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Ferrocene phosphane–carbene ligands in Cu-catalyzed enantioselective 1,4-additions of Grignard reagents to α,β-unsaturated carbonyl compounds

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ABSTRACT

Chiral ferrocene phosphane–carbenes are good ligands for the copper-catalyzed 1,4-addition of Grignard reagents to various Michael acceptors. The products were obtained in high enantiomeric purity (up to e.r. = 95:5) and excellent regioselectivity (r.r. = 99:1). These ligands are also useful for domino conjugate addition followed by enolate trapping with imine and aldehyde.

1. Introduction

Conjugate additions of carbon nucleophiles to α,β-unsaturated carbonyl compounds ranks among the most valuable methods for carbon–carbon bond formation in organic synthesis. Of particular synthetic importance are asymmetric Cu-catalyzed additions of organometallic reagents [1–8].

The first application of an achiral *N*-heterocyclic carbene (NHC) ligands in a copper-catalyzed conjugate addition to enones was reported by Fraser and Woodward in 2001 [9]. The authors also noticed strong acceleration of the Cu-catalyzed addition of dialkylzinc reagents by the NHC-ligand. Later in the year 2001, an asymmetric version of the conjugate addition using chiral NHC ligands was reported by the laboratories of Alexakis [10] and Roland [11]. Enantioselectivities were only medium in these initial reports. However, enantioselectivities of the Cu-catalyzed additions of dialkyzinc to various Michael acceptors soon rose above e.r. 95:5 [12,13]. Further improvement was achieved by Mauduit and Hoveyda, who introduced a weakly coordinating alkoxy or sulfonate group to carbene, which resulted in much improved performance of such ligands [14–18]. Nowadays, Cu–NHC complexes are one of the most versatile catalysts for conjugate additions of a wide range of nucleophiles [19,20]. Apart from above mentioned dialkylzincs, Cu–NHC complexes efficiently catalyze additions of Grignard [21–25], organoaluminium [26,27], alkylboranes [28], organosilanes [29] as well as boron [30] and silicon [31,32] centered nucleophiles.

Bidentate heterodonor ligands often bring interesting new selectivities to asymmetric catalytic reactions. Combining a strong σ-donor with a good π-acceptor unit within the catalyst might be beneficial for its catalytic activity, potentially showing rate acceleration for both oxidative addition and reductive elimination. Therefore, NHC-ligands featuring adjacent phosphorus atom can act as promising ligands for a variety of metal-catalyzed asymmetric transformations. Surprisingly, only a few such ligands were described (Fig. 1). Bappert and Helmchen prepared rigid naphthyl-bridged ligand **1** for a Rh-catalyzed hydrogenation [33]. This ligand was then successfully used also in Rh-catalyzed 1,4-addition of arylboronic acids to enones [34]. Versatile ferrocene scaffold has also been used for the construction of phosphane–carbene ligands. Togni and coworkers reported synthesis of a tridentate PCP ligand **2**, based on a ferrocene scaffold [35,36]. Bolm and coworkers described the synthesis of iridium complexes in which a bidentate carbene-phosphane ligand **3** contains a chiral [2,2]paracyclophane unit. These complexes efficiently catalyzed the asymmetric hydrogenation of functionalized as well as simple alkenes [37].

The synthesis of chiral ferrocene phosphane-NHC ligand **4** was published by Chung's group. This ligand was used in the hydrogenation of dimethyl itaconate, but enantioselectivity of the reaction was low (18% ee) [38]. Shi and co-workers used this ligand in an achiral Pd-catalyzed Suzuki–Miyaura cross-coupling reaction, which proceeded with excellent yields [39,40]. Visentin and Togni tested another ligand of type **4** in a palladium-catalyzed allylic

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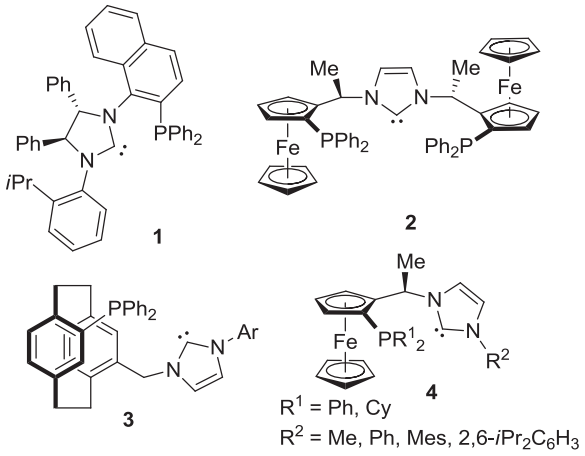
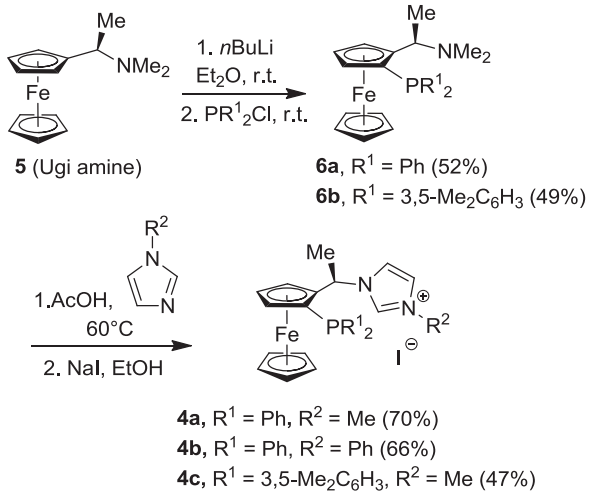


Fig. 1. Phosphane–carbene ligands.



Scheme 1. Synthesis of ligand precursors **4**.

amination. However, only partial conversion of starting materials was observed and the products were racemic [41]. Labande and coworkers prepared a P–NHC ligand, similar to compound **4**, only without α-stereogenic center. The Pd-complex showed moderate enantioselectivity in the asymmetric Suzuki–Miyarua reaction [42]. To the best of our knowledge, carbene-based bidentate P,C-ligands were not used in asymmetric Cu-catalyzed conjugate addition of hard organometallic reagents such as dialkylzinc or Grignard reagents.

In this context, we decided to investigate catalytic efficiency of ligands **4** in the Cu-catalyzed addition of Grignard reagents. Herein, we report the result of this study – successful enantioselective Cu-catalyzed 1,4-addition of Grignard reagents to α,β-unsaturated carbonyl compounds and lactones.

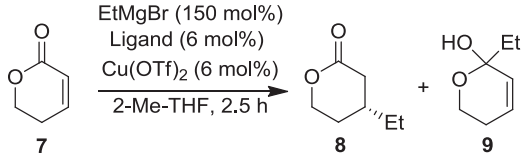
2. Results and discussion

Precursors to phosphanocarbene ligands **4a** and **4b** were prepared according to the literature procedure [38], in which commercially available Ugi amine (**5**) was *ortho*-lithiated with *n*BuLi and then quenched with a chlorophosphane. The resulting amino phosphanes **6a** and **6b** reacted with either 1-methyl or 1-phenylimidazole in acetic acid. Finally, acetate anion was exchanged to iodide by treatment with NaI in ethanol (Scheme 1). The synthesis of compound **4c** followed the similar path, using amino phosphane **6b** and 1-methylimidazole as building blocks.

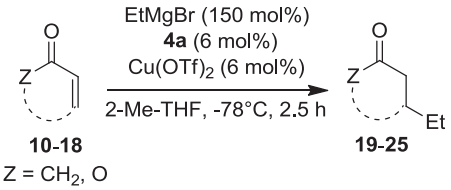
Imidazolium phosphanes **4** were then used in the Cu-catalyzed conjugated addition of Grignard reagents to α,β-unsaturated carbonyl compounds and lactones. We started our research with optimization of asymmetric 1,4-addition of ethylmagnesium bromide to lactone **7** (Schemes 2 and 3). The results are given in Table 1. Reactions proceeded with 1.5 equiv. of EtMgBr, which is also used as a base for deprotonation of the ligand precursor. Catalyst loading was 6 mol%, both the ligand precursor **4** and copper salt. The reactions were monitored by gas chromatography (GC) and full conversion of starting material was usually achieved in 2.5 h. Conversion, yield, ratio of **8**/**9**, and enantiomeric purity of compound **8** were determined by GC.

The conjugated addition using ligand precursor **4a**, $Cu(OTf)_2$ in 2-Me-THF at −60 °C proceeded with 100% conversion, high regioselectivity of 99:1 (**8**/**9**) and enantioselectivity e.r. 5:95. Although there was full conversion of the starting material, only 47% of the product **8** was detected by GC. Usually, less than 20% of various side products were detected by GC. The rest of the material can be accounted by decomposition of the product during aqueous work-up. This notion is also supported by the fact that enolate ion can be successfully intercepted by an electrophile, such as imine or aldehyde, where higher yields were achieved than in the conjugate addition itself (see below). No product of 1,4-addition was detected, if the reaction proceeded under the same conditions in diethyl ether. A decrease of the reaction temperature to −78 °C had no significant effect on the reaction course. On the other hand, an increase of the reaction temperature resulted in decrease of yield to 25% and regioselectivity to 33:67 (**8**/**9**). The enantioselectivity was only slightly affected (e.r. 9:91) (Table 1, Entries 1–4). Using $CuBr.Me_2S$ instead of $Cu(OTf)_2$ in 2-Me-THF at −78 °C again led to lower yield (35%) and enantiomeric purity (e.r. 9:91). Regioselectivity remained the same (Table 1, Entry 5). The presence of the methyl group on N(3) atom of imidazolylidene ring in an active complex seems essential for the regioselectivity. Use of the phenyl substituted ligand **4b** led to the significantly lower regioselectivity (**8**/**9** 63:37) while the satisfactory enantiomeric ratio 5:95 was preserved (Table 1, entry 6). On the other hand, exchange of the diphenylphosphano group in the ligand precursor **4a** for bis(3,5-dimethylfenyl)phosphano group in precursor **4c** resulted in excellent regioselectivity (**8**/**9** 99:1) at the expense of lower enantioselectivity (e.r. 15:85) (Table 1, entry 7).

To assess catalytic profile of ferrocenyl phosphane–carbene ligands in the Cu-catalyzed conjugate addition, we have screened a range of Michael acceptors. The reactions were performed using the best conditions (2-Me-THF as solvent, 6 mol% of the ligand precursor **4a**, 6 mol% of $Cu(OTf)_2$ at −78 °C for 2.5 h). The results are summarized in Table 2. In contrast to lactone **7**, lactone **10** did not undergo 1,4-addition of EtMgBr. The conjugate addition product **19** was detected in 5% (**4a**) and 7% (**4b**) yields, respectively. Enantiomeric ratio was 24:76 (Table 2, Entry 2). Such low yields are probably due to a ring opening and following side reactions. Addition to cyclohex-2-enone (**11**) using **4a** proceeded in 2-Me-THF as well as in CH_2Cl_2 with synthetically useful yield (68%) albeit with only medium enantioselectivity e.r. 79:21 and e.r. 62:38. A higher



Scheme 2. Conjugate addition of EtMgBr to lactone **7**.



Scheme 3. Conjugate additions of EtMgBr to Michael acceptors **10**–**18**.

yield (84%) and better enantioselectivity (e.r. 81:19) were achieved when ligand precursor **4b** was used in 2-Me-THF (Entries 3–5). Cyclopent-2-enone (**12**) underwent 1,4-addition with ethylmagnesium bromide with 42% yield (Table 2, Entry 6). Somewhat disappointing results were obtained when 3-methylcyclohexenone (**13**) was used as a substrate for 1,4-addition of EtMgBr. The reaction under established conditions proceeded with 78% conversion, but only 7% of the product **22** was detected as a virtually racemic mixture (Table 2, Entry 7). Chalcone (**14**) and ketone **15** afforded the products of 1,4-addition in promising yields 60 and 43%, respectively, but practically with no enantioselectivities (Table 2, Entries 8–9). Coumarin (**16**) again gave only traces of 1,4-addition product **25** with EtMgBr (Table 2, Entry 10). 1-Benzyl-1*H*-pyrrole-2,5-dione (**17**) and 1-(cyclopent-1-en-1-yl)ethanone (**18**) were under established reaction condition completely unreactive (Table 2, Entries 11–12).

We also evaluated efficacy of the ligand precursor **4a** in a domino conjugate Grignard addition followed by a Mannich reaction. A chiral enolate produced by the addition of ethylmagnesium bromide to cyclohex-2-enone (**11**) reacted with imine *N*-benzylidenetoluenesulfonamide (**26**) (Scheme 4). Products of these domino reactions are β-amino ketones with three adjacent stereocenters. Two diastereomers (*S*,*R*,*R*)-**27** and (*R*,*R*,*R*)-**27** were isolated in 22 and 21% yield with enantiomeric ratios of e.r. 71:29 and 78:22, respectively. In comparison with originally developed conditions from our laboratory, using Taniaphos ligand, yields were similar but enantioselectivity was higher (32 and 28% yields; e.r. 95:5 and 97:3) [43].

Benzaldehyde was used as another acceptor for trapping of the chiral enolate produced by Cu-catalyzed enantioselective Grignard addition of ethylmagnesium bromide to lactone **7**. The products **28**–**30** were first synthesized by Hoveyda using 1,4-addition of dialkylzinc reagents and Cu-peptide complexes [44]. These products were formed in good yields also using our methodology with ferrocenyl phosphane–carbene ligands **4** and Grignard reagents (Scheme 5, Table 3). Both ligands **4a** and **4b** provided similar results in term of yield, diastereo- and enantioselectivity. Ratio of diastereomers of β-hydroxy lactones (*S*,*R*,*R*)-**28** and (*R*,*R*,*R*)-**28** using **4a** was 85:15 according to ^{1}H NMR and the major diastereomer was isolated in 63% yield with enantiomeric ratio 94:6. Using ligand precursor **4b**, the major isomer of **28** was isolated with 57% yield and e.r. was 97:3. The reaction worked well also with MeMgBr, leading to product **29** (Table 3, entry 5). On the other hand, using *i*PrMgCl, the product **30** was isolated only in 24% yield and with only low e.r. of 57:43. The domino reaction with five-membered lactone **10** (furan-2(5*H*)-one) did not proceed under these reaction conditions (Table 3, entry 3).

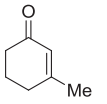
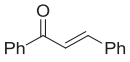
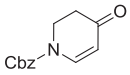
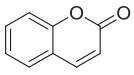
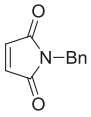
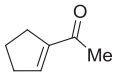
Products of conjugate addition of organometallic reagents to lactones are difficult to isolate. As Hoveyda described for the dialkylzinc reagents [44], the domino conjugate addition and aldol reaction can be used for obtaining products of conjugate addition itself. Similarly, we subjected compound **28** to K_2CO_3 in boiling toluene, what led to ketone **8** in 82% yield and with enantiomeric purity of e.r. 98:2.

Table 1
Screening of various reaction conditions in the asymmetric 1,4-addition of ethylmagnesium bromide to lactone **7**.

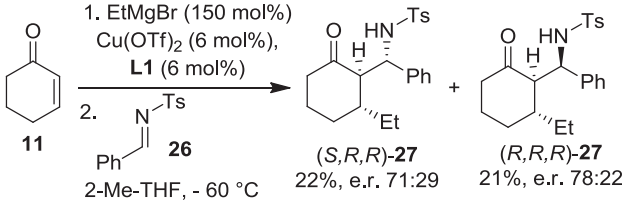
Entry	Ligand	[Cu]	Temp [°C]	Conv. [%]	Yield [%]	r.r. (**8**/**9**)	e.r.
1	**4a**	$Cu(OTf)_2$	−60	100	47	99:1	5:95
2	**4a**	$Cu(OTf)_2$	−60	81[a]	–	–	–
3	**4a**	$Cu(OTf)_2$	−78	100	52	99:1	6:94
4	**4a**	$Cu(OTf)_2$	−40	100	25	33:67	9:91
5	**4a**	$CuBr.Me_2S$	−78	99	35	99:1	9:91
6	**4b**	$Cu(OTf)_2$	−78	100	43	63:37	5:95
7	**4c**	$Cu(OTf)_2$	−78	100	43	99:1	15:85

[a] Reaction was performed in Et_2O.

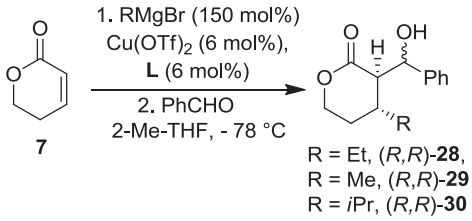
Table 2
Cu-catalyzed 1,4-addition of ethylmagnesium bromide to α,β-unsaturated carbonyl and carboxyl compounds.

Entry	Substrate		Conversion (%)	Yield (%)	e.r. (*R*:*S*)
2		**10**	100	5 (7[c])	76:24
3		**11**	100	68	79:21
4			99[a]	68	62:38
5			100[c]	84	81:19
6		**12**	100	42	n.d.
7		**13**	78	7	54:46
8		**14**	90	60[b]	51:49
9		**15**	64	43[b]	54:46
10		**16**	38	4	n.d.
11		**17**	–	–	–
12		**18**	–	–	–

[a] CH_2Cl_2 was used as a solvent.
[b] Isolated yields.
[c] **4b** was used as a ligand precursor.



Scheme 4. Domino conjugate addition to **11** and reaction with imine **26**.



Scheme 5. Domino conjugate addition to **7** and reaction with benzaldehyde.

We attempted to isolate and characterize catalytically active copper-complexes. We tried several bases (EtMgBr, BuLi, ^{t}BuOK and NaH) and copper salts for generation of the carbene complex. The best results were obtained with NaH as base and $Cu(MeCN)_4PF_6$ as copper source, because of its good solubility in the THF. The projected complex was precipitated with hexane, but resulting crystals were not suitable for X-ray crystallographic analysis. Furthermore, it was quite sensitive. The complex formation was followed by ^{1}H, ^{13}C and ^{31}P NMR. Although we were not able to isolate a carbene complex in pure form, Cu-complex formation is suggested by following observations. In the ^{1}H NMR, extinction of a signal corresponding to imidazolium 2-H proton at 9.3 ppm was observed. In ^{31}P NMR, phosphorus signal in the free ligand is at −27.4 ppm. In the complex, this signal shifts only slightly downfields (−25 ppm) but its significant broadening suggests weak coordination and presence of a dynamic equilibrium. The best evidence for Cu–carbene complex formation comes from ^{13}C NMR. A new signal at 163 ppm appeared, what the expected position for Cu-bound carbene is. It is a combined signal due to coupling with both isotopes of copper. In contrast, in the imidazolium compound **4a**, the corresponding carbon atom appears as a singlet at 136 ppm. This data suggest coordination of carbon with copper.

3. Conclusions

Ferrocenyl phosphane–carbene ligands are useful for Cu-catalyzed 1,4-addition to 5,6-dihydro-2*H*-pyran-2-one and to lesser extent to other substrates. The primary product of the conjugate additions, enolate ions can be trapped with electrophiles such as imine or aldehyde.

4. Experimental

4.1. General information

All reactions were carried out in inert atmosphere of Ar. Solvents were dried and purified by standard methods before use. NMR spectra were recorded on Varian NMR System 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) and Varian NMR System 600 (600 MHz for ^{1}H, 150 MHz for ^{13}C and 242.8 MHz for ^{31}P). Chemical shifts (δ) are given in ppm relative to tetramethylsilane for ^{1}H NMR and ^{13}C NMR.

Table 3
Cu-catalyzed domino addition of alkylmagnesium bromide to lactone **7** and **10** and benzaldehyde.

Entry	Ligand	RMgX	Substrate	Yield [%]	d.r.	e.r.
1	**4a**	EtMgBr	**7**	63	85:15	94:6
2	**4b**	EtMgBr	**7**	57	84:16	97:3
3	**4a**	EtMgBr	**10**	–	–	–
4	**4a**	EtMgCl	**7**	63	75:25	98:2
5	**4a**	MeMgBr	**7**	55	85:15	88:12
6	**4a**	MeMgI	**7**	60	83:17	64:36
7	**4a**	*i*PrMgCl	**7**	24	82:18	57:43

Unified chemical shift scale was used for ^{31}P NMR with 85% H_3PO_4 as secondary standard (δ = 0.0 ppm, Ξ = 40.4807420). Specific optical rotations were measured on Jasco instrument and are given in deg cm^3 g^{-1} dm^{-1}. Gas chromatographic (GC) analysis was performed in an Agilent Technologies 6890N and 6850 series instrument equipped with an FID detector and a capillary column, HP-1 (30m × 0.32 × 0.25 μm), Lipodex E (50 m × 0.25 mm × 0.2 μm) or BETA DEX (30 m × 0.25 mm × 0.25 μm). Enantiomeric ratios were determined by HPLC on Chiralpak, OD-H, IA-H, AD-H, OJ-H (Daicel Chemical Industries), column using hexane/^{i}PrOH as a mobile phase and detection with UV-detector at 254 and 218 nm. Flash chromatography was performed on Merck silica gel 60. Thin-layer chromatography was performed on Merck TLC-plates silica gel 60, F-254. Diastereomeric ratios were determined by ^{1}H NMR and GC.

Precursors for ligands **4a**, **4b** and **4c** are synthesized according to the literature procedure [38,45,46]. See Supporting information for NMR spectra.

4.1.1. 1-[(R)-1-((S)-2-(Bis(3,5-dimethylphenyl))phosphinoferrocenyl) ethyl]3-phenylimidazolium iodide (**4c**)

A suspension of amine **6b** (160 mg, 0.32 mmol) and 1-methylimidazole (32 mg, 0.38 mmol) were dissolved in acetic acid (2 mL) to give a clear orange solution. The solution was heated at 60 °C for 5 h. After evaporating the solvent under vacuum, the residue was dissolved in EtOH (4 mL) with NaI (144 mg, 0.96 mmol). The resulting solution was stirred for 2 h, concentrated and chromatographed (silica gel, CH_2Cl_2 and CH_3OH 2%). Yield: 100 mg (47%), orange solid. M.p. = 125–129 °C, $[\alpha]_D = -144.77$ (c = 0.39, $CHCl_3$), ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.22 (s, 1H, CH^{imid}), 7.05 (s, 1H, Ph), 7.04 (s, 1H, Ph), 7.02 (s, 1H, Ph), 6.83 (t, J = 1.7 Hz, 1H, CH^{imid}), 6.81 (s, 1H, Ph), 6.66 (t, J = 1.5 Hz, 1H, CH^{imid}), 6.45 (s, 1H, Ph), 6.44 (s, 1H, Ph), 5.95 (dq, J = 3.8 Hz, J = 7.0 Hz, 1H, CH), 4.89 (m, 1H, Fc), 4.50 (t, J = 2.5 Hz, 1H, Fc), 4.13 (s, 5H, cp), 3.90 (m, 1H, Fc), 3.55 (s, 3H, CH_3), 2.30 (s, 6H, CH_3), 2.15 (s, 6H, CH_3), 2.06 (d, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 138.21, 138.15, 134.63, 134.59 (2d, 2× Cq^{Ph}), 137.76, 137.70, 137.50, 137.45 (2d, 4× Cq^{Ph}), 136.05 (d, J = 1.5, CH^{imid}), 132.35 (d, J = 20.8 Hz, CH^{Ph}), 131.31 (CH^{Ph}), 130.03 (CH^{Ph}), 129.74 (d, J = 19.5 Hz, CH^{Ph}), 122.02 (CH^{imid}), 118.76 (CH^{imid}), 89.52 (d, J = 24.5 Hz, Cq^{Fc}), 76.72 (Cq^{Fc}), 73.06 (d, J = 4.3 Hz, CH^{Fc}), 70.49 (CH^{Fc}), 70.32 (CH^{Cp}), 69.52 (d, J = 3.3 Hz, CH^{Fc}), 56.28 (d, J = 10.9 Hz, CH), 36.49 (CH_3), 21.31 (2× CH_3), 21.28 (2× CH_3), 21.26 (CH_3). ^{31}P NMR ($CDCl_3$): δ = −27.78 Hz. IR (ATR): ν 2963, 2960, 1579, 1248, Anal. Calcd for $C_{32}H_{36}FeIN_2P.CH_2Cl_2$ (Mr = 747.3): C 53.04, H 5.13, N 3.75; found: C 53.91, H 5.39, N, 3.87.

4.2. General procedure for the addition of EtMgBr

3.0 M Et_2O solution of EtMgBr (0.26 mL, 0.77 mmol) was added dropwise over 3 min at 0 °C to a suspension of copper(II) triflate (11.1 mg, 6 mol-%) and ferrocene phosphane–carbene ligand **4a** (18.5 mg, 6 mol-%) in 2-Me-THF (3 mL) under argon atmosphere and the mixture was stirred at 0 °C for 1 h. Then the mixture was cooled to −78 °C and a solution of 5,6-dihydro-2*H*-pyran-2-one (**7**) (44 μL, 0.51 mmol) in 2-Me-THF (2 mL) was added over 30 min. After stirring for 2.5 h at −78 °C, the reaction was quenched with saturated NH_4Cl (3 mL). The aqueous layer was separated and extracted with Et_2O (3 × 3 mL). The organic layers were dried over sodium sulfate. The data of the conversions and yield were determined by achiral-phase GC analysis using decaline as an internal standard.

4.2.1. (R)-4-Ethyl-tetrahydropyran-2-one (**8**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45–4.38 (m, 1H), 4.30–4.19 (m, 1H), 2.70 (ddd, J = 17.3 Hz, J = 5.9 Hz, J = 1.6 Hz, 1H), 2.15 (dd,

J = 17.3 Hz, J = 10.1 Hz, 1H), 2.04–1.79 (m, 2H), 1.61–1.46 (m, 1H), 1.46–1.33 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). NMR data agree with literature [44]. Enantiomeric excess was determined by chiral GC (Lipodex E, γ-cyclodextrin, 120 °C, 196 kPa), t_R (minor) = 34.4 min (*S*), t_R (major) = 34.9 min (*R*), e.r. = 5:95.

*4.2.2. (R)-4-Ethyl-dihydrofuran-2(3H)-one (**19**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.44 (dd, J = 7.3 Hz, J = 9.4 Hz, 1H), 3.94 (dd, J = 7.6 Hz, J = 9.4 Hz, 1H), 2.63 (dd, J = 17.0 Hz, J = 8.3 Hz, 1H), 2.49 (hept, J = 7.3 Hz, 1H), 2.19 (dd, J = 7.6 Hz, J = 17.0 Hz, 1H), 1.81–1.38 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H). NMR data agree with literature [47]. Enantiomeric excess was determined by chiral GC (Lipodex E, γ-cyclodextrin, 120 °C, 222 kPa), t_R (minor) = 36.8 min (*S*), t_R (major) = 37.3 min (*R*), e.r. = 24:76.

*4.2.3. (R)-3-Ethyl-cyclohexanone (**20**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.48–2.38 (m, 1H), 2.37–2.30 (m, 1H), 2.28–2.20 (m, 1H), 1.92–1.85 (m, 1H), 1.72–1.57 (m, 2H), 1.45–1.24 (m, 3H), 0.91 (t, J = 7.4 Hz, 3H). NMR data agree with literature [48]. Enantiomeric excess was determined by chiral GC (Lipodex E, γ-cyclodextrin, 100 °C, 122 kPa), t_R (major) = 12.5 min (*R*), t_R (minor) = 12.8 min (*S*), e.r. = 81:19.

*4.2.4. Ethyl-cyclopentanone (**21**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.10–2.44 (m, 5H), 1.75–1.85 (m, 1H), 1.41–1.58 (m, 3H), 0.96 (t, J = 7.4 Hz, 3H). NMR data agree with literature [49].

*4.2.5. (R)-3-Ethyl-3-methylcyclohexanone (**22**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.28 (t, J = 6.8 Hz, 2H), 2.14 (d, J = 12.6 Hz, 1H), 2.00 (d, J = 12.6 Hz, 1H), 1.90–1.81 (m, 2H), 1.61–1.46 (m, 2H), 1.31 (q, J = 7.6 Hz, 2H), 0.90 (s, 3H), 0.84 (t, J = 7.4 Hz, 3H). NMR data agree with literature [22]. Enantiomeric excess was determined by chiral GC (BETA DEX, β-cyclodextrin, 110 °C, 171 kPa), t_R (major) = 7.8 min (*R*), t_R (minor) = 8.1 min (*S*), e.r. = 54:46.

*4.2.6. (R)-1,3-Diphenyl-pentan-1-one (**23**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.96–7.84 (m, 2H), 7.53–7.49 (m, 1H), 7.48–7.37 (m, 2H), 7.30–7.13 (m, 5H), 3.30–3.23 (m, 3H), 1.87–1.72 (m, 1H), 1.66–1.60 (m, 1H), 0.80 (t, J = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.19 (C_q), 144.64 (C_q^{Ph}), 137.26 (C_q^{Ph}), 132.86 (CH^{Ph}), 128.49 (CH^{Ph}), 128.37 (CH^{Ph}), 128.03 (CH^{Ph}), 127.61 (CH^{Ph}), 126.23 (CH^{Ph}), 45.59 (CH_2), 42.99 (CH), 29.19 (CH_2), 12.06 (CH_3). NMR data agree with literature [50]. HPLC (Diacel Chiralcel OJ-H, hexane/propan-2-ol, 99.5:0.5, 1 mL/min, 254 nm): t_R (minor) = 29.9 min (*S*), t_R (major) = 43.0 min (*R*), e.r. = 49:51.

*4.2.7. (R)-1-Benzyloxycarbonyl-2-ethyl-4-piperidone (**24**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.43–7.30 (m, 5H), 5.26–5.10 (m, 2H), 4.58 (br, 1H), 4.40 (br, 1H), 3.31–3.13 (m, 1H), 2.65 (dd, J = 14.6 Hz, J = 6.6 Hz, 1H), 2.59–2.40 (m, 1H), 2.38–2.20 (m. 1H), 1.65–1.41 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.60 (C_q), 155.46 (C_q), 136.40 (C_q^{Ph}), 128.55 (CH^{Ph}), 128.17 (CH^{Ph}), 127.94 (CH^{Ph}), 67.57 (CH_2), 53.77 (CH), 45.21 (CH_2), 40.59 (CH_2), 38.38 (CH_2), 25.39 (CH_2), 10.14 (CH_3). NMR data agree with literature [51]. HPLC (Diacel Chiralcel AD-H, hexane/propan-2-ol, 90:10, 1 mL/min): t_R (major) = 5.6 min (*R*), t_R (minor) = 6.5 min (*S*), e.r. = 54:46.

*4.2.8. 4-Ethyl-chroman-2-one (**25**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.90–7.10 (m, 4H), 2.67–3.10 (m, 3H), 1.63 (q, J = 7 Hz, 2H), 0.98 (t, J = 7 Hz, 3H). NMR data agree with literature [52].

4.3. Procedure for domino conjugate addition and Mannich reaction of N-benzylidenetoluenesulfonamide

3.2 M solution of EtMgBr in 2-Me-THF (0.12 mL, 0.38 mmol) was dropwise added over 3 min at 0 °C under argon atmosphere to a suspension of $Cu(OTf)_2$ (5.4 mg, 6 mol%) and ferrocene phosphane–carbene ligand **4a** (9.1 mg, 6 mol%) in 2-Me-THF (3 mL) and the mixture was stirred at 0 °C for 1 h. Then the mixture was cooled to −78 °C and a solution of cyclohex-2-enone (**11**) (35.2 μL, 0.38 mmol) in 2-Me-THF (2 mL) was added over 30 min. The resulting mixture was stirred at −78 °C for an additional 2.5 h. Finally, *N*-benzylidenetoluenesulfonamide (65 mg, 0.25 mmol), dissolved in 2-Me-THF (2 mL), was added, and the reaction mixture was slowly allowed to reach room temperature overnight. The reaction was then quenched with aq. NH_4Cl (3 mL) and extracted with Et_2O (3 × 3 mL). The combined organic extracts were concentrated. The crude product was purified by column chromatography (silica gel, hexane/EtOAc/CH_2Cl_2, 83:14:3). Yield: (*S*,*R*,*R*)-**27a** (21 mg, 22%) (*R*,*R*,*R*)-**27b** (20 mg, 21%).

*4.3.1. (S,R,R)-N-[(2-Ethyl-6-oxocyclohexyl)(phenyl)methyl]-4-methyl-benzenesulfonamide (**27a**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 8.3 Hz, 2H, Ar), 7.14–6.89 (m, 7H, Ar), 6.15 (d, J = 10.1 Hz, 1H, CH), 4.76 (dd, J = 10.2 Hz, 4.2 Hz, 1H, CH), 2.58 (dd, J = 9.2 Hz, 4.0 Hz, 1H, CH), 2.34–2.13 (m, 2H, CH), 2.29 (s, 3H, CH_3), 2.07–1.84 (m, 3H, CH + CH_2), 1.80–1.63 (m, 2H, CH_2), 1.62–1.40 (m, 2H, CH_2), 0.92 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ 213.39 (C_q), 142.64 (C_q), 139.64 (C_q^{Ph}), 138.06 (C_q), 129.03 (CH^{Ph}), 127.93 (CH^{Ph}), 126.88 (CH^{Ph}), 126.82 (CH^{Ph}), 126.64 (CH^{Ph}), 61.38 (CH), 55.60 (CH), 42.36 (CH_2), 42.02 (CH), 28.63 (CH_2), 25.82 (CH_2), 25.31 (CH_2), 21.32 (CH_3), 9.94 (CH_3). NMR data agree with literature [43]. HPLC (Diacel Chiralcel OD-H, hexane/propan-2-ol, 90:10, 0.6 mL/min, 218 nm): t_R (minor) = 17.0 min (*S*), t_R (major) = 23.7 min (*R*), e.r. = 29:71.

*4.3.2. (R,R,R)-N-[(2-Ethyl-6-oxocyclohexyl)(phenyl)methyl]-4-methyl-benzenesulfonamide (**27b**)*

^{1}H NMR (300 MHz, CDCl3) δ 7.46 (d, J = 8.3 Hz, 2H), 7.14–6.95 (m, 7H), 6.31 (d, J = 10.1 Hz, 1H), 4.67 (dd, J = 10.1 Hz, J = 5.8 Hz, 1H), 2.63 (dd, J = 8.8 Hz, J = 6.2 Hz, 1H), 2.32 (s, 3H), 2.30–2.24 (m, 1H), 2.23–2.09 (m, 1H), 1.93–1.82 (m, 2H), 1.68–1.23 (m, 5H), 0.88 (t, J = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 213.15 (C_q), 142.66 (C_q), 138.07 (C_q), 137.46 (C_q), 129.13 (CH^{Ph}), 128.50 (CH^{Ph}), 128.17 (CH^{Ph}), 127.41 (CH^{Ph}), 126.82 (CH^{Ph}), 59.50 (CH), 57.01 (CH), 41.80 (CH_2), 40.12 (CH), 28.05 (CH_2), 25.63 (CH_2), 23.39 (CH_2), 21.36 (CH_3), 10.21 (CH_3). NMR data agree with literature [43]. HPLC (Diacel Chiralcel OD-H, hexane/propan-2-ol, 90:10, 0.6 mL/min, 218 nm): t_R (major) = 14.8 min (*R*), t_R (minor) = 17.9 min (*S*), e.r. = 78:22.

4.4. Procedure for domino conjugate Grignard addition and aldol reaction with benzaldehyde

3.2 M solution of EtMgBr in 2-Me-THF (0.18 mL, 0.57 mmol) was dropwise added over 3 min at 0 °C under argon atmosphere to a suspension of $Cu(OTf)_2$ (8.2 mg, 6 mol%) and ferrocene phosphane–carbene ligand **4a** or **4b** (6 mol-%) in 2-Me-THF (3 mL) and the mixture was stirred at 0 °C for 1 h. Then the mixture was cooled to −78 °C and a solution of 5,6-dihydro-2*H*-pyran-2-one (**7**) (48.2 μL, 0.57 mmol) in 2-Me-THF (2 mL) was added over 30 min. The resulting mixture was stirred at −78 °C for additional 2.5 h. Finally, benzaldehyde (38.4 μL, 0.38 mmol), dissolved in 2-Me-THF (2 mL), was added, and the reaction mixture was slowly allowed to reach room temperature overnight. The reaction was then quenched with aq. NH_4Cl (3 mL) and extracted with Et_2O (3 × 3 mL). The combined organic extracts were concentrated. The crude product was purified

by column chromatography (silica gel, hexane/EtOAc, 7:3). Yield: 55 mg (63%), white solid.

4.4.1. 4-Ethyl-3-(hydroxy(phenyl)methyl)-tetrahydropyran-2-one (**28**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.29 (m, 5H), 5.25 (dd, J = 6.8 Hz, J = 3.7 Hz, 1H), 4.25–4.13 (m, 1H), 4.01 (ddd, J = 2.4 Hz, J = 10.0 Hz, J = 12.6 Hz, 1H), 3.76 (d, J = 6.8 Hz, 1H), 2.72 (dd, J = 7.4 Hz, J = 3.7 Hz, 1H), 1.98–1.75 (m, 2H), 1.16–1.01 (m, 2H), 0.75 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.08 (s, C_q), 141.07 (s, C_q), 128.47 (s, CH), 127.90 (s, CH), 126.24 (s,CH), 74.04 (s, CH), 67.91 (s, CH_2), 53.33 (s, CH), 33.26 (s, CH), 27.73 (s, CH_2), 27.66 (s, CH_2), 10.85 (s, CH_3). NMR data agree with literature [44]. HPLC (Diacel Chiralcel IA-H, hexane/propan-2-ol, 90:10, 0.8 mL/min, 218 nm): t_R (major) = 10.6 min (R), t_R (minor) = 11.3 min (S), e.r. = 97:3.

4.4.2. 3-(Hydroxy(phenyl)methyl)-4-methyltetrahydropyran-2-one (**29**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.26 (m, 5H), 5.27 (s, 1H), 4.36–4.24 (m, 1H), 4.06 (td, J = 10.7 Hz, J = 2.7 Hz, 1H), 3.87 (d, J = 6.0 Hz, 1H), 2.68 (dd, J = 8.4, 3.7 Hz, 1H), 2.10–1.93 (m, 1H), 1.81 (dtd, J = 14.2, 4.7, 2.8 Hz, 1H), 1.67–1.44 (m, 2H), 0.79 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.86 (s, C_q), 141.07 (s, C_q), 128.50 (s, CH), 127.84 (s, CH), 126.26 (s, CH), 73.51 (s, CH), 68.00 (s, CH_2), 55.03 (s, CH), 31.38 (s, CH_2), 27.05 (s, CH), 21.06 (s, CH_3). NMR data agree with literature [44]. HPLC (Diacel Chiralcel IA-H, hexane/propan-2-ol, 90:10, 0.8 mL/min, 218 nm): t_R (major) = 12.7 min (R), t_R (minor) = 13.5 min (S), e.r. = 88:12.

4.4.3. 3-(Hydroxy(phenyl)methyl)-4-isopropyl-tetrahydropyran-2-one (**30**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 5.15 (d, J = 3.9 Hz, 1H), 4.24 (dt, J = 10.9 Hz, J = 3.8 Hz, 1H), 3.84 (td, J = 11.0 Hz, J = 2.5 Hz, 1H), 2.90 (dd, J = 7.7 Hz, J = 4.0 Hz, 1H), 1.92–1.78 (m, 1H), 1.76–1.66 (m, 1H), 1.64–1.45 (m, 5H), 1.43–1.31 (m, 1H), 0.80 (dd, J = 9.0, 6.8 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.20 (s, C_q), 141.03 (s, C_q), 128.52 (s, CH), 128.07 (s, CH), 126.40 (s, CH), 74.74 (s, CH), 68.08 (s, CH_2), 51.59 (s, CH), 37.88 (s, CH), 29.88 (s, CH), 23.08 (s, CH_2), 20.59 (s, CH_3), 16.75 (s, CH_3). NMR data agree with literature [44]. HPLC (Diacel Chiralcel IA-H, hexane/propan-2-ol, 90:10, 0.8 mL/min, 218 nm): t_R (major) = 9.7 min (R), t_R (minor) = 10.9 min (S), e.r. = 54:43.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2013.03.033.

References

[1] S. Woodward, D. Willcox, Ligated Organocuprates: an A–Z Routemap of Mechanism and Application, in: P.G. Andersson (Ed.), Innovative Catalysis in Organic Synthesis, Wiley-VCH, 2012, pp. 233–255.
[2] G.P. Howell, Org. Process Res. Dev. 16 (2012) 1258–1272.
[3] S.-Y. Wang, T.-P. Loh, Chem. Commun. 46 (2010) 8694–8703.
[4] C. Hawner, A. Alexakis, Chem. Commun. 46 (2010) 7295–7306.
[5] A. Alexakis, J.E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, Chem. Rev. 108 (2008) 2796–2823.
[6] T. Jerphagnon, M.G. Pizzuti, A.J. Minnaard, B.L. Feringa, Chem. Soc. Rev. 38 (2009) 1039–1075.
[7] S.R. Harutyunyan, T. den Hartog, K. Geurts, A.J. Minnaard, B.L. Feringa, Chem. Rev. 108 (2008) 2824–2852.
[8] F. Lopez, A.J. Minnaard, B.L. Feringa, Acc. Chem. Res. 40 (2007) 179–188.
[9] P.K. Fraser, S. Woodward, Tetrahedron Lett. 42 (2001) 2747–2749.
[10] F. Guillen, C.L. Winn, A. Alexakis, Tetrahedron Asymmetry 12 (2001) 2083–2086.
[11] J. Pytkowicz, S. Roland, P. Mangeney, Tetrahedron Asymmetry 12 (2001) 2087–2089.
[12] A. Alexakis, C.L. Winn, F. Guillen, J. Pytkowicz, S. Roland, P. Mangeney, Adv. Synth. Catal. 345 (2003) 345–348.
[13] C.L. Winn, F. Guillen, J. Pytkowicz, S. Roland, P. Mangeney, A. Alexakis, J. Organomet. Chem. 690 (2005) 5672–5695.
[14] H. Clavier, L. Coutable, J.-C. Guillemin, M. Mauduit, Tetrahedron Asymmetry 16 (2005) 921–924.
[15] H. Clavier, L. Coutable, L. Toupet, J.-C. Guillemin, M. Mauduit, J. Organomet. Chem. 690 (2005) 5237–5254.
[16] D. Rix, S. Labat, L. Toupet, C. Crévisy, M. Mauduit, Eur. J. Inorg. Chem. (2009) 1989–1999.
[17] K.-s. Lee, M.K. Brown, A.W. Hird, A.H. Hoveyda, J. Am. Chem. Soc. 128 (2006) 7182–7184.
[18] M.K. Brown, T.L. May, C.A. Baxter, A.H. Hoveyda, Angew. Chem. Int. Ed. 46 (2007) 1097–1100.
[19] F. Wang, L.-j. Liu, W. Wang, S. Li, M. Shi, Coord. Chem. Rev. 256 (2012) 804–853.
[20] J. Wencel, M. Mauduit, H. Hénon, S. Kehrli, A. Alexakis, Aldrichim. Acta 42 (2009) 43–50.
[21] Y. Matsumoto, K.-i. Yamada, K. Tomioka, J. Org. Chem. 73 (2008) 4578–4581.
[22] D. Martin, S. Kehrli, M. D'Augustin, H. Clavier, M. Mauduit, A. Alexakis, J. Am. Chem. Soc. 128 (2006) 8416–8417.
[23] S. Kehrli, D. Martin, D. Rix, M. Mauduit, A. Alexakis, Chem. Eur. J. 16 (2010) 9890–9904.
[24] M. Tissot, A. Pérez Hernández, D. Müller, M. Mauduit, A. Alexakis, Org. Lett. 13 (2011) 1524–1527.
[25] M. Tissot, D. Poggiali, H. Hénon, D. Müller, L. Guénée, M. Mauduit, A. Alexakis, Chem. Eur. J. 18 (2012) 8731–8747.
[26] T.L. May, J.A. Dabrowski, A.H. Hoveyda, J. Am. Chem. Soc. 133 (2011) 736–739.
[27] T.L. May, M.K. Brown, A.H. Hoveyda, Angew. Chem. Int. Ed. 47 (2008) 7358–7362.
[28] M. Yoshida, H. Ohmiya, M. Sawamura, J. Am. Chem. Soc. 134 (2012) 11896–11899.
[29] K.-s. Lee, A.H. Hoveyda, J. Org. Chem. 74 (2009) 4455–4462.
[30] J.M. O'Brien, K.-s. Lee, A.H. Hoveyda, J. Am. Chem. Soc. 132 (2010) 10630–10633.
[31] K.-s. Lee, A.H. Hoveyda, J. Am. Chem. Soc. 132 (2010) 2898–2900.
[32] K.-s. Lee, H. Wu, F. Haeffner, A.H. Hoveyda, Organometallics 31 (2012) 7823–7826.
[33] E. Bappert, G. Helmchen, Synlett (2004) 1789–1793.
[34] J.-M. Becht, E. Bappert, G. Helmchen, Adv. Synth. Catal. 347 (2005) 1495–1498.
[35] S. Gischig, A. Togni, Organometallics 23 (2004) 2479–2487.
[36] S. Gischig, A. Togni, Organometallics 24 (2005) 203–205.
[37] T. Focken, G. Raabe, C. Bolm, Tetrahedron Asymmetry 15 (2004) 1693–1706.
[38] H. Seo, H.-j. Park, B.Y. Kim, J.H. Lee, S.U. Son, Y.K. Chung, Organometallics 22 (2003) 618–620.
[39] J.-C. Shi, P.-Y. Yang, Q. Tong, Y. Wu, Y. Peng, J. Mol. Catal. A Chem. 259 (2006) 7–10.
[40] H.-W. Yu, J.-C. Shi, H. Zhang, P.-Y. Yang, X.-P. Wang, Z.-L. Jin, J. Mol. Catal. A Chem. 250 (2006) 15–19.
[41] F. Visentin, A. Togni, Organometallics 26 (2007) 3746–3754.
[42] N. Debono, A. Labande, E. Manoury, J.-C. Daran, R. Poli, Organometallics 29 (2010) 1879–1882.
[43] R. Šebesta, F. Bilčík, P. Fodran, Eur. J. Org. Chem. (2010) 5666–5671.
[44] M.K. Brown, S.J. Degrado, A.H. Hoveyda, Angew. Chem. Int. Ed. 44 (2005) 5306–5310.
[45] T. Hayashi, T. Mise, M. Fukushima, M. Kagotani, N. Nagashima, Y. Hamada, A. Matsumoto, S. Kawakami, M. Konishi, K. Yamamoto, M. Kumada, Bull. Chem. Soc. Jpn. 53 (1980) 1138–1151.
[46] R. Šebesta, A. Almassy, I. Císařová, Š. Toma, Tetrahedron Asymmetry 17 (2006) 2531–2537.
[47] J.W. Bode, M.P. Doyle, M.N. Protopopova, Q.-L. Zhou, J. Org. Chem. 61 (1996) 9146–9155.
[48] M. Magrez, J. Wencel-Delord, A. Alexakis, C. Crévisy, M. Mauduit, Org. Lett. 14 (2012) 3576–3579.
[49] M. Shi, C.-J. Wang, W. Zhang, Chem. Eur. J. 10 (2004) 5507–5516.
[50] A. Hajra, N. Yoshikai, E. Nakamura, Org. Lett. 8 (2006) 4153–4155.
[51] R. Šebesta, M.G. Pizzuti, A.J. Boersma, A.J. Minnaard, B.L. Feringa, Chem. Commun. (2005) 1711–1713.
[52] F.D. Lewis, S.V. Barancyk, J. Am. Chem. Soc. 111 (1989) 8653–8661.