagents

Our interest in further exploring enantioselective Cu-catalyzed reactions with Grignard reagents provided impetus to test ferrocenyl-based Cu-catalysts in related C−C bond-forming processes. We were particularly attracted to the possibility of employing these catalytic systems for enantioselective S_N2' displacement reactions of allylic electrophiles with organometallic reagents. As recently highlighted by Woodward, such reactions are mechanistically related to CAs.[41] Theoretical studies carried out by Nakamura and co-workers for the CAs and allylic alkylations of Gilman's cuprate revealed profound mechanistic similarities between these two processes.[42]

Gratifyingly, our preliminary investigations revealed that the catalyst generated from Josiphos (**13a**, 6 mol %)

Scheme 10[a]



[a] (a) (i) MeMgBr, **14** (1.1 mol %), CuBr·SMe_2 (1 mol %), CH_2Cl_2, −78 °C; (ii) Hoveyda-Grubbs second gen., methyl acrylate, CH_2Cl_2; (b) EtMgBr, (*R*,*S*)-**13b** (6 mol %), CuBr·SMe_2 (5 mol %), CH_2Cl_2, −78 °C; (c) EtMgBr, (*S*,*R*)-**13b** (6 mol %), CuBr·SMe_2 (5 mol %), CH_2Cl_2, −78 °C.

and CuBr·SMe_2 (5 mol %) was effective at promoting the allylic alkylation of cinnamyl bromide (**29a**) with MeMgBr, affording the corresponding products with good regioselectivity (85:15) and high ee (85% ee). In attempts to improve the stereocontrol, we turned our attention to Taniaphos. The allylic alkylation of **29a** with EtMgBr catalyzed by Taniaphos and CuBr·SMe_2 in ^{t}BuOMe provided initially a modest regioselectivity and a disappointing 32% ee. However, a dramatic improvement was observed using CH_2Cl_2 instead of ^{t}BuOMe as the solvent. The desired product **30b** was obtained with a good regioselectivity and an excellent ee (96%). In addition, the catalyst loading could be reduced to only 1 mol % without significant deterioration in the selectivity.[43]

The scope of the method turned out to be particularly broad (Table 5). The allylic substitution of **29a** could also be performed with other linear alkyl Grignard reagents. Most important, the alkylations with MeMgBr afforded the products with almost complete control of regioselectivity and enantioselectivity (≥96%). Moreover, aliphatic allylic bromides such as **29e** turned out to be excellent substrates, providing almost exclusively the branched product **30h** with 92% ee. To the best of our knowledge, this represent the first highly enantioselective allylic substitutions of linear aliphatic allylic halides with Grignard reagents.[44]

We have demonstrated that the catalyst systems developed for the enantioselective CA of Grignard reagents to α,β-unsaturated carbonyl compounds are also able to perform highly enantioselective allylic alkylations. The combined potential of these methodologies for the catalytic and enantioselective preparation of optically active synthons bearing the 1,2-dialkyl motif is shown in Scheme 10. The crude product **30a** (98% ee) was submitted to cross metathesis with methyl acrylate affording (*S*)-**32** in good yield. Gratifyingly, the CA of EtMgBr to **32**, catalyzed by (*R*,*S*)-**13b** or its enantiomer (*S*,*R*)-**13b**, provided the anti- and syn-1,2-dialkyl substituted esters **33** and **34**, respectively, with excellent yields and diastereoselectivities.

Conclusions

We have demonstrated that inexpensive and readily available Grignard reagents can be used to provide excellent stereocontrol in catalytic enantioselective conjugate addition and allylic alkylation reactions. The synthetically useful levels of enantiomeric excess and the versatile asymmetric conjugate addition to α,β-unsaturated esters and thioesters are particularly noteworthy features. These reactions provide access to highly valuable building blocks for natural product synthesis. In addition, an iterative and catalytic approach to deoxypropionate subunits has been developed on the basis of the new methodology and has been applied to the synthesis of multi-methyl-branched natural products.

In view of the success so far, it is evident that in the coming years expansion of the catalytic toolbox for the CA of these readily accessible organometallic reagents will be reported. The development of catalysts with similar stereoselectivities in related C−C bond formation reactions using organolithium reagents remains a major challenge.

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