SUPPLEMENTARY INFORMATION 1

On the Mechanism of the Copper-Catalyzed Enantioselective 1,4-Addition of Grignard Reagents to α, β-Unsaturated Carbonyl Compounds

Syuzanna R. Harutyunyan, Fernando López, Wesley R. Browne, Arkaitz Correa, Diego Peña, Ramon Badorrey, Auke Meetsma, Adriaan J. Minnaard,* Ben L. Feringa*

Department of Organic Chemistry and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands

E-mail: B.L.Feringa@rug.nl

General. Chiral ligands L1, L2 were gifted by Solvias (Basel). Aliphatic enones, CuCl, CuI, and CuBr·SMe₂ were purchased from Aldrich or Acros, and used without further purification. MeLi and Grignard reagents (MeMgBr, MeMgI, MeMgCl, EtMgBr, EtMgCl, EtMgI) were purchased from Aldrich or prepared from the corresponding alkyl halides and magnesium turnings in Et₂O following standard procedures. Grignard reagents were titrated using s-BuOH and catalytic amounts of 1,10-phenanthroline. tBuOMe was purchased as anhydrous grade, stored under 4 MS and used without further purification. Dialkylmagnesium compounds (Me₂Mg, Et₂Mg) were prepared by stirring alkylmagnesium bromides with equimolar amount of dioxane following standard procedures. Trans-1a,b, cis-81d, cis-9-111e were prepared according to the literature procedures. All the solvents used were technical grade and distilled from the indicated drying agents: dichloromethane: P₂O₅; diethyl ether, tetrahydrofuran, 1,4-dioxane and hexane: Na, benzophenone; CD₂Cl₂, d₈-THF, d₈-toluene used for NMR studies were degassed by three freeze-pump-thaw cycles and stored under N₂. ¹H NMR, ¹³C{¹H} NMR, and ³¹P{¹H} NMR spectra were obtained with Varian VXR500, 400, 300 spectrometer equipped with a 5 mm z-gradient broadband probe. ¹H NMR, ³¹P NMR and ¹³C NMR spectra were obtained at 499.9 MHz, 202.2 MHz and 125.69 MHz, respectively. ¹H, ³¹P and ¹³C chemical shifts (δ) are reported in parts per million (ppm) and were measured relative to the residual solvent peak (CD₂Cl₂ δ = 5.30 ppm for hydrogen atoms, δ = 53.5 for carbon atoms, CDCls, δ = 7.26 ppm for hydrogen atoms, δ = 77.0 for carbon atoms). ³¹P chemical shifts are referenced to external standard 85% H₃PO₄ (0 ppm). Coupling constants (J) are reported in hertz (Hz). Due to ³¹P coupling, resonances for certain carbon atoms in the phosphines listed below were observed as doublets. IR spectral data were obtained using a Perkin-Elmer 1600 FTIR spectrometer. Progress of the reaction and conversion were determined by GC-MS (GC,
HP6890: MS HP5973) with HP1 or HP5 columns (Agilent Technologies, Palo Alto, CA). Enantio- and regioselectivities were determined by capillary GC analysis (HP 6890, Chiraldex G-TA column (30 m x 0.25 mm), CPChiralsil-Dex-CB (25 m x 0.25 mm) using flame ionization detector (in comparison with authentic samples of racemic 1,2- and 1,4 addition products). Retention times ($t_R$) and integrated ratios were obtained using Agilent Chemstation Software. Sample injections were made using an HP 6890 Series Auto sample Injector. Optical rotations were measured in CHCl$_3$ on a Perkin Elmer 241 MC polarimeter with a 10 cm cell (concentration $c$ given in g/100 mL). All conjugate addition reactions were performed under nitrogen atmosphere using standard Schlenk techniques. Reaction vessels were flame-dried prior to use. Flash chromatography was performed using Merck 60 Å 230-400 mesh silica gel. All organic extracts were dried over MgSO$_4$, filtered, and concentrated under reduced pressure using a rotary evaporator. Absolute configuration of the products was determined by comparison of the sign of an optical rotation with compounds previously published. Electrochemical measurements were carried out on a Model 630B Electrochemical Workstation (CH Instruments). Analytic concentrations were typically 0.5 to 1 mM in anhydrous acetonitrile containing 0.1 M TBAPF$_6$. Unless otherwise stated a Teflon shrouded glassy carbon working electrode, a Pt wire auxiliary electrode non-aqueous Ag/Ag$^+$ ion reference electrode were employed. Reference electrodes were calibrated using decamethylferrocene as internal reference. Solutions were deoxygenated by purging with dry N$_2$ gas prior to the measurement. Cyclic voltammograms were obtained at sweep rates of between 10 mV s$^{-1}$ to 5 V s$^{-1}$. Redox potentials are +/- 10 mV.

**Preparation and characterization of Cu-complexes**

Typical procedure for Cu bromide complex 1a.

**CuBr complex (R,S)-1a.**

![Figure S1. X-ray structure of copper bromide complex 1a](obtained from CH$_3$CN).

$^2$ (a) $^1$H, $^{13}$C and $^{31}$P NMR spectra for all compounds are presented in supplementary information 2.

$^3$ The X-ray structure of 1a was already published in the short communication in *Angew. Chem. Int. Ed.* **2005**, 44, 2752–2756. CCDC 261573 contains the supplementary crystallographic data.
A solution of (R,S)-JosiPhos (L1, 1.68 µmol) and CuBr-SMe2 (1.68 µmol) in tBuOMe (20 mL) in a Schlenk tube was stirred at RT for 30 min. The solvent was removed under vacuum and the resulting orange crude residue was washed with cold pentane to afford Cu-complex as an orange powder (1230 mg, 99% yield).

CuCl complex (R,S)-1b was prepared from (R,S)-L1 (0.05 mmol) and CuCl (0.05 mmol) in 3 ml CH2Cl2, as described above for 1a. 1H NMR (CD2Cl2 at -60 °C) δ, 7.86 (m, 4H, ArH), 7.41 (m, 6H, ArH), 7.13 (m, 6H, ArH), 6.96 (m, 4H, ArH), 4.43-3.39 (m, 16H, CyH), 3.02 (m, 6CH, 2CH2) 27.33 (d, J = 8.97 Hz, 4CH); 27.68 (d, J = 13.66 Hz, 2CH2); 27.89 (d, J = 5.38 Hz, 2CH2); 29.19 (d, J = 6.90 Hz, 2CH2); 30.06 (m, 4CH); 32.91 (d, J = 9.67 Hz, 2CH2); 69.84 (m, 2CH); 70.33 (m, 10CH): 70.74 (m, 2CH); 73.04 (m, 2CH); 74.10 (m, 2CH); 74.29 (d, J = 8.09 Hz, 4CH); 128.51 (d, J = 10.23 Hz, 4CH); 128.85 (s, 2CH); 130.51 (s, 2CH); 132.37 (d, J = 14.41 Hz, 4CH); 135.07 (d, J = 18.47 Hz, 4CH); 135.25 (s, 2C); 135.49 (s, 2C); 31P NMR (CD2Cl2 at -60 °C) δ, 150.62 (bs, 2CH3); 25.95 (d, J = 17.97 Hz, 4CH2); 26.73 (m, 2CH2, 2CH); 27.33 (d, J = 7.81 Hz, 2CH2); 27.68 (d, J = 13.66 Hz, 2CH2); 27.89 (d, J = 5.38 Hz, 2CH2); 29.19 (d, J = 6.90 Hz, 2CH2); 30.06 (m, 4CH); 32.91 (d, J = 9.67 Hz, 2CH2); 69.84 (m, 2CH); 70.33 (m, 10CH); 70.74 (m, 2CH); 73.04 (m, 2CH); 74.10 (m, 2CH); 74.29 (d, J = 8.09 Hz, 4CH); 128.51 (d, J = 10.23 Hz, 4CH); 128.85 (s, 2CH); 130.51 (s, 2CH); 132.37 (d, J = 14.41 Hz, 4CH); 135.07 (d, J = 18.47 Hz, 4CH); 135.25 (s, 2C); 135.49 (s, 2C); 31P NMR (CD2Cl2 at -60 °C) δ, 150.61 (bs, 2CH3); 25.97 (d, J = 10.99 Hz, 4CH2); 26.79 (m, 2CH2, 2CH); 27.34 (d, J = 8.01 Hz, 2CH2); 27.73 (d, J = 13.71 Hz, 2CH2); 28.57 (d, J = 6.19 Hz, 2CH2); 28.92 (d, J = 7.41 Hz, 2CH2); 29.98 (d, J = 10.84 Hz, 2CH2); 30.22 (bs, 2CH2); 31.58 (m, 2CH); 32.13 (d, J = 8.34 Hz, 2CH); 32.67 (d, J = 9.72 Hz, 2CH2) 69.87 (d, J = 4.39, 2CH); 70.35 (m, 10CH): 70.08 (m, 2CH): 73.08 (d, J = 28.07 Hz, 2C); 94.16 (m, 2C); 128.22 (d, J = 8.28 Hz, 4CH); 128.54 (d, J = 10.24 Hz, 4CH); 128.84 (s, 2CH); 130.63 (s, 2CH); 132.40 (d, J = 13.84 Hz, 4CH); 135.07 (d, J = 17.45 Hz, 4CH); 135.44 (d, J = 8.48 Hz, 2C); 135.79 (d, J = 8.01 Hz, 2C); 31P NMR (CD2Cl2 at -60 °C) δ, 9.20 (d, J = 184.3 Hz), -23.59 (d, J = 180.3 Hz). [α]D20 = -275 (c = 0.5 CH2Cl2); ESI-MS (CH2Cl2): 1568 [M+ (C72H88P4Fe2Cu2I2), 100], 1476 [M+ - I + Cl (C72H88P4Fe2Cu2I), 54], 1441 [M+ - I (C72H88P4Fe2Cu1), 40], 784 [M+ - C36H44P2FeCuI (C36H44P2FeCuI), 50]. All isotopic patterns are in agreement with those of calculated.
CuBr complex (S,R)-2a

(S,R)-2a was prepared from inverted JosiPhos (S,R)-L2 and CuBr-SMe2 in tBuOMe, as described above for 1a: $^1$H NMR $\delta$ 7.62 (m, 4H), 7.44 (m, 4H), 7.36-7.18 (m, 12H), 4.31 (m, 2H), 4.27 (m, 2H), 4.20 (m, 2H), 4.04 (s, 10H), 3.64 (m, 2H), 2.53 (m, 2H), 2.27 (m, 4H), 1.92 -0.83 (m, 44H). $^{13}$C NMR (75.43 MHz, CD$_2$Cl$_2$, RT) $\delta$, 16.92 (bs, 2CH$_3$); 26.09 (d, $J = 12.61$ Hz); 26.82 (d, $J = 10.50$ Hz); 27.22 (m); 27.93 (m); 30.13 (m); 31.43 (d, $J = 8.68$ Hz); 33.77 (d, $J = 8.88$ Hz); 35.3 (m); 39.03 (m); 68.84 (s, 2CH); 69.95 (s, 8CH); 70.19 (m, 2CH); 73.68 (s, 2CH); 74.62 (d, $J = 17.99$ Hz, 2C); 92.35 (m, 2C); 128.29 (d, $J = 7.41$ Hz, 4CH); 128.58 (d, $J = 7.00$ Hz, 4CH); 129.64 (s, 2CH); 19.90 (s, 2CH); 130.20 (m, 2C); 130.20 (m, 2C); 133.05 (m, 2C); 134.47 (m, 4CH); $^{31}$P NMR $\delta$ -10.95 (2 d, $J = 346$ and 180 Hz). $[\alpha]_D^{20} = +5$ (c = 1 CH$_2$Cl$_2$). Elemental analysis C$_{72}$H$_{88}$P$_4$Fe$_2$Cu$_2$Br$_2$: calculated C 58.59; H 6.01; found: C 58.9, H 6.34. ESI-MS (CH$_2$Cl$_2$): 1472 [M$^+$ - Br + Cl (C$_{72}$H$_{88}$P$_4$Fe$_2$Cu$_2$BrCl)], 1393 [M$^+$ - Br (C$_{72}$H$_{88}$P$_4$Fe$_2$Cu$_2$Br)], 100], 1428 [M$^+$ - Br + Cl (C$_{72}$H$_{88}$P$_4$Fe$_2$Cu$_2$BrCl)], 55], 1393 [M$^+$ - Br (C$_{72}$H$_{88}$P$_4$Fe$_2$Cu$_2$Br)], 52]

Figure S2. X-ray structure of copper bromide complex 2a (obtained from Et$_2$O).

CuBr-heterocomplex (R,S,S,R)-3
Figure S3. X-ray structure of copper bromide complex 3 (obtained from hexane/CH$_2$Cl$_2$).

(R,S,S,R)-3 was prepared from (R,S)-L1 (0.05 mmol), (S,R)-L2 (0.05 mmol) and CuBr•SMe$_2$ (0.1 mmol) in 3 ml CH$_2$Cl$_2$, as described above for 1a. $^1$H NMR (CD$_2$Cl$_2$ at -60 0C) δ, 7.85 (m, 2H, ArH), 7.30-6.97 (m, 18H, ArH), 4.45 (m, 1H, FcH), 4.36 (m, 1H, FcH), 4.20-4.03 (m, 14H, FcH), 3.56-3.41 (m, 2H, CH$_2$). $^{13}$C NMR; $^{31}$P-NMR 8.13 (d, $J = 195.2$ Hz), -11.29 (m), -24.10 (d, $J = 194.5$ Hz). [D$_2$O] = -300 (c = 1 CH$_2$Cl$_2$).

NMR experiments, preparation of alkylcopper species.

Alkylcopper species were prepared in situ (in NMR tube), under nitrogen atmosphere at low temperature ((-60 0C) - (-80 0C)) by adding 1.5-4 equiv. of a corresponding freshly prepared Grignard reagent (3M in Et$_2$O) to copper bromide complexes in CD$_2$Cl$_2$. The conversion was monitored by $^1$H and $^{31}$P NMR spectroscopy at -60 0C. Alternatively, alkylcopper species can be prepared in Et$_2$O. The significant precipitation observed in Et$_2$O prevents the use of this solvent for NMR studies and indicates to a low solubility of alkylcopper species formed in Et$_2$O. However similar species to one obtained in CD$_2$Cl$_2$ was observed after evaporation of Et$_2$O and dissolving the residue in CD$_2$Cl$_2$.

Note. Excess of Grignard reagent (at least 1.5 equiv) is necessary to achieve complete transformation of the initial copper complex to the alkylcopper species. Decomposition of alkylcopper species in CH$_2$Cl$_2$ at RT was observed after 30 min with concomitant formation of a black precipitate and a green solution (presumably due to disproportionation to Cu(0) and Cu(II)). However, the solution of alkylcopper species in CH$_2$Cl$_2$ can be stored in the sealed NMR tube at -78 0C during at least 2 d.

1a + MeMgBr in CD$_2$Cl$_2$ (species A): 1a (10 mg, 13.55 mmol) was placed in a flame dried NMR tube (degassed and filled with nitrogen at least three times) under nitrogen atmosphere and CD$_2$Cl$_2$ (0.5 mL) was added. After cooling the solution to (-60 0C) - (-80 0C) 1.5-4 equiv. of MeMgBr (3M) were added, leading to instantaneous formation of species A. $^1$H NMR (CD$_2$Cl$_2$ at -60 0C) δ, 7.98 (m, 2H, ArH), 7.39 (m, 3H, ArH), 7.21 (m, 3H, ArH), 7.06 (m, 2H), 4.52 (m, 1H, FcH), 4.41 (m, 1H, FcH), 4.21 (m, 1H, FcH), 4.06-3.66 (m, 6H, FcH, CH signals overlapped with Et$_2$O peaks derived from the solution of MeMgBr), 2.01-0.36 (m, 25H, CyH, CH$_3$), -0.29 (s, 3H, CuMe), -1.6 (bs, signal corresponding to the excess of MeMgBr). $^{31}$P NMR (CD$_2$Cl$_2$ at -60 0C) δ, 6.41 (d, $J = 143.4$ Hz), -27.03 (d, $J = 143.4$ Hz).

1a + MeMgBr in THF-$d_8$ (species C), was performed as described for CD$_2$Cl$_2$. $^{31}$P NMR (CD$_2$Cl$_2$ at -60 0C) δ, 11.42 (d, $J = 167.8$ Hz), -23.93 (d, $J = 167.6$ Hz).

1a + MeMgBr in toluene-$d_8$ (species A), was performed as described for CD$_2$Cl$_2$: $^{31}$P NMR (CD$_2$Cl$_2$ at -60 0C) δ, 5.99 (d, $J = 141.5$ Hz), -27.45 (d, $J = 141.5$ Hz).

$^4$ $^{13}$C NMR spectrum presented in supplementary information 2.

$^5$NMR experiments were performed only with copper complexes prepared from ligand L1. Very close chemical shifts corresponding to phosphorus atoms in $^{31}$P NMR prevents clear interpretation of the changes observed upon addition of the Grignard reagent.
**1a + 2 equiv. MeLi in CD$_2$Cl$_2$ (species C),** $^1$H NMR (CD$_2$Cl$_2$ at -60 °C) δ, 7.84 (m, 2H, ArH), 7.45 (m, 3H, ArH), 7.15 (m, 3H, ArH), 6.98 (m, 2H), 4.48 (m, 1H, FcH), 4.39 (m, 1H, FcH), 4.31 (m, 1H, FcH), 3.57 (s, 5H, FcH), (CH signals overlapped with Et$_2$O peaks derived from MeMgBr), 1.95 (bs, 1H, CyH), 1.72-0.76 (m, 24H, CyH, CH$_3$, signals overlapped with Et$_2$O peaks), -0.77 (s, 3H, CuMe), -1.6 (bs, excess of MeMgBr). $^{31}$P NMR (CD$_2$Cl$_2$ at -60 °C) δ, 11.6 (d, $^3$J = 163.7 Hz), -25.47 (d, $^3$J = 163.7 Hz).

**1a + 3 equiv. MeLi in CD$_2$Cl$_2$ (species C and L1).** Addition of 3 equiv. of MeLi to 1a led to the species C with simultaneous formation of free ligand L1).

**1a + 4 equiv. MeLi in CD$_2$Cl$_2$.** Addition of 4 equiv. of MeLi to 1a led to a complete release of Cu from the complex with simultaneous formation of the free ligand L1 and Me$_2$CuLi.

**Species B:** To form species B the CD$_2$Cl$_2$ solution of species A was open to the air for 30 min at -60 °C. This led to a complete transformation to the species B. $^1$H NMR (CD$_2$Cl$_2$ at -60 °C) δ, 7.96-6.97 (m, 10H, ArH), 4.62-3.36 (m, 9H, FcH, CH signals overlapped with Et$_2$O peaks derived from MeMgBr), 1.98-0.20 (m, 25H, CyH, CH$_3$, signals overlapped with Et$_2$O peaks), -0.32 (s, 3H, CuMe). $^{31}$P NMR (CD$_2$Cl$_2$ at -60 °C) δ, 13.62 (d, $^3$J = 153.6 Hz), -19.07 (d, $^3$J = 153.6 Hz).

**Experiments with the additives**

**With dioxane.** Species A was prepared as described above from 3 equiv. of MeMgBr and 1a in CD$_2$Cl$_2$ and its complete formation was monitored by NMR. Then 3 equiv. of freshly distilled dioxane was added to the species A at -78 °C under inert atmosphere and full transformation to the species C was observed with the concomitant slurry formation (due to formation of dioxane•MgBr$_2$ complex).

**With Li-crown-4-ether.** Species C was prepared as described above from 2 equiv. of MeLi and 1a in CD$_2$Cl$_2$ and its complete formation was monitored by NMR. Then 2 equiv. of Li-crown-4-ether was added to the species C. at -78 °C under inert atmosphere. No changes were observed in NMR spectra of the species C.

**Stoichiometric CA of octenone to the species A, B and C.** All reactions were performed in the NMR tube at -60 °C under inert atmosphere and monitored by $^1$H and $^{31}$P NMR.

**CA of A to octenone 5.** 1 equiv. of 5 diluted with 0.1 ml of CD$_2$Cl$_2$ was added to A prepared by addition of 2 equiv. of MeMgBr to 1a. Immediate and complete transformation of A to the complex 1a was observed in $^{31}$P NMR, as well as disappearance of signals corresponding to the enone and appearance of the signals corresponding to the double bond of the enolate. The enantioselectivity of the reaction was 92%, similar to the result obtained in catalytic reaction.

**CA of C to octenone 5.** The reaction was performed by adding 5 at -70 °C to C formed via addition of 1.5 equiv. of MeLi to 1a (or 2 equiv. of MeMgCl to 1b). The enantioselectivity was 65 (70%).

**CA of B to octenone 5.** Species B formed by storing A in a common NMR tube closed with plastic cup overnight at low temperature without nitrogen atmosphere. The CA reaction was performed by adding 1 equiv. of 5 diluted with 0.1 ml of CD$_2$Cl$_2$. The enantioselectivity was 89%.
General Procedure for the enantioselective CA

In a Schlenk tube equipped with a septum and stirring bar, the Cu-complex (1a-c, 2a or 3) (0.037 mmol) was dissolved in the corresponding solvent (1.5 mL) and stirred under argon at room temperature for 5 min. The mixture was then cooled to \(-78^\circ\text{C}\) and RMgX (3.0 M solution in Et\(_2\)O, 0.86 mmol) was added. After stirring for 5 min, a solution of enone (enoate) (0.75 mmol) was added at once. After stirring at \(-78^\circ\text{C}\) (1h for enones, 5h-12h for enoates) MeOH (0.25 mL) and NH\(_4\)Cl (1M, 2 mL) were added sequentially, and the mixture was allowed to warm to RT. After extraction with Et\(_2\)O (1 mL, 3x), the combined organic phases were dried and concentrated to a yellow oil, which was used for GC analysis directly.

Note: Alternatively, all reactions can be carried out by using the catalyst (copper complexes) prepared in situ. In both cases, the same conversions and enantioselectivities were obtained.

(R)-(+)
-4-Methyloctan-2-one 6a: from trans-5, (R,S)-1a and MeMgBr, 98% ee, \([\alpha]_D^{20} = +4.9 (c = 0.7)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) 2.39 (1H, dd, \(J = 15.8\) and 5.7 Hz), 2.20 (1H, dd, \(J = 15.9\) and 8.1 Hz), 2.11 (3H, s), 1.97 (1H, m), 1.35-1.20 (6H, m), 0.87 (6H, m); \(^1\)C NMR (100.59 MHz CDCl\(_3\)), \(\delta\) 209.4 (C), 51.3 (CH\(_2\)), 36.6 (CH\(_2\)), 30.3 (CH), 29.3 (CH\(_3\)), 29.1 (CH\(_2\)), 22.8 (CH\(_2\)), 19.8 (CH\(_3\)), 14.0 (CH\(_3\)). LRMS (EI) \(m/z\) 142 (M\(^+\), 27), 127 (M\(^+\) - CH\(_3\), 95), 112, 85 (100), 71, 58: HRMS Calcd. for C\(_9\)H\(_{18}\)O 142.13576, found 142.13503. Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), 90 ºC, retention times: 9.59 / 9.72 min.

(+)-4-(Furan-2-yl)hexan-2-one 12a: from trans-7, (R,S)-1a and EtMgBr, 90% ee \([\alpha]_D^{20} = +14 (c = 1.3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) 7.29 (1H, m), 6.26 (1H, m), 5.99 (1H, m), 3.19 (1H, m), 2.78 (1H, dd, \(J = 16.4\) and 7.6 Hz), 2.64 (1H, dd, \(J = 16.4\) and 6.8 Hz), 2.07 (3H, s), 1.62 (2H, m), 0.83 (3H, t, \(J = 7.6\) Hz); \(^1\)C NMR (100.59 MHz CDCl\(_3\)), \(\delta\) 207.7, 158.3, 141.0, 109.9, 105.2, 45.5, 36.0, 30.4, 26.9, 11.6; LRMS (EI) \(m/z\) 166 (M\(^+\),100), 151 (5), 137, 123, 109, 81; HRMS calcd. for C\(_{10}\)H\(_{14}\)O\(_2\) 166.0994, found 166.0999. Enantioselectivity was determined by chiral GC analysis, Chiraldex ß-PM (30 m x 0.25 mm), initial temp. 70 ºC, initial time 30 min, rate 10 ºC/ min, final temp 140 ºC; retention times : 33.0 / 34.0 min.

Methyl 3-ethylhexanoate 12b: from trans-8, (R,S)-1a and EtMgBr, \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) d 3.58 (s, 3H), 2.16 (d, \(J = 6.9\) Hz, 2H), 1.73 (m, 1H), 1.22 (m, 6H), 0.80 (m, 6H); \(^1\)C NMR (100.59 MHz CDCl\(_3\)), \(\delta\) 174.0 (C), 51.2 (CH\(_3\)), 38.5 (CH\(_2\)), 36.1 (CH), 35.6 (CH\(_2\)), 26.2 (CH\(_2\)), 19.6 (CH\(_2\)), 14.2 (CH\(_3\)), 10.6 (CH\(_3\)); LRMS \(m/z\) 158 (M\(^+\) +1, 1), 143 (1), 127 (3), 115 (7), 85 (32), 74 (100); HRMS calcd. for C\(_9\)H\(_{18}\)O\(_2\) 158.1307, found 158.1319. Enantioselectivity was determined by chiral GC analysis, Chiraldex G-TA column (30 m x 0.25 mm), 60ºC, retention times (min): 20.9 (major) and 21.8 (minor).

(S)-(++)-Methyl 3-phenylpentanoate 12c: from trans-9, (S,R)-2a and EtMgBr, \([\alpha]_D^{20} = +18.7 (c = 1.2)\), \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) d 7.24 (m, 2H), 7.14 (m, 3H), 3.53 (s,3H), 2.96 (m, 1H), 2.56 (m, 2H), 1.65 (m, 1H), 1.58 (m, 1H), 0.75 (dt, \(J = 7.3\) and 1.3 Hz, 3H); \(^1\)C NMR (100.59 MHz CDCl\(_3\)), \(\delta\) 172.9 (C), 143.8 (C), 128.3 (CH), 127.4 (CH), 126.3 (CH), 51.4 (CH\(_3\)), 43.8 (CH), 41.2 (CH\(_2\)), 29.0 (CH\(_2\)), 11.8 (CH\(_3\)); LRMS (EI) \(m/z\) 192 (M+, 32), 160 (21), 132 (45), 121 (100) 91 (95); HRMS calcd. for

C$_{12}$H$_{16}$O$_2$ 192.1150, found 192.1153. Enantioselectivity was determined by chiral GC analysis, Chiraldex G-TA column (30 m x 0.25 mm), 90ºC, retention times (min): 24.7 (minor) and 25.0 (major).

(+)-Methyl 3-(4-(trifluoromethyl)phenyl)pentanoate, 12d$^{6b}$: from trans-10, (S,R)-2a and EtMgBr, $[a]_{D}^{20} = +16.5$ (c = 1.7); $^1$H NMR (400 MHz, CDCl$_3$), $\delta$ d 7.49 (d, $J$ = 8.0 Hz, 2H), 7.24 (d, $J$ = 8.0 Hz, 2H), 3.51 (s, 3H), 3.03 (m, 1H), 2.62 (dd, $J$ = 15.5 and 6.7 Hz, 1H), 2.52 (dd, $J$ = 15.5 and 8.4 Hz, 1H), 1.67 (m, 1H), 1.57 (m, 1H), 0.73 (t, $J$ = 7.4 Hz); $^{13}$C NMR 172.4 (C), 148.1 (C), 128.1 (C), 127.8 (CH), 125.4 (CH), 123.1 (C), 51.5 (CH$_3$), 43.6 (CH), 40.8 (CH$_2$), 29.0 (CH$_2$), 11.7 (CH$_3$); LRMS m/z 260 (M+, 23), 241 (24), 200 (51), 189 (72), 159 (100); HRMS calcd. for C$_{13}$H$_{15}$F$_3$O$_2$ 260.1024, found 260.1026. Enantioselectivity was determined by chiral GC analysis, Chiraldex G-TA column (30 m x 0.25 mm), 90ºC, retention times (min): 57.5 (minor) and 59.3 (major).

(-)-Methyl 3-(4-methoxy-phenyl)pentanoate, 12e: from trans-11, (R,S)-2a and EtMgBr, $[a]_{D}^{20} = -22.8$ (c = 2); $^1$H NMR (400 MHz, CDCl$_3$), $\delta$ d 7.08 (d, $J$ = 8.8 Hz, 2H), 6.83 (d, $J$ = 8.8 Hz, 2H), 3.78 (s, 3H), 3.57 (s, 3H), 2.94 (m, 1H), 2.61 (dd, $J$ = 16.0 and 6.8 Hz, 1H), 2.52 (dd, $J$ = 15.2 and 8.0 Hz, 1H), 1.66 (m, 1H), 1.55 (m, 1H), 0.77 (t, $J$ = 7.2 Hz); $^{13}$C NMR 173.3 (C), 158.3 (C), 136.1 (C), 128.6 (CH), 114.0 (CH), 55.4 (CH$_3$), 51.6 (CH$_3$), 43.3 (CH), 41.7 (CH$_2$), 29.4 (CH$_2$), 12.1 (CH$_3$); LRMS (El) m/z 222 (M+, 23), 193 (47), 149 (100), 121 (40), 91 (20); HRMS calcd. for C$_{13}$H$_{15}$F$_3$O$_2$ 222.1255. Enantioselectivity was determined by chiral HPLC analysis, Chiralcel OB-H column (99:1 heptane:isopropanol), retention times (min): 12.3 and 14.5.

Kinetic analysis

The procedure for determining the rate of the reaction was represented by the reaction under conditions at which the concentrations of 13, EtMgBr and 1a were 90mM, 90mM, 0.9mM, respectively, and the temperature was -87 ºC. The reaction was carried out in Schlenk flask under nitrogen in CH$_2$Cl$_2$. The progress of the reaction was determined by removing aliquots at specific time intervals: the aliquots were hydrolyzed by fast transferring to the cold MeOH solution. The aliquots were analyzed by gas chromatography (chiral G-TA column) using butyl ether as an internal standard in the reaction mixture.

a) Dependence on catalyst. 0.9mM, 1.8mM, 2.7mM, 3.6mM solutions of 1a in 30 ml of CH$_2$Cl$_2$ were prepared and 40µl of internal standard Bu$_3$O was added. The solutions were cooled to -87 ºC and 1.1 equiv. of EtMgBr (3M in Et$_2$O) was added. After 15 min enone 13 (90mM) was added at once. The aliquots were taken every 2-5 min during 4h (minimum 80% conversion was obtained after 4h for all the experiments). The analysis was made by plotting 1/C$_{13}$ versus time. The slope obtained from the 1/C$_{13}$ concentration vs. time (s) was calculated as the reaction rate constant. The determined rate constants are presented in the Table S1.

<table>
<thead>
<tr>
<th>Table S1. Rate constants for different catalyst concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C$_{13}$/mM</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>9.0</td>
</tr>
<tr>
<td>1.8</td>
</tr>
<tr>
<td>2.7</td>
</tr>
<tr>
<td>3.6</td>
</tr>
</tbody>
</table>
b) Dependence on EtMgBr. Four stock solutions of 20 mg (0.027mmol) 1a in the mixture of solvents CH₂Cl₂ and Et₂O with the volume (ml) ratio 26/3, 26/2 26/1, 26/0 were prepared and 40µl of internal standard (Bu₂O) was added. The solutions were cooled to -87 °C and either 1 mL (final concentration in reaction solution, 90 mM), 2 mL (180 mM), 3 mL (279 mM) or 4ml (360 mM) of EtMgBr (3M, in Et₂O) were added to the stock solutions. After 15 min stirring at constant speed, 13 (1 equiv., 90mM) was added in one addition. The aliquots were taken every 2-5 min over 4h. The graph is presented in Figure S4 (The reaction progress was followed by a decrease in the substrate concentration [13], M).

![Figure S4 Kinetic data for different concentrations of EtMgBr (1-4 equiv.)](image)

c) Dependence on substrate 13. Four stock solutions of 20mg (0.027mmol, 0.9mM) 1a in CH₂Cl₂ were prepared and 40µl of internal standard Bu₂O was added. The solutions were cooled to -87 °C and 90mM of EtMgBr (3M, in Et₂O) was added to the stock solutions. After 15 min stirring at constant speed 90mM, 180mM, 270mM, 360mM of substrate 13 were added at once. The aliquots were taken every 5 min during 4h. The graph is presented in Figure S5 (The reaction progress was followed by an increase in the product concentration [14], M).

![Figure S5 Kinetic data for different concentrations of 13 (1-2 equiv.)](image)
d) **Determination of the thermodynamic parameters.** To determine the activation parameters the reactions with the following concentrations of reactants \( \text{13} \) 90mM, EtMgBr 90mM and \( \text{1a} \) 0.9mM were employed at 4 different temperatures. The analysis was made by plotting \( 1/C_{\text{13}} \) versus time. The slope obtained from the \( 1/C_{\text{13}} \) concentration vs. time (s) was calculated as the reaction rate constant. The rate constants obtained are presented in the Table S2, S3

**Table S2.**

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>k / Lmol(^{-1}).s(^{-1})</th>
<th>( t_{1/2} ) (min)</th>
<th>( \Delta G^# ) (kcal.mol(^{-1}))</th>
<th>( \Delta G^# ) (kJ.mol(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>-85.0</td>
<td>1.31E-02</td>
<td>141.19</td>
<td>12.46</td>
<td>52.09</td>
</tr>
<tr>
<td>-79.0</td>
<td>1.96E-02</td>
<td>94.18</td>
<td>12.72</td>
<td>53.15</td>
</tr>
<tr>
<td>-72.0</td>
<td>3.77E-02</td>
<td>48.94</td>
<td>12.93</td>
<td>54.03</td>
</tr>
<tr>
<td>-65.0</td>
<td>4.77E-02</td>
<td>38.69</td>
<td>13.29</td>
<td>55.57</td>
</tr>
</tbody>
</table>

**Table S3.** Thermodynamic parameters.

**Employed equations for the calculation**

- \( \Delta G = \Delta H - T\Delta S \)
- \( \Delta G^\# = -RT\ln(k.h/k_B.T) \)
- \( k = A\exp(-Ea/RT) \)
- \( t_{1/2} = \ln2/(k_0) \)

**Electrochemistry**

The requirement for sufficient electrolyte to be present to allow conductivity requires that the control experiments are carried out to ensure that the catalytic properties of the system remain largely unperturbed with regard to both regio- and enatioselectivity. Although significantly lower enantioselectivity was obtained, it is unlikely that catalyst present in the electrolyte solution is different to that present in the absence of TBAPF\(_6\).

**Figure S6.** \( \text{2a} \) and Cl analogue (0.1 M TBABr) at -80 °C. scan rate = 25 mV s\(^{-1}\).
**Figure S7.** Oxidative electrochemistry of chloride analogue of 2a in DCM (0.1 M TBAPF$_6$) at between -80 °C and rt. scan rate = 25 mV s$^{-1}$.

**Figure S8.** Oxidative electrochemistry of complex formed with L2 and Cu(I)[CH$_3$CN]PF$_6$ in CH$_2$Cl$_2$ (0.1 M TBABr) at -80 °C. scan rate = 25 mV s$^{-1}$.
Figure S9. Oxidative electrochemistry of 1b and chloride analogue of 2a.

Figure S10. IR spectra for complexes 1a, 1b, 1c, 2a in CH₂Cl₂.

Conjugate addition of EtMgBr to methyl crotonate.

Solvent dependence. Solvent and halide dependent experiments were performed for the CA of EtMgBr to methyl crotonate 13 (Scheme S1). The choice of EtMgX as a Grignard reagent in this particular case was made due to very low reactivity of MeMgX towards CA to enoates (see ref. 6c in the article main text). CA of EtMgX to methyl crotonate appeared to be dependent on the solvent character and consequently on the Schlenk equilibrium in a similar manner to the one observed for the CA to enone 5 (see main text). For instance, the CA reaction performed in halogenated and ethereal solvents afforded high conversion and enantioselectivity 88-96% (Table S5, entries 1–4), (the regioselectivity was always 99%). As it was observed for enones the reaction conditions directing the Schlenk equilibrium towards formation of Et₂Mg caused significant drop in both enantioselectivity and conversion (entries 5-7).
Table S5. CA of EtMgBr to 13 catalyzed by copper bromide complex 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conv. [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>92</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>tBuOMe</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>Et₂O</td>
<td>99</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CH₂Cl₂</td>
<td>36</td>
<td>86</td>
</tr>
<tr>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>CH₂Cl₂</td>
<td>85</td>
<td>76</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: reaction time 5 h, 13 0.35 M, MeMgBr 1.5 equiv, -78 °C.  
<sup>b</sup> Conversion and enantioselectivity was determined by GC (chiral dex-CB column).  
<sup>c</sup> Dioxane (1 equiv.) was added to the mixture of catalyst and MeMgBr CH₂Cl₂ prior to addition of 13.  
<sup>d</sup> Me₂Mg and Et₂Mg (1.5 equiv.) were used instead of MeMgBr and EtMgBr for these reactions.

Halide dependence. The reaction conversion and enantioselectivity of CA of EtMgX to crotonate 13 appeared to be dependent also on the halide identity (Table S6). For instance, high conversion and enantioselectivity were obtained for the addition of EtMgBr to 13, catalyzed by copper bromide complexes 1a, 1b and 1c (entries 1-3).

Table S6. CA of RMgX to 13 catalyzed by copper complex 1 in CH₂Cl₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>CuX</th>
<th>I</th>
<th>MeMgX</th>
<th>Conv [%]&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee [%]&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuBr</td>
<td>1a</td>
<td>EtMgBr</td>
<td>92</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>CuCl</td>
<td>1b</td>
<td>EtMgBr</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>CuI</td>
<td>1c</td>
<td>EtMgBr</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>CuBr</td>
<td>1a</td>
<td>EtMgCl</td>
<td>96</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>CuBr</td>
<td>1a</td>
<td>EtMgI</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>CuCl</td>
<td>1b</td>
<td>EtMgCl</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>CuI</td>
<td>1c</td>
<td>EtMgI</td>
<td>50</td>
<td>88</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: reaction time 5h for 13 (0.35 M), RMgBr 1.5 equiv., -78 °C.  
<sup>b</sup> Conversion (GC).  
<sup>c</sup> Regioselectivity is presented in brackets.  
<sup>d</sup> Determined by GC (chiral dex-CB column).
However, addition of EtMgCl and EtMgI to 13 catalyzed by 1a provided low enantioselectivity and moderate yield (entries 4, 5). Similarly, low conversion and enantioselectivity were obtained for the CA of EtMgCl catalyzed by 1b (entry 6). The combination of EtMgI with copper iodide complex 1c afforded the product with relatively high enantioselectivity although conversion was still low (entry 7).