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Enantioselective Copper-Catalysed Allylic Alkylation of Cinnamyl Chlorides by Grignard Reagents using Chiral Phosphine-Phosphite Ligands

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Abstract: The copper(I)-catalysed S_N2'-type allylic substitution of *E*-3-aryl-allyl chlorides (cinnamyl chlorides) using Grignard reagents represents a powerful method for the synthesis of compounds carrying a benzylic stereocentre. By screening a small library of modular chiral phosphine-phosphite ligands a new copper(I)-based catalyst system was identified which allows the performance of such reactions with exceptional high degrees of regio- and enantioselectivity. Best results were obtained using TADDOL-derived ligands (3 mol%), copper(I) bromide·dimethyl sulfide ($CuBr{\cdot}SMe_2$) (2.5 mol%) and methyl *tert*-butyl ether (MTBE) as a solvent. Various (1-alkyl-allyl)benzene derivatives were prepared with up to 99% *ee* (GC) in isolated yields of up to 99%. In most cases the product contained less than 3% of the linear regioisomer (except for *ortho*-substituted substrates). Both electron-rich and electron-deficient cinnamyl chlorides were successfully employed. The absolute configuration of the products was assigned by comparison of experimental and calculated CD spectra. The substrates were prepared from the corresponding alcohols by reaction with thionyl chloride. Initially formed mixtures of regioisomeric allylic chlorides were homogenised by treatment with $CuBr{\cdot}SMe_2$ (2.5 mol%) in the presence of triphenyl phosphine (PPh_3) (3 mol%) in MTBE at low temperature to give the pure linear isomers. In reactions with methylmagnesium bromide (MeMgBr) an *ortho*-diphenylphosphanyl-arylphosphite ligand with an additional phenyl substituent in *ortho'*-position at the aryl backbone proved to be superior. In contrast, best results were obtained in the case of higher alkyl Grignard reagents (such as ethyl-, *n*-butyl-, isopropyl-, and 3-butenylmagnesium bromides) with a related ligand carrying an isopropyl substituent in *ortho'*-position. The method was tested on a multi-mmol scale and is suited for application in natural product synthesis.

Keywords: allylic substitution; asymmetric catalysis; chiral P,P ligands; copper(I); Grignard reagents

Introduction

The development of efficient protocols for catalytic enantioselective C–C bond formation is a central task of chemical synthesis research.[1] While considerable progress has been made towards the development of metal-catalysed allylic substitution reactions in general, comparably few copper-based methods have been established allowing the use of organometallic reagents.[2] Early studies on the regioselectivity of the reaction of allylic esters with cuprates[3] paved the way for the development of asymmetric[4] and even catalytic asymmetric methods.[5] Later, allylic halides were also employed in enantioselective copper-catalysed S_N2'-type allylic alkylations mainly using organo-zinc[6] or Grignard reagents.[7] Recently, Grignard reagents were used in the Cu-catalysed substitution of β-disubstituted allylic halides and 1,4-dihalo-2-butenes.[8]

As summarized in recent reviews[2,9] a variety of chiral catalysts have been employed in these reactions. A preformed arenethiolato-Cu(I) complex was used by Bäckvall and van Koten;[5a,b] however, catalysts are usually prepared *in situ* from a Cu(I) salt and a chiral ligand, such as ferrocenyl-based thiolates,[5c] amino-diphosphanes,[7e] phosphoramidites,[7a–d,8], spiro-phosphoramidites,[6d] aminoalkyl-phosphites,[7a,b] or N-heterocyclic carbenes.[10]

While high enantioselectivities (up to 99% *ee*) were observed in certain cases, the applicability of the

methodology in the context of complex synthesis is still limited. An example is the Cu-catalysed reaction of cinnamyl chlorides with MeMgBr where the enantioselectivity drops from 96% to 66% *ee* on introduction of an *ortho*-substitutent.[7c] Also, regioselectivities are frequently unsatisfactory and rarely exceed 90%. Therefore, the search for new efficient catalyst systems also tolerating a broader substrate scope still represents an important goal.

We have recently developed a new class of chiral phosphine-phosphite ligands of type **1** (Figure 1)

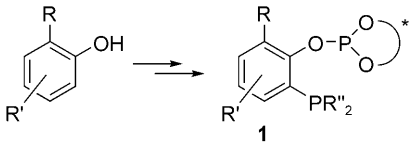
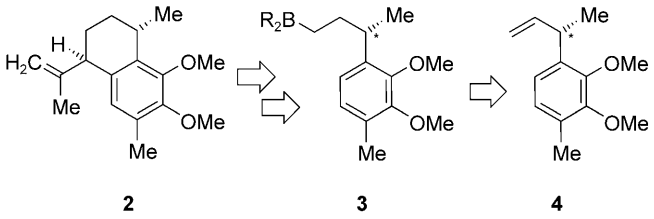


Figure 1. Phenol-derived modular ligands of type **1**.

which are readily synthesized from a phenol and a chiral diol (such as BINOL or TADDOL).[11] The modular nature of these ligands not only allows the synthesis of whole ligand libraries but also facilitates the optimisation of the ligand structure for individual reactions. So far, these ligands were applied with outstanding success in the Rh-catalysed asymmetric hydroboration of styrenes,[11b,12] the Cu-catalysed asymmetric 1,4-addition of Grignard reagents to enones,[13] and the Rh-catalysed asymmetric hydroformylation of styrene.[14]

Encouraged by these results and in continuation of our interests in the field of marine diterpenoid total synthesis[15] we envisioned to exploit these ligands in the enantioselective synthesis of substituted (1-methyl-allyl)benzenes (such as **4**) by means of a Cu-catalysed allylic substitution. As shown in Scheme 1, compound **4** would represent an attractive precursor for organoboron intermediates of type **3** from which the calamenene **2** is accessible in a few efficient steps.[12]

We here disclose the details of a study which has led to the identification of highly selective new catalyst systems (exploiting ligands of type **1**) for the Cu-catalysed enantioselective allylic substitution of cinnamyl chlorides by alkyl Grignard reagents – as a general enantioselective entry to various arene building blocks with a benzylic chirality centre.

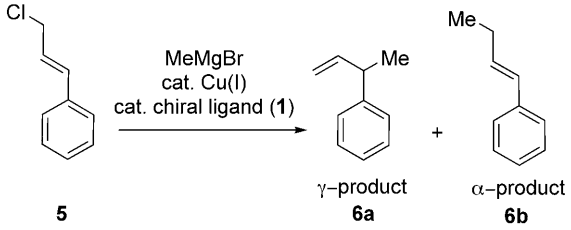


Scheme 1. The (1-methyl-allyl)benzene derivative **4** as a precursor for **2** and related terpenoids.

Results and Discussion

In the present study, fourteen phosphine-phosphite ligands (**1a–n**) were tested (Figure 2). These ligands were all prepared from the corresponding substituted phenols in up to 60% overall yield following the established four-steps protocol.[11c] Most of the ligands used contain a diphenylphosphanyl tooth. Only ligand **1i** carries a bis-3,5-dimethyl-4-methoxyphosphine unit to probe a system with different electronic and steric properties at this position. To build up the phosphite unit, either (*R*,*R*)-TADDOL[16] or (*S*)-BINOL[17] were used as chiral diol. In awareness of the crucial importance of the substituents at the central arene ring (especially in *ortho*-position to the oxy-functionality)[11b,13,14] on the ligand performance, a set of differently substituted phenols was employed for the ligand synthesis.

As a substrate for an initial ligand screening we selected commercial *trans*-cinnamyl chloride (**5**) and studied the regio- and enantioselectivity of its reaction with methyl-magnesium bromide (according to Scheme 2) using either Cu(I)-thiophene carboxylate (CuTC)[18] or $CuBr{\cdot}SMe_2$ as the Cu source.



Scheme 2. The parent reaction investigated in this study.

The results of the first screening of our prototype library, summarised in Table 1, clearly revealed the potential of the phosphine-phosphite ligands of type **1** for Cu-catalysed allylic substitution reactions using Grignard reagents. Best results were obtained with ligands **1c** and **1h**, which both gave a very good enantioselectivity (94% *ee*) and a satisfying (*ca.* 9:1) regioselectivity (γ-selectivity) in favour of the desired branched product **6a**. Again, a dramatic impact of the the substituent(s) at the ligand backbone (especially in the *ortho* position to the phosphite unit) was found, as the comparison of the results obtained with ligands **1a**–**1h** confirms. In contrast to the Cu(I)-catalysed 1,4-addition to cyclic enones,[13] ligands **1e** and **1f** (with a bulky *tert*-butyl substituent in the *ortho*-position) exhibited only a moderate enantioselectivity.

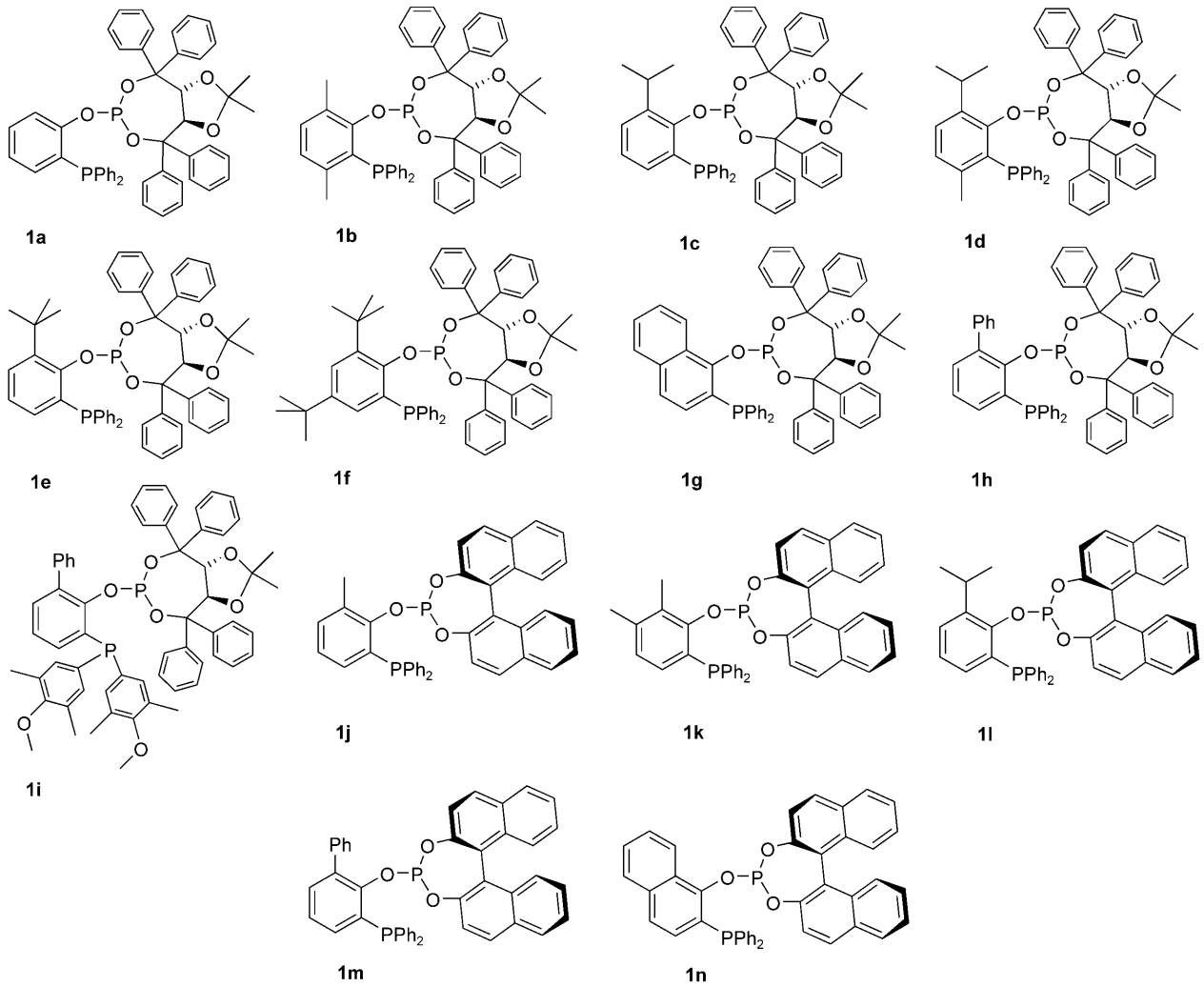


Figure 2. Phosphine-phosphite ligands of type **1** used in the present study.

Also noteworthy is the fact that the TADDOL-derived ligands generally performed much better than the BINOL-derived ligands (**1j**–**1n**). The influence of the specific copper source on the selectivities was not sufficiently pronounced to allow any conclusions at this stage. Noteworthy is also the fact that the *R*-configurated enantiomer (*R*-**6a**) was preferentially formed in all experiments (for the assignments, see below).

We selected the "phenyl-substituted" ligand **1h** for the further optimisation of the reaction conditions. After confirming the high selectivity initially obtained with this ligand (Table 1; entry 16) on a 3.3 mmol scale (using 500 mg of **5**), we next investigated the influence of the solvent. Besides CH_2Cl_2 (used initially), we tested THF, its less coordinating 2-methyl analogue (MeTHF),[13] Et_2O, and methyl *tert*-butyl ether (MTBE). As the results shown in Table 2 indicate, we obtained excellent enantioselectivities (up to >99% *ee*) and regioselectivities (up to 98/2) in the less coordinating ethereal solvents. Moreover, $CuBr{\cdot}SMe_2$ was identified as the preferred source of Cu(I). Remarkably, best results were achieved in MTBE, and, accordingly, this solvent was used in all further experiments.

The outstanding selectivity in the synthesis of **6a** under the above-mentioned conditions (Table 2; entry 9) was obtained using a 2.5-fold excess of the Grignard reagent in the presence of 5% of the catalyst. To further improve the method (also from an ecological point of view) we were interested in reducing the amount of catalyst and Grignard reagent to a minimum. As shown in Table 3 it was indeed possible to reduce the amount of Grignard reagent to 1.2 equivalents and to halve the amount of catalyst without losing selectivity (entry 3). Further reduction of the catalyst load to 1.25 equivalents, however, led to lower (still remarkable) selectivities.

In another series of experiments (Table 4) the effect of the reaction temperature was briefly studied. By successively increasing the temperature in steps of 20 °C a continuous decrease of regio- as well as of enantioselectivity was observed. Nevertheless, the fact

Table 1. Performance of different ligands of type **1** in the Cu-catalysed reaction of **5** with MeMgBr according to Scheme 2 under standard conditions in CH_2Cl_2.[a]

Entry	Ligand	Cu(I) source	**6a/6b**[b]	*ee* [%][b]
1	**1a**	CuBr·SMe_2	59/51	15
2		CuTC	2/98	30
3	**1b**	CuBr·SMe_2	65/35	56
4		CuTC	75/25	49
5	**1c**	CuBr·SMe_2	88/12	**95**
6		CuTC	80/20	**94**
7	**1d**	CuBr·SMe_2	45/55	75
8		CuTC	25/75	36
9	**1e**	CuBr·SMe_2	77/23	61
10		CuTC	51/49	43
11	**1f**	CuBr·SMe_2	98/2	62
12		CuTC	84/16	61
13	**1g**	CuBr·SMe_2	29/71	73
14		CuTC	3/97	5
15	**1h**	CuBr·SMe_2	88/12	**94**
16		CuTC	93/7	**94**
17	**1i**	CuBr·SMe_2	94/6	86
18		CuTC	93/7	85
19	**1j**	CuBr·SMe_2	10/90	23
20		CuTC	29/71	11
21	**1k**	CuBr·SMe_2	11/89	0
22		CuTC	24/76	3
23	**1l**	CuBr·SMe_2	14/86	22
24		CuTC	12/88	7
25	**1m**	CuBr·SMe_2	20/80	3
26		CuTC	40/60	2
27	**1n**	CuBr·SMe_2	7/93	2
28		CuTC	20/80	1

[a] *Conditions:* **5** (300 μmol), Cu(I) source (5 mol%), ligand (6 mol%) in CH_2Cl_2 (2 mL) at −78 °C, addition of MeMgBr in CH_2Cl_2 over 7 h.

[b] The **6a/6b** ratio and the enantiomeric excess (*ee*) of **6a** were determined by CG analysis; the conversion of **5** was always >99%. Values given are the average of two independent experiments. In all experiments *R*-**6a** was formed as the major enantiomer.

Table 2. Influence of the solvent on the Cu-catalysed reaction of **5** with MeMgBr according to Scheme 2 in the presence of ligand **1h**.[a]

Entry	Solvent	Cu(I) source	**6a/6b**[b]	*ee* [%][b]
1	CH_2Cl_2	CuBr·SMe_2	88/12	94
2		CuTC	93/7	94
3	THF	CuBr·SMe_2	10/90	39
4		CuTC	24/76	19
5	MeTHF	CuBr·SMe_2	81/19	>99
6		CuTC	48/52	58
7	Et_2O	CuBr·SMe_2	96/4	99
8		CuTC	86/14	97
9	MTBE	CuBr·SMe_2	**98/2**	**>99**
10		CuTC	**93/7**	**99**

[a] *Conditions:* **5** (300 μmol), Cu(I) source (5 mol%), ligand **1h** (6 mol%) in solvent (2 mL) at −78 °C, addition of MeMgBr in CH_2Cl_2 over 7 h.

[b] The **6a/6b** ratio and the enantiomeric excess (*ee*) of **6a** were determined by CG analysis; the conversion of **5** was always >99%. Values given are the average of two independent experiments.

Table 3. Influence of the catalyst loading on the Cu-catalysed reaction of **5** with MeMgBr according to Scheme 2 in the presence of ligand **1h**.[a]

Entry	Cu(I) [mol%]	Ligand [mol%]	MeMgBr (equiv.)	**6a/6b**[b]	*ee* [%][b]
1	5	6	2.5	98/2	>99
2	2.5	3	5	98/2	>99
3	2.5	3	1.2	98/2	>99
4	1.9	1.7	1.2	98/2	98
5	1.25	1.5	1.2	87/13	98

[a] *Conditions:* **5** (300 μmol), CuBr·SMe_2, ligand **1h** in MTBE (2 mL) at −78 °C, slow addition of MeMgBr in CH_2Cl_2 over 7 h.

[b] The **6a/6b** ratio and the enantiomeric excess (*ee*) of **6a** were determined by CG analysis; the conversion of **5** was always >99%. Values given are the average of two independent experiments.

that useful regio- and enantioselectivities were still obtained at 0 °C (or even at 20 °C) convincingly reflects the robustness of the reaction system.

Substituted Cinnamyl Chlorides

Having developed efficient and reliable conditions for the reaction of **5** as the parent substrate we next turned our attention to the study of other *trans*-cinnamyl chlorides (**8**) with different substitution patterns at the arene ring (see Table 5). The required allylic chlorides (**8**) were prepared from the corresponding cinnamic acid derivatives (**7**) by reduction of an *in situ*-activated derivative[19] and subsequent treatment of the intermediate allylic alcohols with thionyl chloride in ether[20] (Scheme 3). As a complication, the products of type **8** were frequently obtained as inseparable mixtures together with the isomeric allylic chlorides of type **9** (for instance in the case of compounds **10**, **12**, **14**, **26** and **28**). However, this problem was solved by simply stirring an MTBE solution of the mixtures with catalytic amounts of CuBr·SMe_2 and PPh_3 at −78 °C. Under these conditions, an isomerisation-equilibration process[21] cleanly produced the thermodynamically more stable linear allylic chlorides (**8**), which could then be isolated in pure form.

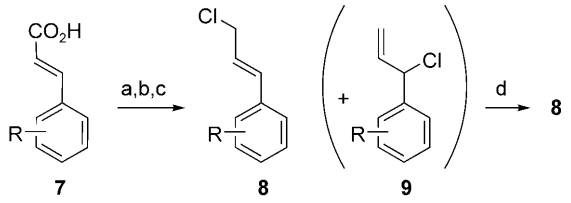
Substrate **24** (with a triple substituted double bond) was synthesised from *4-tert*-butylbenzaldehyde through aldol condensation with propionaldehyde, followed by reduction and chlorination (Scheme 3). In the case of **24** only a 1:1 mixture of regioisomeric al-

Table 4. Influence of the reaction temperature on the Cu-catalysed reaction of **5** with MeMgBr according to Scheme 2 in the presence of ligand **1h**.[a]

Entry	Temp. [°C]	**6a/6b**[b]	*ee* [%][b]
1	−78	98/2	99
2	−60	97/3	95
3	−40	89/11	92
4	−20	95/5	94
5	0	91/9	92
6	20	89/11	86

[a] *Conditions:* **5** (300 μmol), CuBr·SMe_2 (2.5 mol%), ligand **1h** (3 mol%) in MTBE (2 mL), slow addition of MeMgBr in CH_2Cl_2 over 7 h.

[b] The **6a/6b** ratio and the enantiomeric excess (*ee*) of **6a** were determined by CG analysis; the conversion of **5** was always >99%. Values given are the average of two independent experiments.



Scheme 3. Preparation of substituted cinnamyl chlorides. *Conditions:* a) NEt_3, THF, ethyl chloroformate; b) $NaBH_4$ THF, then MeOH; c) $SOCl_2$, Et_2O; d) CuBr·SMe_2 (2.5 mol%), PPh_3, (3 mol%), MTBE, −78 °C.

lylic chlorides was obtained after isomerisation of the initial 1.4:1 mixture with CuBr·SMe_2 and PPh_3. The isomerisation of **28** lead to a 2:1 mixture in favour of the branched allylic chloride.

The differently substituted cinnamyl chlorides (**10**, **12**, **14**, **16**, **18**, **20**, **22**, **24**, **26** and **28**) were then reacted with MeMgBr in the presence of CuBr·SMe_2 (2.5 mol%) and ligand **1h** (3 mol%), according to the optimum conditions for the parent substrate **5** (Table 3; entry 3). Much to our satisfaction we found that under these standard conditions all substrates afforded the desired branched substitution products in high yield with good to excellent selectivity. As the results given in in Table 5 reveal, all *para*- or *meta*-substituted substrates gave rise to high enantio- (96–99% *ee*) and regioselectivities (≥94:6). While a low regioselectivity was observed for the *ortho*-chloro-substituted substrate **12**, the result obtained for the *ortho*-methoxycinnamyl chloride (**18**) is still in a suitable range for possible synthetic applications.

The reaction of compound **24** to give **25a** (Table 5, entry 8) deserves attention because it suggests that cinnamyl chlorides with a substituent in the β-position are also suitable substrates. Noteworthy is also the unprecedented employment of substrates with reactive functional groups such as ester or cyano (entries 9 and 10). All in all, the results shown in Table 5 document a useful scope of differently substituted *trans*-cinnamyl chlorides (**8**), which can be transformed using the standard protocol. Further improvement of the selectivity may even be achieved in specific cases by individual optimisation of the reaction conditions.

Variation of the Grignard Reagent

Having demonstrated that the standard catalyst system developed (based on ligand **1h**) allows for the Cu-catalysed allylic substitution of a broad range of substrates of type **8** in a highly selective fashion using methylmagnesium bromide, we were also interested in the question whether different Grignard reagents can also be employed.

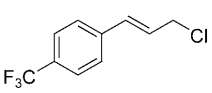
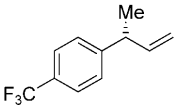
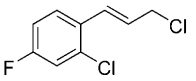
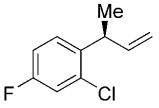
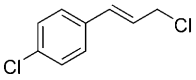
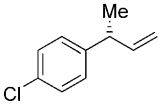
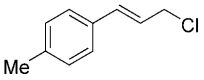
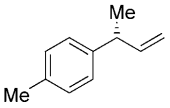
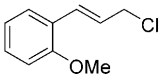
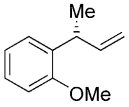
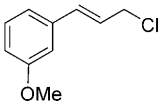
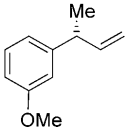
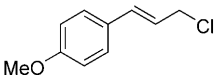
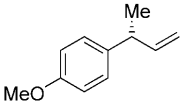
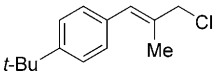
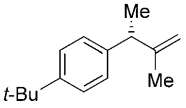
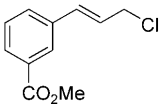
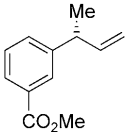
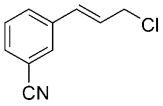
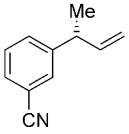
In a first experiment using the parent substrate **5** and EtMgBr the expected product (**30a**) was obtained in high yield and with excellent γ-selectivity; however, the enantioselectivity was only 66% *ee* (Table 6, entry 1). At this point we remembered that ligand **1c** had shown a similar performance as **1h** in the initial ligand screening (Table 1). Therefore, we tested this less bulky ligand (**1c**) in the reaction of cinnamyl chloride **5** with EtMgBr and were pleased to find a significantly improved enantioselectivity of 85% *ee* (Table 6, entry 2).

As Table 6 also shows, the reaction of **5** with *n*-butyl-MgBr (as a higher *n*-alkyl Grignard reagent) proceeded under the same conditions with a remarkable γ-selectivity but with only 76% *ee* (Table 6, entry 3). In contrast, 3-butenyl-MgBr afforded the corresponding product (**32a**) with virtually perfect enantioselectivity and a respectable regioselectivity of 94:6 (Entry 4). Finally, it was found that isopropyl-MgBr (as a sterically more demanding, secondary Grignard reagent) reacted with high γ-selectivity to give the branched hydrocarbon **33a** with an enantioselectivity of 82% *ee*.

Configuration Assignments

The absolute configuration of **6a** and the various allylic substitution products given in Table 5 and Table 6 was assigned by comparison of experimental and calculated circular dichroism (CD) spectra. For this purpose, the CD spectra of these compounds in MeOH were calculated through time-dependent density-functional theory (TDDFT)[22] using Gaussian '03W[23], the B3LYP functional[24] and the TZVP basis set.[25] This methodology had previously been used successfully for the prediction of CD spectra of related chiral benzene derivatives.[26]

Table 5. CuI)-catalysed reaction of substituted cinnamyl chlorides with MeMgBr in the presence of ligand **1h**.[a]

Entry	Substrate	Product	Yield[b]	Regioselectivity (γ/α)[c]	*ee* [%][c]	Configuration[d]
1	**10** 	**11a** 	93	94/6	97	*R*
2	**12** 	**13a** 	99	55/45	87	*S*
3	**14** 	**15a** 	99	98/2	97	*R*
4	**16** 	**17a** 	82	99/1	98	*R*
5	**18** 	**19a** 	93	85/15	93	*R*
6	**20** 	**21a** 	99	98/2	99	*R*
7	**22** 	**23a** 	100	99/1	96	*R*
8[e]	**24** 	**25a** 	86	87/13	94	*R*
9	**26** 	**27a** 	76	97/3	99	*R*
10[f]	**28** 	**29a** 	98	97/3	84	*R*

[a] *Conditions:* substrate (300 μmol), CuBr·SMe_2 (2.5 mol%), ligand **1h** (3 mol%) in MTBE (2 mL), slow addition of MeMgBr (1.2 equiv.) in CH_2Cl_2 over 7 h. Conversion was >99%.

[b] Yield of isolated products (γ+α) after purification by filtration over silica gel.

[c] The ratio of regioisomers and the enantiomeric excess (*ee*) of the γ-product were determined by CG analysis; the conversion of substrate was always >99%. Values given are the average of two independent experiments.

[d] The absolute configuration was determined by correlation of experimental and calculated CD spectra.

[e] In this case, the substrate (**24**) was employed as a 1.4:1 mixture of the regioisomeric allylic chlorides (compare Scheme 3).

[f] In this case, the substrate (**28**) was employed as a 2:1 mixture of the regioisomeric allylic chlorides (compare Scheme 3).

As an illustration, the measured and calculated CD spectra of compounds (*R*)-**15a** and (*R*)-**33a** are depicted in Figure 3. The clear consensus in the region from 210 nm to 235 nm (emerging from ^1L_a transitions) indicates them in both cases belonging to the same enantiomer.[26c,d] Meanderings in the area of smaller wavelengths (>240 nm) arise from weak contrary vibrational contributions of the arene *via* ^1L_b transitions, which change their sign depending on the temperature and therefore are of little value for the configuration assignment.[26d,27] The thus determined absolute configurations are in agreement with the literature for compounds **6a**, **15a**, **17a**, **23a**, **30a**, **31a**, and **32a** based on the sign of the $[\alpha]_D$ values.[28] The only

disagreement was found for compound **33a**. We obtained this product with an enantiomeric purity of 82% *ee* (GC) and the sample (containing 2% of the achiral linear regioisomer) showed a positive $[\alpha]_D^{20}$ value of +42 (*c* 1.22 in $CHCl_3$). In trust of the CD correlation (Figure 3), we suggest that the (+)-enantiomer is (*R*)-configurated which contradicts the previous assignment.[29]

Conclusions

The Cu(I)-catalysed S_N2'-type allylic substitution of cinnamyl chlorides by Grignard reagents was investigated using chiral phosphine-phosphite ligands of type **1**. By screening a small prototype ligand library we identified the two TADDOL-derived ligands **1c** and **1h** as being particularly powerful. Under optimised conditions the reaction of the parent substrate **5** with MeMgBr could be performed with an unprecedented degree of regio- and enantioselectivity. Furthermore it was shown that the protocol developed allows the use of a rather broad scope of substituted cinnamyl chlorides and of different Grignard reagents.

We are confident that the modular nature of the ligands and their ease of preparation offer promising options for the optimisation of individual transformations in the context of future applications, for instance, in the synthesis of bioactive compounds processing a benzylic stereocentre.

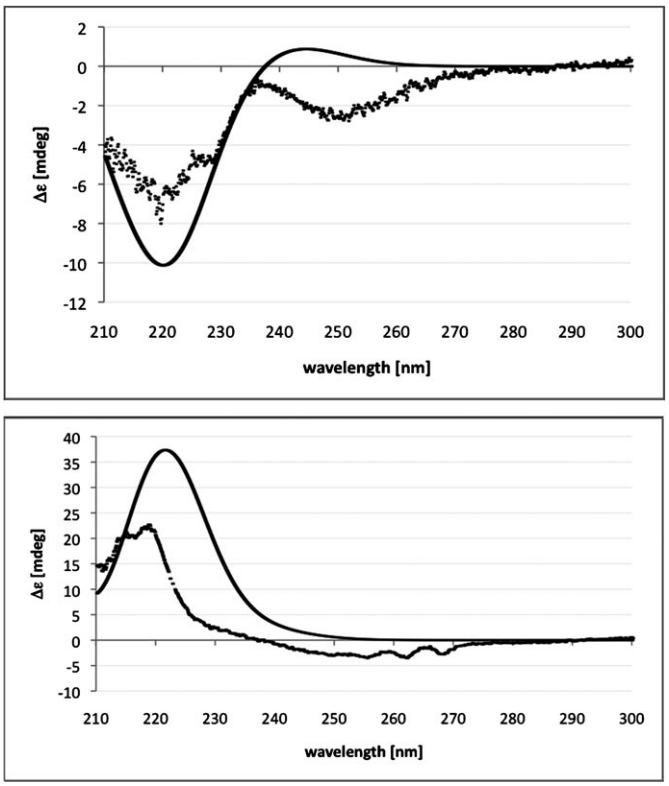


Figure 3. Calculated (line) and experimental (dotted) CD spectra of compounds **15a** (*top*) and **33a** (*bottom*) in MeOH.

Table 6. Cu(I)-catalysed reaction of the parent cinnamyl chloride (**5**) with different Grignard reagents in the presence of ligands **1h** and **1c**, respectively.[a]

Entry	RMgBr		Product	Ligand	Yield[b]	Regioselectivity (γ/α)[c]	*ee* [%][c]	Configuration
1	Et-MgBr			**1h**	90	99/1	66	*R*
2	Et-MgBr	**30a**		**1c**	88	94/6	85	*R*
3	*n*-Bu-MgBr	**31a**		**1c**	100	99/1	76	*R*
4	3-butenyl-MgBr	**32a**		**1c**	100	94/6	>99	*R*
5	*i*-Pr-MgBr	**33a**		**1c**	99	98/2	82	*R*

[a] *Conditions:* **5** (300 μmol), $CuBr{\cdot}SMe_2$ (2.5 mol%), ligand **1c** or **1h** (3 mol%) in MTBE (2 mL), slow addition of RMgBr in CH_2Cl_2 over 7 h. Conversion was >99%.

[b] Yields of isolated products (γ+α) after purification by filtration over silica gel.

[c] The ratio of regioisomers and the enantiomeric excess (*ee*) of the γ-product were determined by CG analysis; the conversion of substrate was always >99%. Values given are the average of two independent experiments.

Experimental Section

Typical Procedure for the Cu(I)-Catalysed Asymmetric Allylic Substitution using Grignard Reagents

A dry argon-flushed, 100-mL Schlenk flask was charged with a chiral ligand of type **1** (24.6 μmol, 3 mol%) and $CuBr{\cdot}SMe_2$ (20.5 μmol, 2.5 mol%) dissolved in 5.5 mL of dry MTBE. The mixture was stirred for 30 min at room temperature before a cinnamyl chloride was added. After 10 min the solution was cooled to −78 °C and 0.45 mL of MeMgBr (2.21 M in Et_2O) (0.99 mmol, 1.2 equiv.) diluted in 2.5 mL of dry CH_2Cl_2 were added over 7 h by means of a syringe pump. The solution was stirred for additional 8 h before the reaction was quenched with 0.1 mL of 1 M HCl and the mixture was allowed to warm to room temperature. After addition of 15 mL of Et_2O and 10 mL of 1 M HCl the layers were separated and the aqueous layer was re-extracted with 15 mL of Et_2O. The combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The product was purified by filtration through a small column of silica gel with Et_2O.

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References

[1] a) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, in: *Comprehensive Asymmetric Catalysis*, Springer-Verlag; Berlin, **1999**; b) R. Noyori, in: *Asymmetric Catalysis in Organic Synthesis*, John Wiley and Sons, New York, **1994**; c) H.-U. Blaser, E. Schmidt, in: *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*, Wiley-VCH, Weinheim, **2004**.

[2] Z. Lu, S. Ma, *Angew. Chem.* **2008**, *120*, 264–303; *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297.

[3] a) H. L. Goering, V. D. Singleton, *J. Org. Chem.* **1983**, *48*, 1531; b) H. L. Goering, S. S. Kantner, *J. Org. Chem.* **1984**, *49*, 422; c) H. L. Goering, S. S. Kantner, E. P. Seitz, *J. Org. Chem.* **1985**, *50*, 5495; d) M. J. Sellén, J.-E. Bäckvall, *J. Chem. Soc. Chem. Commun.* **1987**, 827; e) M. Sellén, B. Grant, J.-E. Bäckvall, *J. Am. Chem. Soc.* **1990**, *112*, 6615–6621; f) A. J. Bombrun, E. S. M. Persson, J.-E. Bäckvall, *J. Org. Chem.* **1994**, *59*, 4126; g) E. S. M. Persson, J.-E. Bäckvall, *Acta. Chem. Scand.* **1995**, *49*, 899; h) A. S. E. Karlström, J.-E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 1981.

[4] a) C. C. Tseng, S. D. Paisley, H. L. Goering, *J. Org. Chem.* **1986**, *51*, 2884; b) M. van Kalveren, E. S. M. Persson, D. M. Grove, J.-E. Bäckvall, *Tetrahedron Lett.* **1994**, *35*, 5931; c) E. S. M. Persson, M. van Klaveren, D. M. van Grove, J.-E. Bäckvall, G. van Koten, *Chem. Eur. J.* **1995**, *1*, 351.

[5] a) M. van Klaveren, E. S. M. Persson, A. del Villar, D. M. Grove, J.-E. Bäckvall, G. van Koten, *Tetrahedron Lett.* **1995**, *36*, 3059–3062; b) G. J. Meuzelaar, A. S. E. Karlström, M. van Klaveren, E. S. M. Persson, A. del Villar, G. van Koten, J.-E. Bäckvall, *Tetrahedron* **2000**, *56*, 2895; c) A. S. E. Karlström, F. F. Huerta, G. J. Meuzelaar, J.-E. Bäckvall, *Synlett* **2001**, 923–926.

[6] a) F. Dübner, P. Knochel, *Angew. Chem.* **1999**, *111*, 391–393; *Angew. Chem. Int. Ed.* **1999**, *38*, 379–381; b) F. Dübner, P. Knochel, *Tetrahedron Lett.* **2000**, *41*, 9233–9237; c) H. Malda, A. W. van Zijl, L. A. Arnold, B. L. Feringa, *Org. Lett.* **2001**, *3*, 1169; d) W.-J. Shi, L.-X. Wang, Y. Fu, S.-F. Zhu, Q.-L. Zhou, *Tetrahedron: Asymmetry* **2003**, *14*, 3867–3872; e) A. W. van Zijl, L. A. Arnold, A. J. Minaard, B. L. Feringa, *Adv. Synth. Catal.* **2004**, *346*, 413–420; f) P. J. Goldsmith, S. J. Teat, S. Woodward, *Angew. Chem.* **2005**, *117*, 2275–2277; *Angew. Chem. Int. Ed.* **2005**, *44*, 2235–2237; g) C. Börner, J. Gimeno, S. Gladiali, P. J. Goldsmith, D. Ramazzotti, S. Woodward, *Chem. Commun.* **2000**, 3433–3434.

[7] a) A. Alexakis, C. Malan, L. Lea, C. Benhaim, X. Fournioux, *Synlett* **2001**, 927; b) A. Alexakis, K. Croset, *Org. Lett.* **2002**, *4*, 4147–4149; c) K. Tissot-Croset, A. Alexakis, *Tetrahedron Lett.* **2004**, *45*, 7375–7378; d) K. Tissot-Croset, D. Polet, A. Alexakis, *Angew. Chem.* **2004**, *116*, 2480–2482; *Angew. Chem. Int. Ed.* **2004**, *43*, 2426–2428; e) F. López, A. W. van Zijl, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2006**, 409–411; f) A. Alexakis, C. Malan, L Lea, K. Tissot-Croset, D. Polet, C, Falciola, *Chimia* **2006**, *60*, 124–130.

[8] a) C. A. Falciola, K. Tissot-Croset, A. Alexakis, *Angew. Chem.* **2006**, *118*, 6141–6144; *Angew. Chem. Int. Ed.* **2006**, *45*, 5995–5998; b) C. A. Falciola, A. Alexakis, *Angew. Chem.* **2007**, *119*, 2673–2676; *Angew. Chem. Int. Ed.* **2007**, *46*, 2619–2622; c) C. A. Falciola, K. Tissot-Croset, H. Reyneri, A. Alexakis, *Adv. Synth. Catal.* **2008**, *350*, 1090–1100.

[9] a) A. Alexakis, J.-E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796; b) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824–2852; c) K. Geurts, S. P. Fletcher, A. W. van Zijl, A. J. Minnaard, B. L. Feringa, *Pure. Appl. Chem.* **2008**, *80*, 1025–1037.

[10] a) S. Tominaga, Y. Oi, T. Kato, D. K. An, S. Okamoto, *Tetrahedron Lett.* **2004**, *45*, 5585–5588; b) K. B. Selim, Y. Matsumoto, K. Yamada, K. Tomioka, *Angew. Chem.* **2009**, *121*, 8889–8891; *Angew. Chem. Int. Ed.* **2009**, *48*, 8733–8735.

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

[12] S. Werle, T. Fey, J.-M. Neudörfl, H.-G. Schmalz, *Org. Lett.* **2007**, *9*, 3555–3558.

[13] T. Robert, J. Velder, H.-G. Schmalz, *Angew. Chem.* **2008**, *120*, 7832–7835; *Angew. Chem. Int. Ed.* **2008**, *47*, 7718–7721.

[14] T. Robert, Z. Abiri, J. Wassenaar, A. J. Sandee, S. Romanski, J.-M. Neudörfl, H.-G. Schmalz, J. N. H. Reek, *Organometallics* **2010**, *29*, 478–483.
[15] a) H.-G. Schmalz, J. Hollander, M. Arnold, G. Dürner, *Tetrahedron Lett.* **1993**, *34*, 6259–6262; b) H.-G. Schmalz, M. Arnold, J. Hollander, J. W. Bats, *Angew. Chem.* **1994**, *106*, 77–79; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 109–111; c) H.-G. Schmalz, A. Schwarz, G. Dürner, *Tetrahedron Lett.* **1994**, *35*, 6861–6864; d) H.-G. Schmalz, A. Majdalani, T. Geller et al., *Tetrahedron Lett.* **1995**, *36*, 4777–4780; e) A. Majdalani, H.-G. Schmalz, *Synlett* **1997**, 1303–1305; f) T. Geller, H.-G. Schmalz, J. W. Bats, *Tetrahedron Lett.* **1998**, *39*, 1537–1540; g) D. Hörstermann, G. Kociok-Köhn, H.-G. Schmalz, *Tetrahedron* **1999**, *55*, 6905–6916; h) F. Dehmel, J. Lex, H.-G. Schmalz, *Org. Lett.* **2002**, *4*, 3915–3918.
[16] a) D. Seebach, A. K. Beck, R. Imwinkelried, S. Roggo, A. Wonnacott, *Helv. Chim. Acta* **1987**, *70*, 954–974; b) A. K. Beck, B. Astani, D. A. Plattner, W. Petter, D. Seebach, H. Braunschweiger, P. Gysi, L. La Vecchia, *Chimia* **1991**, *45*, 238–244; c) A. K. Beck, P. Gysi, L. La Vecchia, D. Seebach, *Org. Synth.* **1999**, *76*, 12–22; for reviews see: d) D. Seebach, A. K. Beck, A. Heckel, *Angew. Chem.* **2001**, *113*, 96–142; *Angew. Chem. Int. Ed.* **2001**, *40*, 92–138; e) H. Pellissier, *Tetrahedron* **2008**, *64*, 10279–10317.
[17] a) V. von Richter, *Ber. Dtsch. Chem. Ges.* **1873**, *6*, 1252; b) R. J. Kazlauskas, *J. Am. Chem. Soc.* **1989**, *111*, 4953; c) Y. Fujimoto, H. Iwadate, N. Ikekawa, *J. Chem. Soc. Chem. Commun.* **1985**, 1333; for reviews see: d) J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857–897; e) B. E. Love, *Curr. Org. Synth.* **2006**, *3*, 169–185.
[18] G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749.
[19] P. A. Wender, T. E. Smith, *Tetrahedron* **1998**, *54*, 1255–1275.
[20] A. Bouzine, M. Hélou, B. Carboni, F. Carreaux, B. Demerseman, C. Bruneau, J.-L. Renaud, *Chem. Eur. J.* **2008**, *14*, 5630–5637.
[21] To the best of our knowledge, no comparable preparative method for the isomerisation of regioisomeric cinnamyl chlorides has ever been reported. For a mechanistic investigation of an acid-catalysed process, see: G. Valkanas, E. S: Waight, *J. Chem. Soc.* **1959**, 2720–2727.
[22] For recent examples for the assignment of absolute configurations through TDDFT-calculated CD spectra, see: a) K. Krohn, I. Kock, B. Elsässer, U. Flörke, B. Schulz, S. Draeger, G. Pescitelli, S. Antus, T. Kurtán, *Eur. J. Org. Chem.* **2007**, 1123–1129; b) H. Hussain, K. Krohn, U. Flörke, B. Schulz, S. Draeger, G. Pescitelli, S. Antus, T. Kurtán, *Eur. J. Org. Chem.* **2007**, 292–295; c) A. Krick, S. Kehraus, C. Gerhäuser, K. Klimo, M. Nieger, A. Maier, H. H. Fiebig, I. Atodiresei, G. Raabe, J. Fleischhauer, G. M. König, *J. Nat. Prod.* **2007**, *70*, 353–360; d) K. Krohn, U. Farooq, U. Flörke, B. Schulz, S. Draeger, G. Pescitelli, P. Salvadori, S. Antus, T. Kurtán, *Eur. J. Org. Chem.* **2007**, 3206–3211; e) K. Krohn, Zia-Ullah, U. Flörke, B. Schulz, S. Draeger, G. Pescitelli, S. Antus, T. Kurtán, *Chirality* **2007**, *19*, 464–470; f) L. Di Bari, G. Pescitelli, P. Salvadori, M. Rovini, M. Anzini, A. Cappelli, S. Vomero, *Tetrahedron: Asymmetry* **2006**, *17*, 3430–3436.
[23] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03, Revision d.02*, Gaussian, Inc., Pittsburgh PA, **2003**.
[24] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372; c) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623.
[25] The TZVP is a triple-ξ basis set with polarisation functions.
[26] a) M. Parac, S. Grimme, *Chem. Phys.* **2003**, *292*, 11–21; b) S. Grimme, M. Parac, *Chem. Phys. Chem.* **2003**, *292–295*; c) H. H. Jaffé, M. Orchin in *Theory and applications of ultraviolet spectroscopy*, Wiley, New York, **1962**, p. 242; d) G. Pescitelli, L. Di Bari, A. M. Caporusso, P. Salvadori, *Chirality* **2008**, *20*, 393–399.
[27] M. Pecul, K. Ruud, T. Helgaker, *Chem. Phys. Lett.* **2004**, *388*, 110–119.
[28] a) For **6a**: T. Hayashi, T. Hagihara, Y. Katsuro, M. Kumada, *Bull. Chem. Soc. Jpn* **1983**, *56*, 363–364; b) for **15a**: G. Franciò, F. Faraone, W. Leitner, *J. Am. Chem. Soc.* **2002**, *124*, 736–737; c) for **17a**: A. Zhang, T. V. RajanBabu, *Org. Lett.* **2004**, *6*, 3156–3161; d) for **23a**: C. R. Smith, T. V. RajanBabu, *Org. Lett.* **2008**, *10*, 1657–1659; e) for **26a**: see ref.[7b]; f) for **27a** and **28a**: J. J. Van Veldhuizen, J. E. Campbell, R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882.
[29] a) See also ref.[7b]; b) V. Calò, A. Nacci, V. Fiandanese, *Tetrahedron* **1996**, *52*, 10799; c) M. Ahmar, C. Girard, R. Bloch, *Tetrahedron Lett.* **1989**, *30*, 7053–7056; d) H. Yoshioka, *Agric. Biol. Chem.* **1975**, *39*, 267; e) C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohashi, H. S. Mosher, *J. Org. Chem.* **1967**, *32*, 2797–2803.

