Asymmetric Cu-catalyzed 1,2 and 1,4-additions of Grignard reagents

Calvo Gonzalez, Beatriz Carmen

Chapter 2: Cu-catalyzed conjugate addition of Grignard reagents to 2-methylcyclopentenone and sequential enolate alkylation

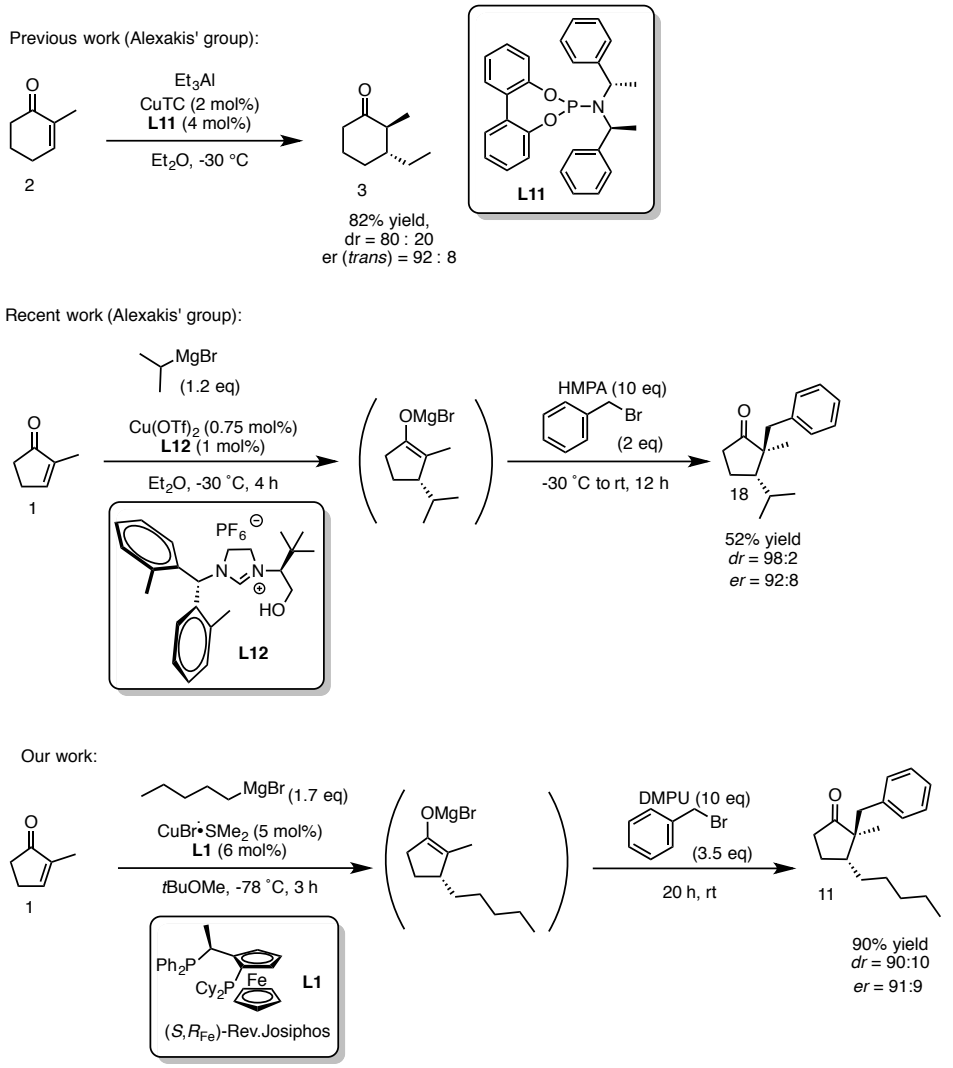
Introduction

The enantioselective Cu-catalysed conjugate addition of organometallic reagents has over the years become a well-established tool for asymmetric C-C bond formation.[1–10] Various organometallic reagents are employed in this transformation and the substrate scope comprises a variety of Michael acceptors, both cyclic and acyclic. In our recent work,[11–13] we focus on the use of Grignard reagents, because of their straightforward preparation from readily available alkyl bromides. In the cyclic series, the use of Grignard reagents in the copper-catalyzed asymmetric Michael addition has been reported for cyclopentenone,[14–16] cyclohexenone,[5,14,16–22] cycloheptenone,[14–17] β-substituted cyclic enones,[22,23] and lactones.[15,17,18,24,25] In these studies, however, α-substitution (2-substitution) is lacking, a situation no different from reports with other organometallic reagents. Until very recently, the sole report in this field came from Vuagnoux-d'Augustin and Alexakis, and comprized the enantioselective addition of Me_3Al and Et_3Al to 2-methyl cyclohexenone[23] (Scheme 1). This knowledge was subsequently used by Helmchen et al. in a synthesis of pumiliotoxin C.[26] Neither the use of Grignard reagents nor 2-methyl cyclopentenone had been used until during the preparation of this manuscript Mauduit, Alexakis *et al*. reported the successful application of Cu(I)-N-heterocyclic carbene complexes in the asymmetric addition of Grignard reagents to 2-

(B. C. Calvo; A. V. R. Madduri; S. R. Harutyunyan and A. J. Minnaard; **2014**, *Advanced Synthesis and Catalysis*; 356, 9, p. 2061)

methyl cyclopentenone and –hexenone.[27] The resulting magnesiumenolates were subsequently alkylated to provide a quaternary stereocenter vicinal to the initially formed tertiairy stereocenter.

Here we report the asymmetric conjugate addition of Grignard reagents to 2-methyl cyclopentenone with a copper catalyst based on Rev-JosiPhos (L1) and the subsequent enolate alkylation with a variety of electrophiles.

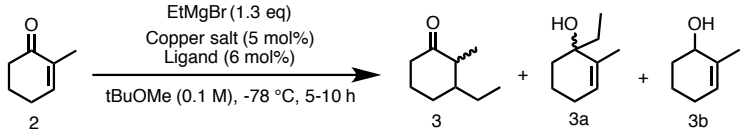


Scheme 1. Previous and current work.

Results and Discussion

As a starting point, 2-methyl cyclohexenone (2) was chosen as the model substrate. Various copper salts, and chiral ligands (Table 1, Figure 1) were studied in the conjugate addition of ethylmagnesium bromide.

Table 1. Conjugate addition of ethylmagnesium bromide to (2); variation in copper salt and ligand



Entry	Ligand	Copper salt	3: 3a [b]	*er*(trans)[d] [e]
1	-	CuBr•SMe_2	38:56	-
2	L1	CuBr•SMe_2	96:3	70:30
3	L2	CuI	73:26	60:40
4	L3	CuCl	29:62[c]	50:50
5[a]	L3	CuCl	42:56[c]	50:50
6	L3	CuBr•SMe_2	35:64[c]	50:50
7[a]	L3	CuBr•SMe_2	21:79[c]	50:50
8	L4	CuBr•SMe_2	61:37	55:45
9	L5	CuBr•SMe_2	94:5	52:48
10	L6	CuBr•SMe_2	91:9	55:45
11	L7	CuBr•SMe_2	65:32	54:46

12	L8	CuBr•SMe_2	91:6	63:39
13	L9	CuBr•SMe_2	94:4	52:48
14	L10	CuBr•SMe_2	95:5	53:47

[a] Reactions were performed at –10 °C. [b] Selectivity determined by GC-MS. [c] No *ee* found for 3a. [d] Enantioselectivities determined by chiral GC, see SI. [e] Diastereomeric ratios between 60 : 40 and 80 : 20.

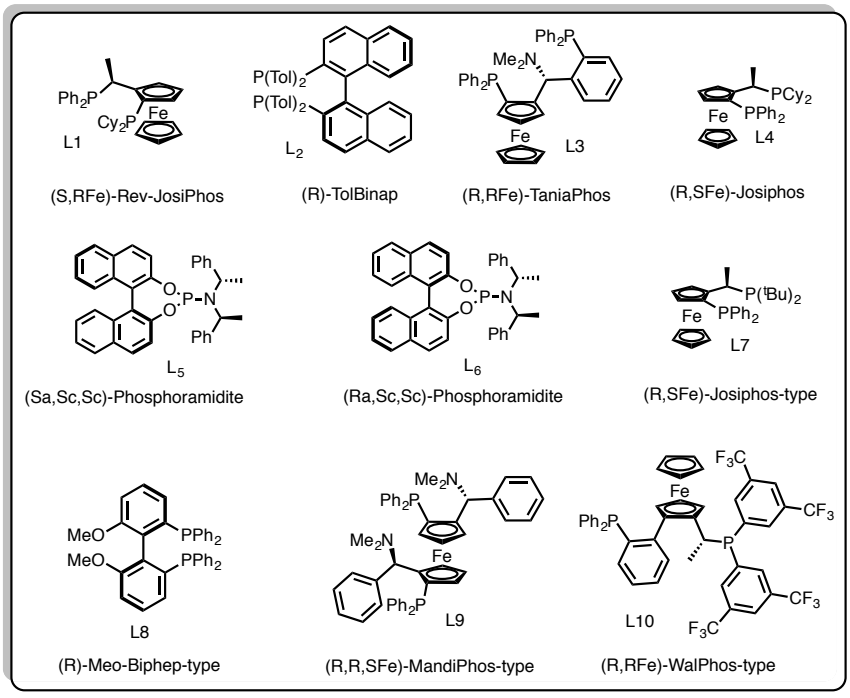
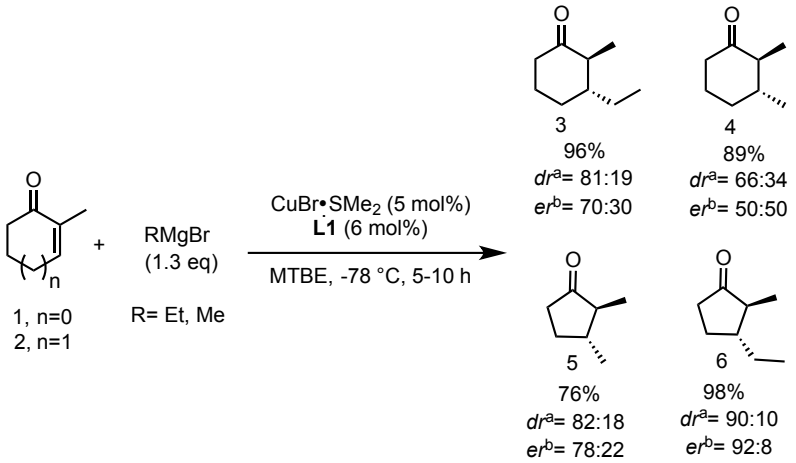


Figure 1. Chiral ligands used in this study.

The combination of L1 and CuBr•SMe_2 resulted in a very high selectivity for the conjugate addition product (3), considerably higher than the reaction with just catalytic copper. A moderate but distinct enantioselectivity was obtained as well (entry 2). With (L2) only low enantioselectivity was

obtained whereas (L3) provided the racemate, as did (L4 – L7). Notably, only when employing (L3), no catalyst control was observed, while on the contrary, (L5 – L6) did provide an excellent regioselectivity in favour of (3). (L8) provided a small enantioselectivity whereas (L9) and (L10) gave racemates, though with very high regioselectivity. With all ligands, the *trans*:*cis* ratio in (3) varied as expected[23,28] between 60 : 40 and 80 : 20.

The situation improved when 2-methyl cyclopentenone (1) was studied in the conjugate addition of methyl- and ethylmagnesium bromide, employing the combination of CuBr•SMe_2 and (L1) as the most successful catalyst thus far (Scheme 2).

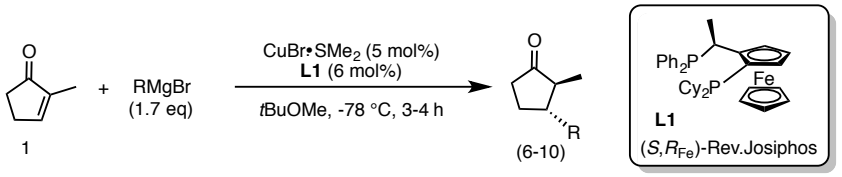


Scheme 2. Cu/L1 catalyzed asymmetric conjugate addition reactions. [a] *dr* = *trans*:*cis* ratio. [b] *er* of the major *trans* diastereomer. The absolute configuration of (5), and in analogy (6), was established by comparison of the optical rotation with the literature value.[29]

The addition of methylmagnesium bromide to (2) showed like in the case of EtMgBr a high selectivity for the formation of the conjugate addition product, however without enantioselectivity. The same reaction with 2-

methyl cyclopentenone (1), however, resulted in a significant *er* (78 : 22). Rewarding results were obtained in the Cu/(L1) catalyzed addition of EtMgBr to (1); virtually full regioselectivity and an *er* of 92 : 8! Therefore we decided to focus on (1) as the substrate, and determine the scope of Grignard reagents that could be added enantioselectively (Table 2).

Table 2. Grignard reagent scope of the conjugate addition to 2-methyl cyclopentenone (1).



1 (6-10)

Entry	R	Product	Conversion [a]/ Yield	*er* [c] [d] [e]
1		6	98%/ n.d[b]	92:8
2		7	99%/ 95%	91:9
3		8	95%/ n.d[b]	50:50
4		9	94%/ n.d[b]	92:8
5		10	76%/ 70%	85:15

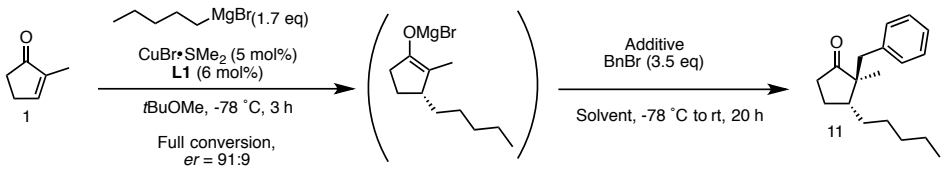
[a] Conversions determined by GC-MS. [b] Not determined due to the volatility of the product. [c] Enantioselectivities determined by chiral GC, see SI. [d] *er* of the major *trans* diastereomer. [e] Diastereomeric ratio's between 85:15 and 90 : 10.

Table 2 shows that high *er*'s are obtained with a set of linear saturated and unsaturated Grignard reagents. Linear alkyl and alkenyl substituents, or

substituents branched at the δ-position, perform very well. This makes the catalyst system highly complementary to the aforementioned Mauduit-Alexakis system that performs best with sterically more hindered α-branched Grignard reagents. Unfortunately, when the substrate was changed for a more sterically hindered one, 2-pentyl cyclopentenone, the conjugate addition resulted in very poor conversions. Conjugate addition to cyclic enones results, in addition to a C–C bond and a stereocenter, also in regioselective formation of an enolate. Especially in the current case, subsequent reaction with a carbon electrophile is attractive, as a second, quaternary, stereocenter is formed. Reaction of *in situ* formed enolates has been reported a number of times,[20,30–33] however, unlike lithium enolates, magnesium enolates react only sluggishly and additives or co-solvents are mostly used to accelerate the reaction.

Protonation of the enolate formed, gave already reasonable diastereomeric ratio's in the range of 6 : 4 to 8 : 2 in favour of the *trans* compound.[29] Benzyl bromide was selected to study the alkylation under various conditions[34] (Table 3). In the absence of additives and cosolvents no reaction took place (entry 1).

Table 3. Conjugate addition followed by benzylation



Entry	Additive (No. of eq. A)	Co-solvent (MTBE:Co-solvent)	Conversion [a]	*dr* [b]
1	-	-	-	-

2	HMPA(5)	-	95%	90:10
3	TMEDA(3)	-	20%	89:11
4	-	THF (1:2)	20%	98:2
5	HMPA(5)	THF (2:3)	51%	90:10
6	-	DME (1:2)	-	-

[a] Conversions determined by GC-MS. [b] Diastereoselectivity determined by GC-MS. The absolute configuration was established by comparison of the optical rotation with analogues in the literature.[27] The relative configuration was determined by NMR (NOESY), see SI.

When HMPA was added, the reaction reached almost full conversion with high diastereoselectivity (entry 2), whereas with TMEDA the conversion decreased dramatically (entry 3). The addition of coordinating solvents was also studied. The use of THF as a co-solvent did not improve the conversion although it afforded a nearly complete diastereoselectivity. Addition of DME resulted in no reaction. In order to get a more complete picture, a set of additional electrophiles was studied as well, under mostly identical conditions.

Table 4. Conjugate addition followed by reaction with allyl iodide.

Entry	**Additive (No. of eq. A)**	**Co-solvent (MTBE:Co-solvent)**	**Conversion [d)]**	***dr*[e)]**
1[a)]	-	-	-	-
2[a)]	HMPA(3)	-	40%	80:20
3[b]	HMPA(5)	-	65%	70:30

4[c]	HMPA(5)	-	43%	70:30
5	-	THF (1:2)	60%	90:10
6	HMPA(5)	THF (2:3)	89%	80:20
7	-	DME (1:2)	93%	90:10

[a] Allyl bromide was used as electrophile. [b] Reaction performed at 42 °C. [c] Reaction performed at 70 °C. [d] Conversions determined by GC-MS. [e] Determined by GC-MS.

As in the benzylation, the allylation reaction with no additives showed no conversion (Table 4, entry 1). Remarkably, however, addition of HMPA now only showed moderate improvement whereas DME increased the conversion to 93%! (entry 7). *Tert*-butyl bromoacetate (Table 5), turned out to be rather unreactive in this reaction and also the diastereomeric ratio dropped. Reaction with propargyl bromide gave upon addition of 3 eq HMPA incomplete conversion (75%) and a *dr* of 85 : 15.

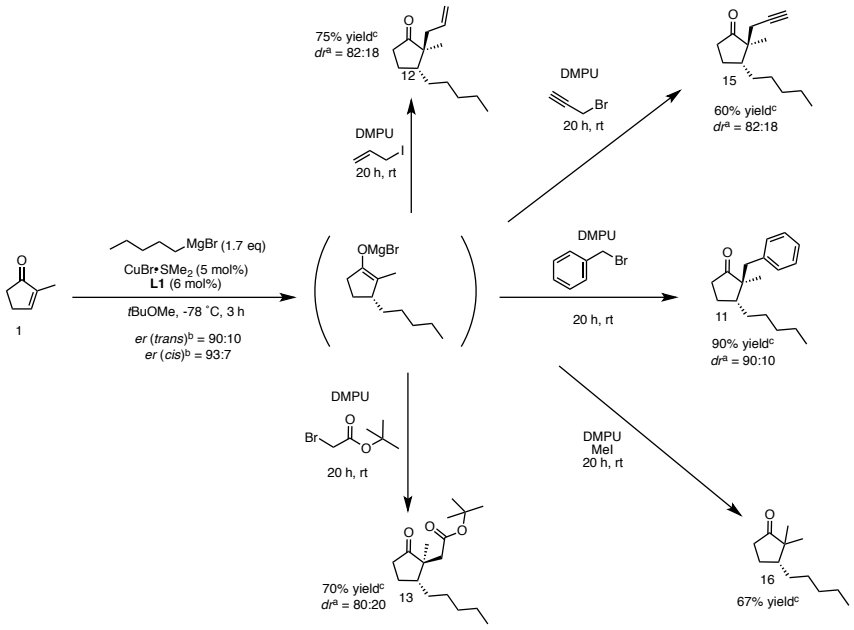
Table 5. Alkylation reaction followed by reaction with tert-butyl bromoacetate.

Entry	**Additive (No. of eq. A)**	**Co-solvent (MTBE:Co-solvent)**	**Conversion**[c)]	***dr***[d)]
1[a)]	HMPA (5)	-	25%	60:40
2[b)]	HMPA(5)	-	50%	60:40
3	HMPA(5)	THF (2:3)	53%	50:50
4	-	DME (1:2)	52%	50:50

[a] Reaction performed at 42 °C. [b] Reaction performed at 70 °C. [c] Conversions

determined by GC-MS. [d] Determined by GC-MS.

The picture that arose from this study is that although high conversion and diastereoselectivities could be obtained for most electrophiles (*tert*-butyl bromoacetate being an exception), the optimal reaction conditions are highly dependent on the electrophile. The addition of HMPA was in general most effective but, on the other hand, is toxic. DMPU (1,3-dimethyltetrahydropyrimidine-2(1H)-one) can often be used as a versatile alternative, and is mostly applied in somewhat larger amounts.[35] The addition of 10 eq of DMPU was therefore studied (Scheme 3). We were pleased to see that this procedure gave consistently excellent conversions, good isolated yields and diastereomeric ratio's for the various electrophiles.[36] Also *tert*-butyl bromoacetate performed well now, and also methyl iodide (not used earlier) gave close to complete conversion (Scheme 3). The diastereoselectivity is not strongly dependent on substitution at the 3-position. The similar reaction sequence with EtMgBr and benzyl bromide afforded a *dr* of 84 : 16, whereas the combination of isobutylmagnesium bromide and tert-butyl bromoacetate afforded a dr of 85 : 15.



Scheme 3. Conjugate addition followed by α-alkylation in ^{t}BuOMe/DMPU. (3.5 eq of the electrophile and 10 eq of DMPU were used.)[37] [a] Determined by GC-MS. [b] Determined by chiral GC, see SI. [c] *cis*/ *trans* mixture

Conclusions

An efficient catalyst system has been identified for the conjugate addition of Grignard reagents to 2-methyl cyclopentenone (1). The products are obtained in good yields, and in high enantioselectivities employing CuBr•SMe_2 and Rev-JosiPhos (L1) in *t*-BuOMe at –78 °C. The method is nicely complimentary with the one recently reported by Mauduit and Alexakis. Linear Grignard reagents perform well, whereas

with their reported Cu-NHC catalyst system, branched Grignard reagents perform superior. A thorough study on the subsequent alkylation of the regioselectively formed enolate identified DMPU as an essential and superior additive. This sequential conjugate addition – enolate alkylation leads in a one-pot reaction to the formation of two vicinal stereocenters one of which is quaternary. The products made this way are highly useful building blocks in the synthesis of natural products.

Experimental Section

General experimental

All reactions were performed under nitrogen atmosphere, using flame-dried glassware and dry solvents. *t*-BuOMe and THF were taken from a MBraun solvent purification system (SPS-800). All other reagents were purchased from Sigma-Aldrich or Acros Organics and were used without further purification. Racemic products were synthesized by reacting (1) with the corresponding Grignard reagent and 1 equiv of CuBr•SMe_2 in MTBE at –78 °C. ^{1}H-NMR and ^{13}C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) using $CDCl_3$ as the solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. High resolution mass spectra (HRMS) were recorded on a AEI-MS-902 and FTMS orbitrap (Thermo Fisher Scientific) mass spectrometer. Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g / 100 mL). Enantiomeric excesses were determined by capillary GC analysis (Agilent Technologies 7890, CP-Chiralsil-Dex-CB column (25m x 25 mm x 25 μm)) using a flame ionization detector. Progress and conversion of the reactions were determined by GC-MS (GC, HP6890: MS HP5973) with and HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Flash chromatography: Merck silica gel type 9385 230-400 mesh. TLC: Merck silica gel 60, 0.25 mm. Compounds were visualized by UV, Seebach's reagent

(phosphomolybdic acid, 25 g; cerium sulfate, 7.5 g; H_2O, 500 mL; H_2SO_4, 25 mL) and potassium permanganate staining. Synthetized Grignard reagents were titrated according to literature procedures.[38]

General procedure for the enantioselective conjugate addition: (+)-(2*S*,3*R*)-3-pentyl-2-methylcyclopentanone (7):

To a flame dried Schlenk tube, containing a magnetic stirring bar, CuBr•SMe_2 (15 mmol, 3.08 mg), (L1) (18 mmol, 10.7 mg) and 3 mL of dry *t*-BuOMe were added. The mixture was left to stir for 15 min. After that, 2-methyl cyclopentenone (1) (0.3 mmol, 28.8 mg) dissolved in 1 mL of dry *t*-BuOMe was added to the solution. The mixture was left to stir for 30 min at –78 °C. Pentylmagnesium bromide (2 M in Et_2O, 1.7 eq, 0.25 mL) was then added dropwise over 15 min and the reaction was left to stir for 3 to 4 h at –78 °C. The reaction was quenched with MeOH (2 mL), allowed to warm up to rt and diluted with Et_2O. NH_4Cl_{aq} was added and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated at reduced pressure to afford (7) in 95% yield as a yellowish oil after flash chromatography (SiO_2, *n*-pentane : Et_2O (92:8)). *trans*:*cis* = 85:15, *er* (*trans*)= 91:9, *er* (*cis*)= 87:13 Retention times on chiral GC: 13.5 min and 13.6 min (major *trans* diastereomer), 14.4 min and 14.6 min (minor *cis* diastereomer).

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers) δ 2.41 – 2.28 (m, 1H), 2.20 – 2.02 (m, 2H), 1.77 – 1.55 (m, 3H), 1.40 – 1.23 (m, 8H), 1.05 (d, J = 5.8 Hz, 3H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR (major *trans*) (101 MHz, $CDCl_3$) δ = 221.5, 50.5, 44.8, 37.4, 34.5, 32.0, 27.2, 26.7, 22.6, 14.0,

12.6. $[\alpha]_D^{20}$ = +27.7 (c = 1.1, $CHCl_3$). HRMS (ESI+, m/z): calcd. for $C_{11}H_{20}ONa$ $[M + Na]^+$ = 191.140; found: 191.140.

(+)-(2*S*,3*R*)-3-ethyl-2-methylcyclopentanone (6):

96% conversion, *trans*/*cis* 90/10, *er* (*trans*)= 92:8, *er* (*cis*)= 91:9. The product was obtained as a colourless oil, the volatility of the product did not allow complete removal of the solvents after column chromatography (SiO_2, *n*-pentane: Et_2O (90:10)) hampering the determination of an accurate isolated yield. Retention times on chiral GC: 8.8 min and 8.9 min (major *trans* diastereomer), 9.9 min and 10.1 min (minor *cis* diastereomer).

^1H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers) δ 2.23 – 2.11 (m, 1H), 2.08 – 1.84 (m, 2H), 1.67 – 1.47 (m, 2H), 1.47 – 1.31 (m, 1H), 1.29 – 1.08 (m, 2H), 0.90 (d, J = 6.9 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (major *trans*) ^{13}C NMR (101 MHz, $CDCl_3$) δ = 220.5, 49.9, 46.2, 37.0, 26.8, 26.4, 12.3, 11.1. $[\alpha]_D^{20}$ = +84.1 (c = 2.5, $CHCl_3$). HRMS (ESI+, m/z): calcd. for $C_8H_{14}ONa$ $[M + Na]^+$ = 149.093; found: 149.093.

(+)-(2*S*,3*R*)-3-(but-3-en-1-yl)-2-methylcyclopentanone (9):

98% conversion, *trans*:*cis* = 86:14, *er* (*trans*)= 92:8. The product was obtained as a colourless oil, the volatility of the product did not allow to completely remove the solvents after column chromatography (SiO_2, *n*-pentane: Et_2O (90:10)) hampering the determination of an accurate

isolated yield. Retention times on chiral GC for the major *trans* diastereomer 5.5 min and 5.7 min.

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers) δ 5.84 – 5.68 (m, 1H), 4.98 (d, J = 17.1 Hz, 1H), 4.91 (d, J = 10.2 Hz, 1H), 2.34 – 2.24 (m, 1H), 2.24 – 1.98 (m, 4H), 1.81 – 1.69 (m, 1H), 1.69 – 1.52 (m, 2H), 1.40 – 1.25 (m, 2H), 1.01 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (major trans) δ = 220.8, 138.3, 114.7, 50.3, 44.1, 37.3, 33.6, 31.2, 27.0, 12.5. $[\alpha]_D^{20}$ = +72.1 (c =2.7, $CHCl_3$). HRMS (ESI+, m/z): calcd for $C_{10}H_{16}ONa$ $[M + Na]^+$:175.109; found: 175.109.

(+)-(2*S*,3*R*)-2-methyl-3-(4-methylpent-3-en-1 yl)cyclopentanone (10):

76% conversion, 70% yield, *trans*:*cis* = 84:16, *er* (*trans*)= 85:15, *er* (*cis*)= 83:17. The product was obtained as a colourless oil after column chromatography (SiO_2, *n*-pentane: Et_2O (92:8)). Retention times on chiral GC: 25.6 min and 26.0 min (major *trans* diastereomer), 30.0 min and 31.0 min (minor *cis* diastereomer).

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers) δ = 5.12 (t, J=7.1, 1H), 2.42 – 2.29 (m, 1H), 2.27 – 1.92 (m, 5H), 1.79 – 1.59 (m, 2H), 1.70 (s, 3H), 1.62 (s, 3H), 1.49 – 1.16 (m, 2H), 1.07 (d, J=6.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (major *trans*) ^{13}C NMR (101 MHz, $CDCl_3$) δ = 221.3, 131.8, 124.2, 50.5, 44.4, 37.4, 34.6, 27.1, 25.7, 25.6, 17.7, 12.6. $[\alpha]_D^{20}$ = +35.8 (c = 0.12, $CHCl_3$). HRMS (ESI+, m/z): calcd. for $C_{12}H_{21}O$ $[M + H]^+$ = 181.158; found: 181.158.

General procedure for the enantioselective conjugate addition followed by trapping of the enolate: (+)-*tert*-butyl 2-((1*S*,5*R*)-1-methyl-2-oxo-5-pentylcyclopentyl)acetate (13):

To a flame dried Schlenk tube, containing a magnetic stirring bar, CuBr•SMe_2 (15 μ mol, 3.08 mg), ligand (L1) (18 μ mol, 10.7 mg) and 3 mL of dry *t*-BuOMe were added. The mixture was left to stir for 15 min. After that, 2-methyl cyclopentenone (1) (0.3 mmol, 28.8 mg) dissolved in 1 mL of dry *t*-BuOMe was added to the solution. The mixture was left to stir for 30 min at -78 °C. Pentylmagnesium bromide (2 M in Et_2O, 0.51 mmol, 0.25 mL) was dropwise added over 15 min and the reaction mixture was left to stir for 3 h at –78 °C. Dry DMPU (3 mmol, 0.36 mL) was added to the reaction mixture which was left to stir for 10 min at –78 °C. *tert*-butyl 2-bromoacetate (1.05 mmol, 0.15 mL) was added, the reaction mixture was allowed to warm up to rt was left to stir for 16 h. The mixture was diluted with Et_2O, NH_4Cl_{aq} was added and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed at reduced pressure. Compound (13) was obtained in 70% yield as a colorless oil after flash column chromatography (SiO_2, *n*-pentane : Et_2O (92:8)). *trans:cis* = 80:20, *er* (*trans*)= 90:10, *er* (*cis*)= 87:13 Retention times on chiral GC: 13.5 min and 13.6 min (major *trans* diastereomer), 14.4 min and 14.6 min (minor *cis* diastereomer).

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers) δ 2.68 (d, J = 16.5 Hz, 1H), 2.39 – 2.27 (m, 3H), 2.30 (d, J = 16.5 Hz, 1H), 2.26 – 2.08 (m, 2H), 1.51 – 1.36 (m, 8H), 1.40 (s, 9H), 0.89 (t, J = 6.6 Hz, 3H), 0.79 (s, 3H). ^{13}C

NMR (101 MHz, $CDCl_3$) (*trans* diastereomer): δ = 222.3, 170.6, 80.7, 49.3, 42.4, 41.7, 37.1, 32.0, 29.8, 28.1, 27.4, 25.4, 22.6, 17.6, 14.0. $[\alpha]_D^{20}$ = +18.1 (c = 0.11, $CHCl_3$). HRMS (ESI+, m/z): calcd. for $C_{17}H_{30}O_3Na$ $[M + Na]^+$ = 305.209; found: 305.208.

(+)-(2*S*,3*R*)-2-benzyl-2-methyl-3-pentylcyclopentanone (11):

90% yield, *trans*:*cis* = 90:10, *er* (*trans*)= 90 : 10, er (*cis*)= 87 : 13. The product was obtained as a yellowish oil after flash column chromatography (SiO_2, *n*-pentane : Et_2O 95 : 5)). Retention times on chiral GC: 13.5 min and 13.6 min (major *trans* diastereomer), 14.4 min and 14.6 min (minor *cis* diastereomer).

^1H NMR (400 MHz, $CDCl_3$) mixture of diastereomers: δ 7.31 – 7.13 (m, 4H), 7.05 (d, J = 7.6 Hz, 1H), 3.10 (d, J = 13.6 Hz, 1H), 2.52 (d, J = 13.6 Hz, 1H), 2.30 (dd, J = 18.8, 7.9 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.86 – 1.72 (m, 2H), 1.49 – 1.10 (m, 9H), 0.92 (s, 3H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 221.8, 137.5, 130.3, 128.0, 126.5, 48.5, 37.8, 36.5, 32.3, 29.9, 29.6, 27.8, 24.4, 22.8, 20.6, 14.2. $[\alpha]_D^{20}$ = +30.8 (c = 0.17, $CHCl_3$). HRMS (ESI+, m/z): calcd. for $C_{18}H_{26}ONa$ $[M + Na]^+$ = 281.188; found: 281.187.

(+)-(2*S*,3*R*)-2-allyl-2-methyl-3-pentylcyclopentanone (12):

75% yield, trans:cis = 82:18, *er* (*trans*)= 90 : 10, *er* (*cis*)= 87 : 13. The product was isolated as a yellowish oil after flash column chromatography (SiO_2, *n*-pentane : Et_2O 95 : 5)). Retention times on chiral GC: 13.5 min and 13.6 min (major *trans* diastereomer), 14.4 min and 14.6 min (minor *cis* diastereomer).

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers) δ = 5.56 (m, 1H), 4.99 – 4.90 (m, 2H), 2.36 – 2.23 (m, 2H), 2.07 – 1.87 (m, 4H), 1.45 – 1.29 (m, 3H), 1.30 – 1.16 (m, 6H), 0.83 (t, J=6.9, 3H), 0.77 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (major trans) δ = 223.5, 134.4, 117.9, 51.3, 42.5, 40.4, 37.4, 32.1, 29.6, 27.3, 25.0, 22.6, 17.5, 14.0. $[\alpha]_D^{20}$ = +61.4 (c = 0.10, $CHCl_3$). HRMS (ESI+, m/z): calcd. for $C_{14}H_{25}O$ $[M + H]^+$ = 209.190; found: 209.189.

(+)-(*R*)-2,2-dimethyl-3-pentylcyclopentanone (16):

67% yield, *er* (*trans*)= 90 : 10, er (*cis*)= 87 : 13. The product was isolated as a colorless oil after flash column chromatography (SiO_2, *n*-pentane : Et_2O 95 : 5)). Retention times on chiral GC: 13.5 min and 13.6 min (major *trans* diastereomer), 14.4 min and 14.6 min (minor *cis* diastereomer).

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers) δ 2.42 – 2.31 (m, 1H), 2.20 – 2.03 (m, 2H), 1.76 – 1.65 (m, 1H), 1.51 – 1.38 (m, 3H), 1.39 – 1.14 (m, 6H), 1.02 (s, 3H), 0.90 (t, J = 6.5 Hz, 3H), 0.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (major trans) δ = 224.3, 47.9, 47.4, 36.4, 32.1, 29.7, 27.5, 25.0, 22.7, 22.6, 17.9, 14.0. $[\alpha]_D^{20}$ = +44.0 (c = 0.17, $CHCl_3$). HRMS (ESI+, m/z): calcd. for $C_{12}H_{23}O$ $[M +H]^+$ = 183.174; found: 183.173.

(+)-(2*S*,3*R*)-2-benzyl-3-ethyl-2-methylcyclopentanone (17):

95% conversion, 54% yield, *trans*:*cis* = 84:16, *er* (*trans*)= 92 : 8, *er* (*cis*)= 91 : 9. The product was isolated as a colorless oil after flash column chromatography (SiO_2, *n*-pentane : Et_2O 95 : 5)). Retention times on

chiral GC: 8.8 min and 8.9 min (major *trans* diastereomer), 9.9 min and 10.1 min (minor *cis* diastereomer).

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers) δ 7.27 – 7.14 (m, 4H), 7.06 (d, J = 6.7 Hz, 1H), 3.10 (d, J = 13.5 Hz, 1H), 2.53 (d, J = 13.5, 3.2 Hz, 1H), 2.30 (dd, J = 18.7, 7.8 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.85 – 1.68 (m, 2H), 1.58 – 1.46 (m, 1H), 1.40 – 1.23 (m, 2H), 0.92 (s, 3H), 0.92 (t, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (major *trans*) δ = 223.6, 138.3, 130.2, 128.1, 126.2, 53.2, 43.2, 41.6, 37.8, 24.5, 22.5, 18.4, 12.2. $[\alpha]_D^{20}$ = +60.7 (c = 0.14, $CHCl_3$). HRMS (ESI+, m/z): calcd. for $C_{15}H_{21}O$ $[M + H]^+$ = 217.159; found: 217.158.

(+)-(2*S*,3*R*)-2-methyl-3-pentyl-2-(prop-2-yn-1 yl)cyclopentanone (15):

95% conversion, 60% yield, *trans*:*cis* = 82:18, *er* (*trans*)= 90 : 10, *er* (*cis*)= 87 : 13. The product was isolated as a colorless oil after flash column chromatography (SiO_2, *n*-pentane : Et_2O 95 : 5)). Retention times on chiral GC: 13.5 min and 13.6 min (major *trans* diastereomer), 14.4 min and 14.6 min (minor *cis* diastereomer).

^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers) δ 2.47 (dd, J = 16.9, 2.5 Hz, 1H), 2.43 – 2.34 (m, 2H), 2.22 (dd, J = 17.1, 2.5 Hz, 1H), 2.33 – 2.04 (m, 5H), 1.95 (t, J = 2.5 Hz, 1H), 1.61 – 1.37 (m, 6H), 0.90 (t, J = 6.1 Hz, 3H), 0.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) (major *trans*) δ = 221.8, 81.1, 70.4, 50.8, 43.0, 37.1, 32.1, 29.8, 27.3, 25.6, 25.1, 22.6, 16.8, 14.0. $[\alpha]_D^{20}$ = +39.0 (c = 0.10, $CHCl_3$). HRMS (ESI+, m/z): calcd. for $C_{14}H_{22}ONa$ $[M + Na]^+$ = 229.156; found: 229.156 .

References

(1) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L.; *Chem. Rev.*, **2008**, 108, p.2824

(2) López, F.; Minnaard, A. J.; Feringa, B. L.; *Acc. Chem. Res.*, **2007**, 40, p.179

(3) Rossiter, B. E.; Swingle, N. M.; *Chem. Rev.*, **1992**, 92, p.771

(4) Feringa, B. L.; de Vries, A. H. M.; *Advances in Catalytic Processes: Asymmetric Chemical Transformations*, 1st ed., vol. 1 (Eds.: M.P. Doyle) JAI Press Inc., **1995**, pp. 1-13.

(5) Alexakis, A.; Benhaim, C.; *Eur. J. Org. Chem.*, **2002**, 2002, p.3221

(6) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M.; *Chem. Rev.*, **2008**, 108, p.2796

(7) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L.; *Chem. Soc. Rev.*, **2009**, 38, p.1039

(8) Endo, K.; Shibata, T.; *Synthesis*, **2012**, 44, p.1427

(9) Copper-Catalyzed Asymmetric Synthesis, 1st ed., (Eds.: A. Alexakis, N. Krause, S. Woodward) Wiley, **2014**.

(10) Lopez, F.; Minnaard, A. J.; Feringa, B. L.; in *The Chemistry of Organomagnesium Compounds*, 1st ed., Part 1 (Eds.: Z. Rappoport, I. Marek), **2008**, pp. 771–802.

(11) Madduri, A. V. R.; Minnaard, A. J.; Harutyunyan, S. R.; *Chem. Commun.*, **2012**, 48, p.1478

(12) Wu, Z.; Madduri, A. V. R.; Harutyunyan, S. R.; Minnaard, A. J.; *Eur. J. Org. Chem.*, **2014**, p.575

(13) Madduri, A. V. R.; Harutyunyan, S. R.; Minnaard, A. J.; *Angew. Chem. Int. Ed.*, **2012**, 51, p.3164

(14) Zhou, Q. L.; Pfaltz, A.; *Tetrahedron Lett.*, **1993**, 34, p.7725

(15) Naeemi, Q.; Robert, T.; Kranz, D. P.; Velder, J.; Schmalz, H. G.; *Tetrahedron: Asymmetry*, **2011**, 22, p.887

(16) Stangeland, E. L.; Sammakia, T.; *Tetrahedron*, **1997**, 53, p.16503

(17) Kanai, M.; Nakagawa, Y.; Tomioka, K.; *Tetrahedron*, **1999**, 55, p.3843

(18) Feringa, B. L.; Badorrey, R.; Peña, D.; Harutyunyan, S. R.; Minnaard, A. J.; *Proc. Natl. Acad. Sci. U. S. A.*, **2004**, 101, p.5834

(19) Robert, T.; Velder, J.; Schmalz, H. G.; *Angew. Chem. Int. Ed.*; **2008**, 47, p.7718

(20) Galeštoková, Z.; Šebesta, R.; *Eur. J. Org. Chem.*, **2012**, 2012, p.6688

(21) Bilčík, F.; Drusan, M.; Marák, J.; Šebesta, R.; *J. Org. Chem.*, **2012**, 77, p.760

(22) Kehrli, S.; Martin, D.; Rix, D.; Mauduit, M.; Alexakis, A.; *Chem. A Eur. J.*, **2010**, 16, p.9890

(23) Vuagnoux-d'Augustin, M.; Alexakis, A.; *Chem. A Eur. J.*, **2007**, 13, p.9647

(24) Mao, B.; Fañanás-Mastral, M.; Feringa, B. L.; *Org. Lett.*, **2013**, 15, p.286

(25) Teichert, J. F.; Feringa, B. L.; *Chem. Commun.*, **2011**, 47, p.2679

(26) Gärtner, M.; Qu, J.; Helmchen, G.; *J. Org. Chem.*, **2012**, 77, p.1186

(27) Germain, N.; Guénée, L.; Mauduit, M.; Alexakis, A.; *Org. Lett.*, **2014**, 16, p.118

(28) d'Augustin, M.; Palais, L.; Alexakis, A.; *Angew. Chem. Int. Ed.*, **2005**, 44, p.1376

(29) Lord, M.; Negri, J.; Paquette, L.; *J. Org. Chem.*, **1995**, 60, p.191

(30) Bleschke, C.; Tissot, M.; Müller, D.; Alexakis, A.; *Org. Lett.*, **2013**, 15, p.2152

(31) den Hartog, T.; Rudolph, A.; Maciá, B.; Minnaard, A. J.; Feringa, B. L.; *J. Am. Chem. Soc.*, **2010**, 132, p.14349

(32) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H.; *J. Am. Chem. Soc.*, **2001**, 123, p.755

(33) Suzuki, M.; Noyori, R.; in *Organocopper Reagents A Practical Approach*, 1st ed., (Ed.: R.J.K. Taylor), IRL Press, Oxford, UK, **1995**, pp. 185–216.

(34) The *trans* relationship between the substituent at the 3-position and the incoming electrophile at the 2-position was establised by NOESY experiments, see SI.

(35) Mukhopadhyay, T.; Seebach, D.; *Helv. Chim. Acta*, **1982**, 65, p.385

(36) The application of 5 eq of DMPU gave a lower conversion though still significantly higher than 5 eq of HMPA.

(37) Conversions in the second step were all >90% but isolated yields were somewhat decreased due to the volatility of the products.

(38) Lin, H. S.; Paquette, L. A.; *Synth. Commun.*, **1994**, 24, p.2503