VIP Grignard Reagents

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Enantioselective Cu-Catalyzed 1,4-Addition of Grignard Reagents to Cyclohexenone Using Taddol-Derived Phosphine–Phosphite Ligands and 2-Methyl-THF as a Solvent**

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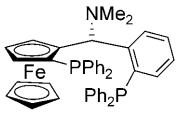
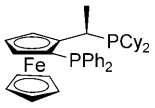
The 1,4-addition (conjugate addition) of C nucleophiles to α,β-unsaturated carbonyl compounds and related activated olefins belongs to the most powerful and reliable tools for C–C bond formation. Accordingly, it is frequently exploited in the synthesis of natural products and other complex organic molecules.[1] Three decades of research on asymmetric[2] and, in particular, asymmetric catalytic[3] versions of conjugate addition reactions have resulted in the development of a broad variety of methods.[1–3] However, the important task of performing the 1,4-addition of simple Grignard reagents, the most common type of organometallic reagents, in an enantioselective fashion still remains a particular challenge.

As recently reviewed,[4a] several Cu-based catalyst systems have been suggested in the past for the catalytic asymmetric 1,4-addition of Grignard reagents.[4] Nevertheless, high enantioselectivities (≥90% *ee*) were achieved only in a few special cases, and the reported methods did not find much application owing to limited substrate scope, operational convenience, and accessibility of the chiral ligands required. In 2004, an important advance was made by Feringa and co-workers who, by screening a set of commercially available chiral P,P ligands, identified ferrocene-based diphosphines, in particular Taniaphos (**1**)[5] and Josiphos (**2**),[6] as promising ligands for such transformations.[7]

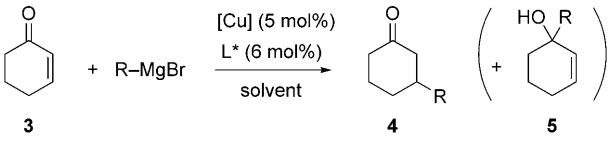


Taniaphos (**1**)



Josiphos (**2**)

For instance, the reaction of *n*-alkyl Grignard reagents with cyclohexenone (**3**) proceeded smoothly in the presence of 5 mol% of a catalyst generated in situ from **1** and CuCl to give the 1,4-addition products **4** with excellent enantioselectivity (up to 96% *ee*) and good regioselectivity (**4**/**5** ≥4:1) (Scheme 1).[4,7] Furthermore, Feringa and co-workers were



R = *n*-alkyl: L* = **1**; [Cu] = CuCl; Et_2O, 0°C; 90-96% *ee*

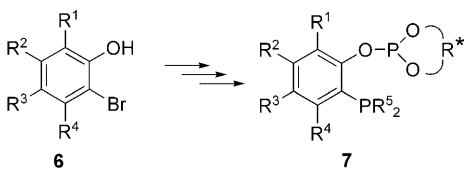
R = *i*Pr: L* = **2**; [Cu] = CuBr-SMe_2; Et_2O, -60°C; 54% *ee*

R = Ph : L* = **2**; [Cu] = CuBr-SMe_2; Et_2O, -60°C; 40% *ee*

Scheme 1. Cu-catalyzed 1,4-addition of Grignard reagents to cyclohexenone according to Feringa.[7]

able to apply this catalytic system to other substrates and in the synthesis of natural products.[8] However, the reaction of **3** with other relevant Grignard reagents such as *i*PrMgBr or PhMgBr proceeded only with low selectivity under these conditions, and also with an alternative catalyst (formed from **2** and CuBr–SMe_2) *ee* values did not exceed 54% (R = *i*Pr) and 40% (R = Ph). Thus, the challenge remained open.

Considering that chiral diphosphine ligands possess an obvious potential for the Cu-catalyzed 1,4-addition of Grignard reagents[7,8] we wondered whether phosphine–phosphite ligands of type **7**[9] (developed in our laboratory) would also be suited for this purpose.[10] These ligands are efficiently prepared from *o*-bromophenols **6** and chiral diols (such as Binol (2,2′-dihydroxy-1,1′-binaphthyl)[11] and Taddol (α,α,α′-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol)[12]), and the modular synthesis facilitates structural variation and optimization (Scheme 2). We herein report that compounds of this class indeed represent highly useful ligands for the Cu-catalyzed 1,4-addition of various Grignard



Scheme 2. Modular phosphine-phosphite ligands of type **7** derived from *o*-bromophenols **6** and chiral diols.

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reagents (including PhMgBr and *i*PrMgBr) to cyclohexenone giving enantioselectivities of up to 92% *ee*.

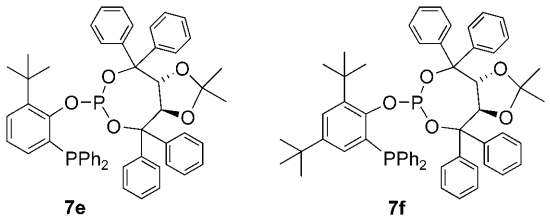
In a first series of experiments a library of ten ligands of type **7** was screened in the Cu-catalyzed addition of ethyl magnesium bromide to cyclohexenone under conditions similar to those used by Feringa et al. (4 mol% CuCl, 6 mol% ligand, Et_2O, 0°C), which also in our hands gave complete conversion within 20 min. As the results summarized in Table 1 show, the Taddol-derived ligands **7e** and **7f** gave the highest enantioselectivities of 68 and 70% *ee*, respectively.[13] Apparently the enantioselectivity strongly depends on the size of R^1 (cf. Scheme 2) as the ligands with a bulky *tert*-butyl substituent in the position *ortho* to the phosphite group performed much better than ligands with sterically less demanding substituents in this position. Also noteworthy is the fact that the Binol-derived ligands (**7i** and **7j**) not only exhibited low enantioselectivities but also mainly gave rise to the regioisomeric products resulting from 1,2-addition.

Table 1: Results of the screening of ligands of type **7** in the Cu-catalyzed reaction of EtMgBr with cyclohexenone according to Scheme 1 (R = Et).[a]

Ligand	Ligand specification[b]	**4a/5a**[c]	*ee*[d] [%]	Config.
7a	$R^1=R^2=R^3=R^4=H$ $R^*(OH)_2$ = (*R*,*R*)-Taddol	95:5	<5	n.d.
7b	$R^1=R^2$ = Me, $R^3=R^4=H$ $R^*(OH)_2$ = (*R*,*R*)-Taddol	99:1	8	*S*
7c	R^1 = Ph, $R^2=R^3=R^4=H$ $R^*(OH)_2$ = (*R*,*R*)-Taddol	99:1	10	*S*
7d	R^1 = *i*Pr, $R^2=R^3=R^4=H$ $R^*(OH)_2$ = (*R*,*R*)-Taddol	99:1	20	*S*
7e	R^1 = *t*Bu, $R^2=R^3=R^4=H$ $R^*(OH)_2$ = (*R*,*R*)-Taddol	95:5	70	*S*
7f	$R^1=R^3$ = *t*Bu, $R^2=R^4=H$ $R^*(OH)_2$ = (*R*,*R*)-Taddol	95:5	68[e]	*S*
7g	$R^1=R^4$ = Me, $R^2=R^3=H$ $R^*(OH)_2$ = (*R*,*R*)-Taddol	92:8	16	*R*
7h	$R^3=R^4=H$, $R^1/R^2=(CH)_4$ $R^*(OH)_2$ = (*R*,*R*)-Taddol	99:1	16	*S*
7i	$R^1=R^2$ = Me, $R^3=R^4=H$ $R^*(OH)_2$ = (*S*)-Binol	21:79	2	*S*
7j	$R^1=R^3$ = *t*Bu, $R^2=R^4=H$ $R^*(OH)_2$ = (*S*)-Binol	23:77	6	*S*

[a] Reaction conditions: 6 mol% L*, 4 mol% CuCl, Et_2O, 0°C, full conversion after 20 min. [b] Only ligands with R^5 = Ph were used. [c] Determined by GC-MS. [d] Determined by GC on a chiral stationary phase. [e] Conducted on a 3 mmol scale; the pure 1,4-product was obtained in 68% yield after distillation.

Having identified **7e** and **7f** (Figure 1) as promising ligands, we decided to continue our examinations with these compounds and to vary the reaction parameters such as copper source, solvent, and reaction temperature (Table 2). Much to our surprise, the choice of the solvent had an extraordinary influence on the enantioselectivity. While replacing Et_2O by *tert*-butyl methyl ether (MTBE) did not have a major effect on the *ee* value, the use of THF as a stronger coordinating solvent led to almost a complete loss of enantioselectivity. However, when the solvent was changed to 2-methyltetrahydrofuran (2-Me-THF),[14] a significant increase of the enantioselectivity by almost 20% *ee* was observed. Lowering the reaction temperature to −78°C led to a further enhancement of the enantioselectivity. The choice of the copper source did not have much effect at 0°C; however, the use of CuBr–SMe_2 resulted in better *ee* values at low temperatures, probably because it is better soluble than CuCl. Under optimized conditions (Table 2, entry 11) the 1,4-addition product **4a** (R = Et) was obtained with a pleasing enantioselectivity of 90% *ee*. This result could be reproduced also on a multi-mmol scale (60% yield of **4a** after distillation and flash chromatography) when the diluted Grignard solution (0.1–0.5 M) was added very slowly to the stirred reaction mixture by means of a syringe pump.



7e **7f**

Figure 1. Taddol-derived phosphine–phosphite ligands **7e** and **7f**.

Table 2: Influence of solvent and temperature on the Cu-catalyzed addition of EtMgBr to cyclohexenone according to Scheme 1 (R = Et)[a] using the Taddol-derived chiral ligand **7f**.

Entry	Solvent	*T* [°C]	Cu source	**4a/5a**[b]	*ee*[c] [%]
1	Et_2O	0	CuCl	95:5	68
2	THF	0	CuCl	95:5	<5
3	MTBE	0	CuCl	96:4	56
4	toluene	0	CuCl	86:14	58
5	toluene/Et_2O	0	CuCl	96:4	60
6	Me-THF	0	CuCl	95:5	84
7	Me-THF	−20	CuCl	96:4	86
8	Me-THF	−40	CuCl	95:5	82
9	Me-THF	−40	CuBr–SMe_2	90:10	86
10	Me-THF	−60	CuBr–SMe_2	89:11	88
11	Me-THF	−78	CuBr–SMe_2	89:11	90

[a] Reaction conditions: 6 mol% **7f**, 4 mol% Cu source. [b] Determined by GC-MS. [c] Determined by GC on a chiral stationary phase (BGB 176 SE).

Encouraged by this result (Table 2, entry 11) we decided to probe the scope of our methodology by applying other Grignard reagents. Besides PhMgBr and *i*PrMgBr, which (as mentioned above) gave only unsatisfactory enantioselectivities with ligands **1** and **2**,[7] we considered 3-butenyl and isopropenyl magnesium bromide as particularly relevant, because the corresponding 1,4-addition products would represent interesting building blocks for natural product synthesis. To our satisfaction, the reaction proceeded well with all of these Grignard reagents under the standard conditions (using ligands **7e** and **7f**) to give the 1,4-addition products **4a–e** with high to excellent enantioselectivities (82–92% *ee*; see Table 3).

Again, 2-Me-THF was found to be a superior solvent in most cases; however, there are exceptions. For instance, the highest *ee* for 3-butenyl-MgBr was achieved in neat Et_2O. In the case of *i*PrMgBr optimal results were obtained when Et_2O

Table 3: Cu-catalyzed asymmetric 1,4-addition of various Grignard reagents to cyclohexenone according to Scheme 1.[a]

Entry	RMgBr	L*	Solvent	**4**/**5**[b]	*ee* [%][b]	Config.[c]
1	EtMgBr	**7f**	Me-THF	89:11	90	(−)-*S*
2		**7f**	Et_2O	91:9	91	(−)-*R*
3	*i*PrMgBr	**7f**	Et_2O[d]	98:2	67	(+)-*R*
4	*i*PrMgBr	**7e**	Et_2O[d]	99:1	82	(+)-*R*
5		**7e**	Me-THF	91:9	92	(+)-*R*
6	PhMgBr	**7f**	Me-THF	60:40	74	(+)-*R*
7	PhMgBr	**7e**	Me-THF	91:9	92	(+)-*R*

[a] Reaction conditions: 6 mol% ligand, 5 mol% CuBr–SMe_2, −78 °C, full conversion after 2 h. [b] Determined by GC on a chiral stationary phase. [c] Sign of the optical rotation at 589 nm in CH_2Cl_2 and absolute configuration as determined by CD spectroscopy. [d] A solution of the Grignard reagent in Me-THF was used.

was used to dissolve the substrate (**3**) and the catalyst, while the Grignard reagent was prepared and used as a solution in 2-Me-THF. Performing the reaction with *i*PrMgBr in either neat 2-Me-THF or Et_2O resulted in low enantioselectivities and, moreover, slow conversion in the latter case. Also noteworthy is the fact that at −78 °C ligand **7e** proved to be superior for branched Grignard reagents, while the 1,4-addition of both linear Grignard reagents proceeded most selectively when ligand **7f** was employed. The other ligands of type **7** (Table 1) were found to be much less selective.

The absolute configuration of the products (as given in Table 3) was determined by means of CD spectroscopy (Figure 2) applying the octant rule.[14] As Figures 2 and 3 illustrate, the stereochemical outcome of the reactions

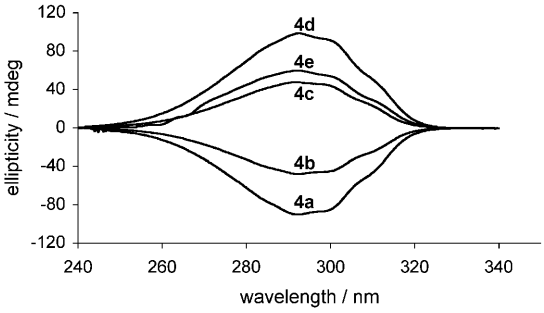


Figure 2. CD spectra of compounds **4a–e** in CH_3CN.

depends on the Grignard reagent used. In the case of the unbranched reagents (EtMgBr and 3-butenylmagesium bromide) the main enantiomers of the products (**4a**, **4b**) result from a *Si*-face attack at the position β to the ketone. However, using the same (*R*,*R*)-Taddol-derived catalysts, the 1,4-addition of the branched reagents afforded products **4c**–**4e**, resulting from a *Re*-face attack. We consider this switch of the enantiofacial selectivity with the type of Grignard reagent as a remarkable phenomenon which challenges any future attempts to rationalize the stereochemical outcome of these reactions based on detailed transition-state models. As Figure 3 summarizes, the methodology developed opens access to a variety of 3-substituted cyclohexanones with

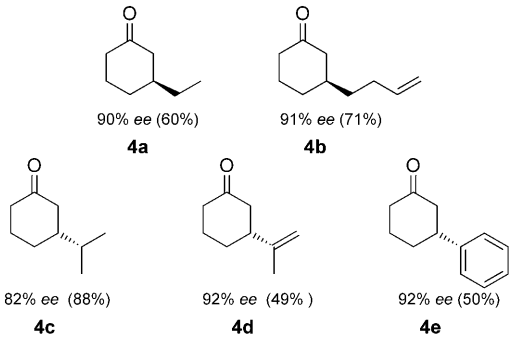


Figure 3. Structure and enantiomeric purities (and yields) of 3-substituted cyclohexanones synthesized in this study.

high enantioselectivities (82–92 % *ee*) and preparative yields of up to 88 %.[15]

In conclusion, we have identified phosphine–phosphite ligands of type **7** as a novel (second) class of chiral P,P ligands suitable for the Cu-catalyzed asymmetric 1,4-addition of Grignard reagents to cyclohexenone.[16,17] These readily accessible ligands proved to be compatible with an unsurpassed range of Grignard reagents, and owing to their modular nature it should be possible to achieve further (individual) ligand tuning for specific reaction systems.[9b,10]

Furthermore, we came across a very interesting solvent effect with (racemic) 2-methyl-THF, which has only recently been recognized as an environmentally benign solvent because of its low water miscibility and its origin from renewable resources.[18] Our results suggest that this solvent should be generally considered as an alternative to diethyl ether and THF whenever organometallic reactions are optimized.

Experimental Section

Typical procedure for the 1,4-addition on a preparative scale: Under an atmosphere of argon, CuBr–SMe_2 (0.05 equiv, 0.45 mmol) and the ligand (0.06 equiv, 0.54 mmol) were dissolved in 15 mL of solvent and stirred for 15 min at RT. After addition of enone **3** (1.0 equiv, 9 mmol) the reaction mixture was cooled to −78 °C and a dilute (0.1–0.5 mol L^{-1}) solution of the Grignard reagent (1.2 equiv, 10.8 mmol) was slowly added over 2 h by means of a syringe pump. The mixture was then stirred for another 30 min at −78 °C and quenched by addition of MeOH (5 mL) and 1 M aqueous NH_4Cl solution (10 mL). The layers were separated, and the aqueous phase was extracted with *tert*-butyl methyl ether. The combined organic solutions were washed with brine and dried over $MgSO_4$, and the solvent was evaporated in vacuo. The crude product (yellowish oil) was purified by distillation (0.2 mbar) and subsequent flash chromatography (cyclohexane/EtOAc 10:1) to give the pure 1,4-addition product **4** as a colorless oil.

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[1] Reviews: a) P. Perlmutter, *Tetrahedron Organic Chemistry Series 9*; Pergamon, Oxford, UK, **1992**; b) V. J. Lee in *Comprehensive*

Organic Synthesis, *Vol. 4* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 69–137; c) V. J. Lee in *Comprehensive Organic Synthesis*, *Vol. 4* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 139–168; d) J. A. Kozlowski in *Comprehensive Organic Synthesis*, *Vol. 4* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 169–198.

[2] Reviews: a) H.-G. Schmalz in *Comprehensive Organic Synthesis*, *Vol. 4* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 199–236; b) B. E. Rossiter, N. M. Swingle, *Chem. Rev.* **1992**, *92*, 771–806.

[3] a) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171–196; b) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279–1300; c) K. Tomioka, Y. Nagaoka in *Comprehensive Asymmetric Catalysis*, *Vol. III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 1105–1120.

[4] a) Review: F. López, A. J. Minaard, B. L. Feringa, *Acc. Chem. Res.* **2007**, *40*, 179–188; for key publications in this field, see: b) K.-H. Ahn, R. B. Klassen, S. J. Lippard, *Organometallics* **1990**, *9*, 3178–3181; c) D. M. Knotter, D. M. Grove, W. J. J. Smeets, A. L. Spek, G. van Koten, *J. Am. Chem. Soc.* **1992**, *114*, 3400–3410 d) D. Spescha, G. Rihs, *Helv. Chim. Acta* **1993**, *76*, 1219–1230; e) Q.-L. Zhou, A. Pfaltz, *Tetrahedron* **1994**, *50*, 4467–4478; f) A. L. Braga, S. J. N. Silva, D. S. Lüdtke, R. L. Drekener, C. C. Silveira, J. B. T. Rocha, L. A. Wessjohann, *Tetrahedron Lett.* **2002**, *43*, 7329–7331; g) D. Seebach, G. Jaeschke, A. Pichota, L. Audergon, *Helv. Chim. Acta* **1997**, *80*, 2515–2519; h) M. Kanai, Y. Nakagawa, K. Tomioka, *Tetrahedron* **1999**, *55*, 3843–3854; i) E. L. Stangeland, T. Sammakia, *Tetrahedron* **1997**, *53*, 16503–16510.

[5] T. Ireland, G. Grossheimann, C. Wieser-Jeunesse, P. Knochel, *Angew. Chem.* **1999**, *111*, 3397–3400; *Angew. Chem. Int. Ed.* **1999**, *38*, 3212–3215.

[6] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062–4066.

[7] B. L. Feringa, R. Badorrey, D. Peña, S. R. Harutyunyan, A. J. Minaard, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5834–5838.

[8] a) F. López, S. R. Harutyunyan, A. J. Minaard, B. L. Feringa, *J. Am. Chem. Soc.* **2004**, *126*, 12784–12785; b) F. López, S. R. Harutyunyan, A. Meetsma, A. J. Minaard, B. L. Feringa, *Angew. Chem.* **2005**, *117*, 2812–2816; *Angew. Chem. Int. Ed.* **2005**, *44*, 2752–2756; c) S. R. Harutyunyan, F. López, W. R. Browne, A. Correa, D. Peña, R. Badorrey, A. Meetsma, A. J. Minaard, B. L. Feringa, *J. Am. Chem. Soc.* **2006**, *128*, 9103–9118; d) R. Des Mazery, M. Pullez, F. López, S. R. Harutyunyan, A. J. Minaard, B. L. Feringa, *J. Am. Chem. Soc.* **2005**, *127*, 9966–9967; e) S.-Y. Wang, S.-J. Ji, T.-P. Loh, *J. Am. Chem. Soc.* **2007**, *129*, 276–277; f) T.-K. Lum, S.-Y. Wang, T.-P. Loh, *Org. Lett.* **2008**, *10*, 761–764.

[9] a) J. Velder, T. Robert, I. Weidner, J.-M. Neudörfl, J. Lex, H.-G. Schmalz, *Adv. Synth. Catal.* **2008**, *350*, 1309–1315; b) F. Blume, S. Zemolka, T. Fey, R. Kranich, H.-G. Schmalz, *Adv. Synth. Catal.* **2002**, *344*, 868–883; c) R. Kranich, K. Eis, O. Geis, S. Mühle, J. W. Bats, H.-G. Schmalz, *Chem. Eur. J.* **2000**, *6*, 2874–2894.

[10] For the application of ligands of type **7** in the highly enantioselective Rh-catalyzed hydroboration of styrenes, see Ref. [9b] as well as: S. Werle, T. Fey, J. M. Neudörfl, H.-G. Schmalz, *Org. Lett.* **2007**, *9*, 3555–3558; Erratum: S. Werle, T. Fey, J. M. Neudörfl, H.-G. Schmalz, *Org. Lett.* **2007**, *9*, 4085.

[11] For a recent review, see: a) J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857–898; Erratum: J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857–898; for an update, see b) J. M. Brunel, *Chem. Rev.* **2007**, *107*, 1–45.

[12] a) D. Seebach, A. K. Beck, R. Imwinkelried, S. Roggo, A. Wonnacott, *Helv. Chim. Acta* **1987**, *70*, 954. For a review, see: b) D. Seebach, A. K. Beck, A. Heckel, *Angew. Chem.* **2001**, *113*, 96–142; *Angew. Chem. Int. Ed.* **2001**, *40*, 92–138.

[13] In a control experiment under exactly the same conditions, ligand **1** (Taniaphos) afforded the product (**4**, R = Et) with 92% *ee*, which is in acceptable agreement to the results of Feringa and coworkers (Ref. [7]) who reported 96% *ee* with a slightly higher catalyst loading.

[14] For reviews, see: a) E. L. Eliel, S. H. Wilen, L. N. Mander in *Stereochemistry of Carbon Compounds*, VCH, New York, **1994**, pp. 1007–1043; b) D. N. Kirk, *Tetrahedron* **1986**, *42*, 777–818; c) J. K. Gawronski, *Tetrahedron* **1982**, *38*, 3–26; d) R. D. Burnett, D. N. Kirk, *J. Chem. Soc. Perkin Trans. 1* **1981**, 1460–1468.

[15] Yields (obtained on a 9 mmol scale) are in the same range as reported by Feringa et al. (Ref. [7]); they are sometimes impaired through the formation of by-products resulting from aldol-type processes.

[16] For asymmetric Cu-catalyzed 1,4-additions of Grignard reagents to 3-alkylcyclohexenones using chiral N-heterocyclic carbene ligands, see: a) D. Martin, S. Kehrli, M. d'Augustin, H. Clavier, M. Mauduit, A. Alexakis, *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417; b) Y. Matsumoto, K.-i. Yamada, K. Tomioka, *J. Org. Chem.* **2008**, *73*, 4578–4581.

[17] To the best of our knowledge, only one example for the use of a chiral phosphine–phosphite ligand in the Cu-catalyzed asymmetric conjugate addition (of Et_2Zn and Et_3Al) has been reported; see: M. Diéguez, S. Deerenberg, O. Pàmies, C. Claver, P. W. N. M. van Leeuwen, P. C. J. Kamer, *Tetrahedron: Asymmetry* **2000**, *11*, 3161–3166.

[18] D. F. Aycock, *Org. Process Res. Dev.* **2007**, *11*, 156–159.

