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Highly Enantioselective Cu-catalysed Allylic Substitutions with Grignard Reagents

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General Procedures: ^{1}H NMR spectra were recorded at 300 or 400 MHz with $CDCl_3$ as solvent. ^{13}C NMR spectra were obtained at 75.4 or 100.59 MHz in $CDCl_3$, (Varian VXR300 or AMX400 spectrometers). Carbon types were determined from APT ^{13}C NMR experiments. Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ = 7.26 ppm for hydrogen atoms, δ = 77.0 for carbon atoms). The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Progress and conversion of the reaction was determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 columns (Agilent Technollogies, Palo Alto, CA). Enantio- and regioselectivities were determined by capillary GC analysis (HP 6890, Chiraldex G-TA column (30 m x 0.25 mm), CP-Chiralsil-Dex-CB (25 m x 0.25 mm)) using flame ionization detector (in comparison with racemic products). Optical rotations were measured in $CHCl_3$ on a *Schmidt + Haensdch* polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). Absolute configuration of the products was determined by comparison with compounds previously published. Thin-layer chromatography (TLC) was performed on commercial Kieselgel $60F_{254}$ silica gel plates, and components were visualized with $KMnO_4$ reagent. Flash chromatography was performed on silica gel. Drying of solutions was performed with Na_2SO_4. Concentrations were conducted with a rotary evaporator.

Ligands **1a-1b** were generously donated by Solvias.[1] Ligand Taniaphos (**2**) was prepared according to literature procedures.[2] CuCl, CuI, and CuBr SMe_2 were purchased from Aldrich or Acros, and used without further purification. CuTC refers to copper thiophene-2-carboxylate.[3] Hoveyda-Grubbs 2nd generation catalyst,[4] (*E*)-cinnamyl bromide (**3a**) and (*E*)-cinnamyl chloride (**3b**) were purchased from Aldrich. The substrates **3b**,[5] **3d-3f**,[6] **3g**,[7] and **3h**[8] were prepared according to literature procedures. Grignard reagents were purchased from Aldrich (EtMgBr, MeMgBr) or prepared from the corresponding alkyl bromides and magnesium turnings in Et_2O following standard procedures. Grignard reagents were titrated using ^{s}BuOH and catalytic amounts of 1,10-phenanthroline. ^{t}BuOMe was purchased as anhydrous grade, stored over 4Å MS and used without further purification. Et_2O was distilled from Na/benzophenone. CH_2Cl_2 was distilled from CaH_2. All reactions were conducted under argon atmosphere using standard Schlenk techniques.

Racemic products **4** and regioisomers **5** were obtained by reaction of the bromides **3** with the corresponding Grignard reagent (5.0 equiv) at -25 ^{o}C in CH_2Cl_2 in the presence of CuCN (100 mol %). In some cases, the racemic products were also obtained by using *racemic*-**2** ligand, following the general procedure described in the next page.

Spectroscopic and analytical data of products **4b**, **4e-h** were obtained from their mixtures with **5**. The products **4a-4l**, and **6** have been previously described (see appropriate references in the following pages).

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[1] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc*., 1994, **116**, 4062.
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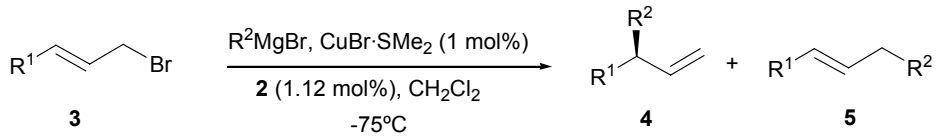
[4] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc*., 2000, **122**, 8168.
[5] C. A. Luchaco-Cullis, H. Muzitani, K. E. Murphy, A. H. Hoveyda, *Angew. Chem. Int. Ed*. 2001, **40**, 1456.
[6] A. W. van Zijl, L. A. Arnold, A. J. Minnaard, B. L. Feringa, *Adv. Synth. Catal.,* 2004, **346**, 413 and references therein.
[7] M. R. Binns, R. K. Haynes, D. E. Lambert, P. A. Schober, S. G. Turner, *Aust. J. Chem*., 1987, **40**, 281.
[8] G. Kottirsch, G. Koch, R. Feifel, U. Neumann *J. Med. Chem*., 2002, **45**, 2289.

General Procedure for the Enantioselective Cu-catalysed Allylic Alkylation with Grignard Reagents



3 **a** R^1 = Ph **f** R^1 = *p*-CO_2Me-Ph
d R^1 = 1-Naphthyl **g** R^1 = ^{n}Bu
e R^1 = *p*-Cl-Ph **h** R^1 = $BnOCH_2$

In a Schlenk tube equipped with septum and stirring bar, CuBr SMe_2 (15.0 μmol, 3.08 mg) and ligand **2** (18 μmol, 12.4 mg) were dissolved in CH_2Cl_2 (3.0 mL) and stirred under argon at room temperature for 10 min. The mixture was cooled to – 75 °C and the corresponding Grignard reagent (solution in Et_2O, 1.73 mmol) was added dropwise. Allylic bromide **3** (1.50 mmol) was then added dropwise as a solution in CH_2Cl_2 at that temperature over 15 min *via* a syringe pump. Once the addition was complete the resulting mixture was further stirred at – 75 °C for 4-12h. The reaction was quenched by addition of MeOH (0.5 mL) and the mixture was allowed to reach rt. Then, aqueous NH_4Cl solution (1M, 2 mL) was added to the mixture. The organic phase was separated, and the resulting aqueous layer is extracted with Et_2O (0.5 mL, 3x). The combined organic phases were dried and concentrated to a yellow oil which was flash chromatographed (2 : 98 Et_2O/pentane) to yield the corresponding allylic substrates as a mixture of S_N2' (**4**) and S_N2 (**5**) regioisomers.

Note: GC analysis was carried out on a sample obtained after aqueous extraction with Et_2O, which has been passed through a short plug of silica gel to remove transition metal residues.

(+)-1-((*S*)-but-3-en-2-yl)benzene (4a):[9] Reaction time: 4h. Purification by column chromatography (2 : 98 Et_2O/pentane) afforded a 97 : 3 mixture of **4a** and **5a** as a colorless oil. [91% yield , **4a**: 98% ee, $[\alpha]_D$ = +5.4 (*c* 1.2, $CHCl_3$), lit.[9a] (81% ee) $[\alpha]_D$ = + 4.8 (neat), lit.[9b] for **(*R*)-4a** (60% ee) $[\alpha]_D$ = –2.2 (*c* 0.7, $CHCl_3$)]. **4a**: ^{1}H-NMR δ 7.28-7.14 (m, 5H), 6.02-5.93 (m, 1H), 5.04-4.98 (m, 2H), 3.47-3.40 (m, 1H), 1.33 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR δ 145.5 (C), 143.2 (CH), 128.3 (CH), 127.2 (CH), 126.0 (CH), 113.0 (CH_2), 43.1 (CH), 20.7 (CH_3). Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 75 ºC, retention times (min): 15.6 (minor) and 15.8 (major); Retention time **5a**: 23.7 min.

(+)-1-((*S*)-pent-1-en-3-yl)benzene (4b):[10] Reaction time: 4h. Purification by column chromatography (2 : 98 Et_2O/pentane) afforded a 81 : 19 mixture of **4b** and **5b** as a colorless oil.

[9] (a) T. Hayashi, M. Konishi, M. Fukushima, K. Kanehira, T. Hioki, M. Kumada, *J. Org. Chem*., 1983, **48**, 2195. (b) M. Kawatsura, Y. Uozumi, M. Ogasawara, T. Hayashi, *Tetrahedron*, 2000, **56**, 2247.
[10] (a) A. W. van Zijl, L. A. Arnold, A. J. Minnaard, B. L. Feringa, *Adv. Synth. Catal.,* 2004, **346**, 413. (b) K. Tissot-Croset, D. Polet, A. Alexakis, *Angew. Chem., Int. Ed.*, 2004, **43**, 2426. (c) A. Alexakis, K. Tissot-Croset, *Org. Lett.,* 2002, **4**, 4147. (d) M. A. Kacprzynski, A. H. Hoveyda, *J. Am. Chem. Soc.,* 2004, **126**, 10676.

[92% yield, **4b**: 95% ee, $[\alpha]_D$ = +47 (*c* 1.0, $CHCl_3$), lit.[10b] (96% ee) $[\alpha]_D$ = + 55 (*c* 1.1, $CHCl_3$); lit.[10d] for **(*R*)-4b** (95% ee) $[\alpha]_D$ = - 51 (*c* 0.5, $CHCl_3$)]. **4b**: ^{1}H-NMR δ 7.32-7.12 (m, 5H), 5.91 (m, 1H), 5.01-4.97 (m, 2H), 3.11 (q, *J* = 7.4 Hz, 1H), 1.74-1.64 (m, 2H), 0.83 (t, *J* = 7.31 Hz, 3H); ^{13}C-NMR δ 144.4, 142.2, 128.4, 127.6, 126.1, 114.0, 51.7, 28.3, 12.1.. LRMS (EI) *m/z* 146 (M^+, 32), 128 (10), 117 (100), 91 (62). Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 75 °C for 30 min, then 5 °C/min to 100 °C (final temp), retention times (min): 26.0 (minor) and 26.2 (major); Retention time **5b**: 38.0 min.

(*R*)-3-methylhept-1-ene (4c):[11] Reaction carried out using 5.0 mol% CuBr·SMe_2 and 6.0 mol% **2** Reaction time: 12 h. Purification by column chromatography (2 : 98 Et_2O/pentane) afforded a 100 : 0 mixture of **4c** and **5c** as a colorless oil. [99% conversion,[12] 92% ee].[13] **4c**: ^{1}H-NMR δ 5.67-5.58 (m, 1H), 4.83 (dd, *J* = 10.4 and 7.3 Hz, 2H), 2.05-2.01 (m, 1H), 1.28-1.19 (m, 6H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.82 (t, *J* = 7.0 Hz, 3H); ^{13}C-NMR δ 144.9 (CH), 112.1 (CH_2), 37.7 (CH), 36.3 (CH_2), 29.4 (CH_2), 22.8 (CH_2), 20.1 (CH_3), 14.0 (CH_3). Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 55°C for 20 min, retention times (min): 5.4 (minor) and 5.5 (major).

(*R*)-3-ethylhept-1-ene (4d):[14] Reaction carried out using 5.0 mol% CuBr·SMe_2 and 6.0 mol% **2**. Reaction time: 12 h. Purification by column chromatography (2 : 98 Et_2O/pentane) afforded a 100 : 0 mixture of **4d** and **5d** as a colorless oil. [99% conversion,[12] 93% ee].[15] **4d**: ^{1}H-NMR δ 5.51-5.42 (m, 1H), 4.92-4.86 (m, 2H), 1.80-1.77 (m, 1H), 1.37-1.15 (m, 8H), 0.85-0.78 (m, 6H); ^{13}C-NMR δ 143.4 (CH), 113.9 (CH_2), 45.8 (CH), 34.4 (CH_2), 29.4 (CH_2), 27.7 (CH_2), 22.8 (CH_2), 14.1 (CH_3), 11.6 (CH_3); LRMS (EI) *m/z* 126 (M^+, 3), 97 (18), 84 (72), 69 (81), 55 (100). Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 55°C for 20 min, retention times (min): 9.8 (minor) and 9.9 (major).

(−)-1-((*S*)-pent-1-en-3-yl)naphthalene (4e):[10a,16] Reaction time: 4h. Purification by column chromatography (2 : 98 Et_2O/pentane) afforded a 87 : 13 mixture of **4e** and **5e** as a colorless oil. [86% yield, 90% ee, $[\alpha]_D$ = – 26 (*c* 1.0, $CHCl_3$)]. **4e**: ^{1}H-NMR δ 8.12 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.51-7.36 (m, 4H), 6.11-6.02 (m, 1H), 5.11-5.07 (m, 2H), 4.01 (q, *J* = 7.1 Hz, 1H), 1.95-1.88 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR δ 142.8 (CH), 141.5 (C), 135.3 (C), 132.9 (C), 130.0 (CH), 127.7 (CH), 126.7 (CH), 126.6 (CH), 126.4 (CH), 125.0 (CH), 124.5 (CH), 115.7 (CH_2), 47.1 (CH), 29.1 (CH_2), 13.5 (CH_3); LRMS (EI) *m/z* 196 (M^+, 26),

[11] T. L. Underiner, S. D. Paisley, J. Schmitter, L. Lesheski, H. L. Goering, *J. Org. Chem*., 1989, **54**, 2369.
[12]. Conversion based on GC. The high volatility of the products **4c** and **4d** did not allow to completely remove the solvents after the chromatography, impeding the calculation of an accurate isolated yield.
[13] With 1.0 mol% CuBr·SMe_2 and 1.12 mol% **2** the product **4c** was obtained with 99% conversion, a regioselectivity of 100: 0, but a slightly lower enantioselectivity (84% *vs*. 92%ee).
[14] A. Pelter, K. Smith, S. Elgendy, M. Rowlands, *Tetrahedron Lett*., 1989, **30**, 5647.
[15] With 1.0 %CuBr·SMe_2 and 1.1 % **2**, **4d** was obtained with 99% conversion, 97 : 3 regioselectivity and 88% ee.
[16] A. O. Larsen, W. Leu, C. N. Oberhuber, J. E. Campbell, A. H. Hoveyda, *J. Am. Chem. Soc*., 2004, **126**, 11130.

152 (42), 139 (11), 115 (14). Enantioselectivity determined by chiral HPLC analysis, Chiralcel OD-H (99.75% heptane/*i*PrOH), 40ºC, retention times (min): 20.4 (major) and 23.2 (minor).

1-Chloro-4-((*S*)-pent-1-en-3-yl)benzene (4f):[10a] Reaction time: 4h. Purification by column chromatography (2 : 98 Et_2O/pentane) afforded a 82 : 18 mixture of **4f** and **5f** as a colorless oil. [80% yield, 96% ee] **4f**: ^{1}H-NMR δ 7.25 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.88 (m, 1H), 5.00 (m, 2H), 3.10 (dt, *J* = 7.7 and 7.3 Hz, 1H), 1.69 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 50°C, then 10ºC/min to 120 ºC (final temp) for 30 min, retention times (min): 19.7 (minor) and 20.1 (major).

(+)-1-((*S*)-hept-1-en-3-yl)benzene (4g):[10a,17] Reaction time: 4h. Purification by column chromatography (2 : 98 Et_2O/pentane) afforded a 87 : 13 mixture of **4g** and **5g** as a colorless oil. [92% yield, 94% ee, $[\alpha]_D$ = +47 (*c* 0.5, $CHCl_3$), lit.[10a] (88% ee) $[\alpha]_D$ = + 44 (*c* 0.1, $CHCl_3$)]. **4g**: ^{1}H-NMR δ 7.21 (m, 5H), 5.95 (m, 1H), 5.02 (m, 2H), 3.32 (q, *J* = 7.5 Hz, 1H), 1.70 (q, *J* = 7.4 Hz, 2H), 1.39-1.02 (m, 4H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C-NMR δ 144.7, 142.5, 128.4, 127.6, 126.0, 113.8, 49.9, 35.1, 29.7, 22.6, 14.0. Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 80 °C for 60 min, then 10 °C/min to 140 °C (final temp), retention times (min): 53.7 (minor) and 54.2 (major); retention time **5g**: 70.4 min.

(+)-1-((*S*)-hepta-1,6-dien-3-yl)benzene (4h):[10b,c] Reaction time: 4h. Purification by column chromatography (2 : 98 Et_2O/pentane) afforded a 91 : 9 mixture of **4h** and **5h** as a colorless oil. [93% yield, 95% ee, $[\alpha]_D$ = +36 (*c* 1.5, $CHCl_3$), lit.[10b] (92% ee) $[\alpha]_D$ = + 33 (*c* 1.0, $CHCl_3$)]. **4h**: ^{1}H-NMR δ 7.30-7.16 (m, 5H), 5.95 (m, 1H), 5.79 (m, 1H), 5.03-4.92 (m, 4H), 3.26 (q, *J* = 7.5 Hz, 1H), 2.10-1.94 (m, 2H), 1.81-1.75 (m, 2H); ^{13}C-NMR δ 144.1 (C), 142.1 (CH), 138.4 (CH), 128.4 (CH), 127.6 (CH), 126.1 (CH), 114.6 (CH_2), 114.1 (CH_2), 49.1 (CH), 34.4 (CH_2), 31.5 (CH_2);. LRMS (EI) *m/z* 172 (M^+, 13), 159 (6), 130 (33), 117 (100), 115 (41), 91 (48); HRMS Calcd. for $C_{13}H_{16}$ 172.12520, found 172.12554. Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 90°C for 45 min, then 5 °C/min to 140 °C (final temp), retention times (min): 30.0 (minor) and 30.3 (major); retention time **5h**: 56.0 min.

(–)-1-((*S*)-but-3-en-2-yl)naphthalene (4i):[9b,16,18] Reaction time: 4h. Purification by column chromatography (2 : 98 Et_2O/pentane) afforded a 100 : 0 mixture of **4i** and **5i** as a colorless oil. [87% yield, 96% ee, $[\alpha]_D$ = - 29.8 (*c* 1.1, $CHCl_3$); lit.[16] $[\alpha]_D$ = – 29 (*c* 1.0, $CHCl_3$); lit.[18a] $[\alpha]_D$ = – 37 (neat); lit.[9b] for **(*R*)-4i** (90% ee) +16.3 (*c* 0.4, $CHCl_3$)]. **4i**: ^{1}H-NMR δ 8.15 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.54-7.41 (m, 4H), 6.23-6.15 (m, 1H), 5.17-5.13

[17] (a) A. Yanagisawa, N. Nomura, H. Yamamoto, *Tetrahedron* 1994, **50**, 6017. (b) J. J. Van Veldhuizen, J. E. Campbell, R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc*., 2005, **127**, 6877.
[18] (a) R. Menicagli, O. Piccolo, L. Lardicci, M. L. Wis, *Tetrahedron*, 1979, **35**, 1301. (b) Y. Obora, Y. Tsuji, *J. Org. Chem*. 1995, **60**, 4647.

(m, 2H), 4.36-4.29 (m, 1H), 1.54 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR δ 142.9 (CH), 141.4 (C), 134.0 (C), 131.4 (C), 128.9 (CH), 126.8 (CH), 125.7 (CH), 125.6 (CH), 125.3 (CH), 123.6 (CH), 123.5 (CH), 113.6 (CH_2), 37.8 (CH), 20.2 (CH_3); LRMS (EI) *m/z* 182 (M^+, 50), 167 (100), 165 (31), 152 (24), 84 (27), 51 (11); HRMS Calcd. for $C_{14}H_{14}$ 182.10955, found 182.11070. Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 120°C for 60 min, retention times (min): 35.8 (minor) and 36.3 (major); retention time **5i**: 56.3 min.

(+)-1-((*S*)-but-3-en-2-yl)-4-chlorobenzene (4j):[19] Reaction time: 4h. Purification by column chromatography (2 : 98 Et_2O/pentane) afforded a 99 : 1 mixture of **4j** and **5j** as a colorless oil. [95% yield, 97% ee, $[\alpha]_D$ = + 12 (*c* 1.6, $CHCl_3$)]. **4j**: ^{1}H-NMR δ 7.29 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.00-5.90 (m, 1H), 5.06-4.97 (m, 2H), 3.44-3.36 (m, 1H), 1.32 (d, *J* = 7.0 Hz, 3H); LRMS (EI) *m/z* 166 (M^+, 47), 165 (9), 151 (46), 139 (10), 131 (68), 91 (100); HRMS Calcd. for $C_{10}H_{11}Cl$ 166.05492, found 166.05570. Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 95°C for 45 min, then 2ºC/min to 140 ºC (final temp), retention times (min): 25.8 (minor) and 26.1 (major); retention time **5j**: 40.8 min.

(+)-Methyl 4-((*S*)-but-3-en-2-yl)benzoate (4k):[20] Reaction time: 4h. Purification by column chromatography (2 : 98 Et_2O/pentane) afforded a 98 : 2 mixture of **4k** and **5k** as a colorless oil. [94% yield, 97% ee, $[\alpha]_D$ = +12 (*c* 0.9, $CHCl_3$)]. **4k**: ^{1}H-NMR δ 7.91 (d, *J* = 8.30 Hz, 2H), 7.22 (d, *J* = 8.30 Hz, 2H), 5.97-5.90 (m, 1H), 5.03-4.98 (m, 2H), 3.84 (s, 3H), 3.49-3.44 (m, 1H), 1.32 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR δ 167.0 (C), 150.9 (C), 142.2 (CH), 129.7 (CH), 128.0 (C), 127.2 (CH), 113.8 (CH_2), 51.9 (CH_3), 43.1 (CH), 20.5 (CH_3); LRMS (EI) *m/z* 190 (M^+, 44), 159 (33), 131 (100), 115 (25), 91 (22), 59 (8); HRMS Calcd. for $C_{12}H_{14}O_2$ 190.09937, found 190.09969. Enantioselectivity determined by chiral GC analysis, CP-Chiralsil-Dex-CB (25 m x 0.25 mm), initial temp. 105 °C for 70 min, then 1ºC/min to 140 ºC (final temp), retention times (min): 71.7 (minor) and 72.1 (major); retention time **5k**: 93.8 min.

(–)-(((*S*)-2-methylbut-3-enyloxy)methyl)benzene (4l):[21] Reaction time: 12 h. Purification by column chromatography (2 : 98 Et_2O/pentane) afforded a 100 : 0 mixture of **4l** and **5l** as a colorless oil. [93% yield, 92% ee, $[\alpha]_D$ = – 6 (*c* 1.1, $CHCl_3$); lit.[21a] $[\alpha]_D$ = – 3 (*c* 1.0, $CHCl_3$)]; **4l**: ^{1}H-NMR δ 7.32 (d, *J* = 4.5 Hz, 4H), 7.29-7.21 (m, 1H), 5.83-5.74 (m, 1H), 5.07-4.99 (m, 2H), 4.50 (s, 2H), 3.36 (dd, *J* = 9.1 and 6.5 Hz, 1H), 3.28 (dd, *J* = 9.1 and 6.8 Hz, 1H), 2.52-2.44 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR δ 141.3 (CH), 138.6 (C), 128.3 (CH), 127.5 (CH), 127.4 (CH), 114.0 (CH_2), 75.0 (CH_2), 72.9 (CH_2), 37.8 (CH), 16.6 (CH_3); LRMS (EI) *m/z* 176 (M^+, 12), 175 (5), 92 (11), 91 (100), 65 (7); HRMS Calcd. for $C_{12}H_{16}O$ 176.12011, found 176.12262. Enantioselectivity

[19] (a) G. Franciò, F. Faraone, W. Leitner, *J. Am. Chem. Soc.*, 2002, **124**, 736. (b) K. Tissot-Croset, A. Alexakis, *Tetrahedron Lett.*, 2004, **45**, 7375.
[20] P. Gomes, C. Gosmini, J. Périchon, *J. Org. Chem*., 2003, **68**, 1142.
[21] (a) H. Lebel, V. Paquet *J. Am. Chem. Soc.,* 2004, **126**, 320. (b) J. C. Grandguillot, F. Pouessac, *Tetrahedron*, 1991, **47**, 5133.

determined by chiral HPLC analysis, Chiralcel OD-H (99.75% heptane/*i*PrOH), 40ºC, retention times (min): 10.9 (minor) and 11.2 (major).

(+)-1-(((*S*)-2-ethylbut-3-enyloxy)methyl)benzene (4m): Reaction time: 12 h. Purification by column chromatography (2 : 98 Et_2O/pentane) afforded a 98 : 2 mixture of **4m** and **5m** as a colorless oil. [97% yield, 94% ee, $[\alpha]_D$ = + 19 (*c* 1.1, $CHCl_3$)]. **4m**: ^{1}H-NMR δ 7.30-7.21 (m, 5H), 5.66-5.57 (m, 1H), 5.06-5.01 (m, 2H), 4.47 (s, 2H), 3.35 (d, *J* = 6.5 Hz, 2H), 2.22 (m, 1H), 1.56-1.47 (m, 1H), 1.27-1.20 (m, 1H), 0.83 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR δ 140.0 (CH), 138.6 (C), 128.3 (CH), 127.5 (CH), 127.4 (*CH*), 115.6 (CH_2), 73.6 (CH_2), 73.0 (CH_2), 45.7 (CH), 24.0 (CH_2), 11.4 (CH_3); LRMS (EI) *m/z* 190 (M^+, 11), 189 (11), 123 (21), 105 (100), 91 (79), 77 (30); HRMS Calcd. for $C_{13}H_{18}O$ 190.13576, found 190.13505. Enantioselectivity determined by chiral HPLC analysis, Chiralcel OD-H (99.75% heptane/*i*PrOH), 40ºC, retention times (min): 9.9 (minor) and 10.9 (major).

(–)-(*S,E*)-methyl 4-phenylpent-2-enoate (6):[22] Following the general procedure, in a Schlenk tube equipped with septum and stirring bar, CuBr SMe_2 (15.0 μmol, 3.08 mg) and ligand **2** (18.0 μmol, 12.4 mg) were dissolved in CH_2Cl_2 (3.0 mL) and stirred under argon at room temperature for 10 min. The mixture was cooled to – 75 ^{o}C and MeMgBr (3.0 M solution in Et_2O, 1.73 mmol, 0.575 ml) was added dropwise. Cinnamyl bromide **3a** (296 mg, 1.50 mmol) was then added dropwise over 15 min *via* a syringe pump at that temperature. Once the addition was complete the resulting mixture was further stirred at – 75 ^{o}C for 4h. The reaction was quenched by addition of MeOH (0.5 mL) and the mixture was allowed to reach rt. Then, aqueous NH_4Cl solution (1M, 2 mL) was added to the mixture. The organic phase was separated, and the resulting aqueous layer is extracted with Et_2O (0.5 mL, 3x). The combined organic phases were dried and concentrated to a yellow oil which was dissolved in CH_2Cl_2 (3 mL) in a dried Schlenk tube. Methyl acrylate (645 mg, 7.5 mmol) and Hoveyda-Grubbs 2nd generation catalyst (18 mg, 0.03 mmol) were sequentially added producing a light green solution which was stirred for 36 h at rt. The mixture was then concentrated in *vacuo* to a dark brown oil. Purification of this residue by silica gel chromatography (2 : 98 to 5/ 95 Et_2O/pentane) affords **6** as a colorless oil [66% yield, $[\alpha]_D$ = – 20 (*c* 0.3, $CHCl_3$)]; ^{1}H-NMR δ 7.29-7.25 (m, 2H), 7.21-7.14 (m, 3H), 7.07 (dd, *J* = 15.7 and 6.7 Hz, 1H), 5.77 (dd, *J* = 15.7 and 1.5 Hz, 1H), 3.67 (s, 3H), 3.61-3.54 (m, 1H), 1.38 (d, *J* = 7.1 Hz, 3H); ^{13}C-NMR δ 167.1, 152.9, 143.2, 128.6, 127.3, 126.7, 119.6, 51.4, 42.0, 20.1; LRMS (EI) *m/z* 190 (M^+, 40), 159 (18), 131 (100), 91 (22), 51 (13); HRMS Calcd. for $C_{12}H_{14}O_2$ 190.09937, found 190.09953.

Enantioselective Catalytic Conjugate Addition of EtMgBr to (*S*)-6.[23]

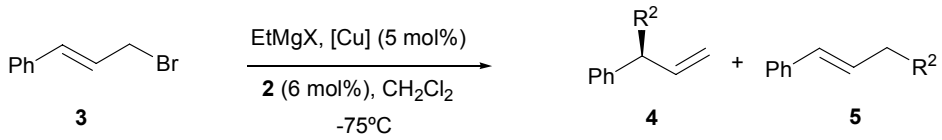
[22] (a) J. M. Concellón, E. Bardales, *Org. Lett*., 2002, **4**, 189. (b) D. B. Barma, A. Kundu, A. Bandyopadhyay, A. Kundu, B. Sangras, A. Briot, C. Mioskowski, J. R. Falck, *Tetrahedron Lett*. 2004, **45**, 5917.
[23] F. López, S. R. Harutyunyan, A. Meetsma, A. J. Minnaard, B. L. Feringa, *Angew. Chem., Int. Ed.*, 2005, **44**, 2752.

(+)-(*3S,4S*)-methyl 3-ethyl-4-phenylpentanoate (7): In a Schlenk tube CuBr SMe_2 (8.0 μmol, 1.62 mg) and ligand (*R,S*)-**1b** (9.4 μmol, 5.60 mg) were dissolved in CH_2Cl_2 (1.5 mL) and stirred under argon at room temperature for 10 min. The mixture was cooled to -75 ºC and EtMgBr (3.0 M in Et_2O, 0.78 mmol) was added dropwise. After stirring for 5 min at that temperature a solution of **6** (30 mg, 0.16 mmol) in CH_2Cl_2 (0.25 mL) was added dropwise over 10 min. After stirring at –75 ^oC for 22 h, MeOH (0.25 mL) and NH_4Cl (1M, 2 mL) were sequentially added, and the mixture was warmed to rt. After extraction with Et_2O (0.5 mL, 3x), the combined organic phases were dried and concentrated to a yellow oil which was flash chromatographed (2 : 99 Et_2O/pentane) to yield **7** as a colourless oil [81% yield, 98% de, $[\alpha]_D$ = + 25 (*c* 0.2, $CHCl_3$)]; ^{1}H-NMR δ 7.26-7.12 (m, 5H), 3.57 (s, 3H), 2.82-2.73 (m, 1H), 2.30-2.15 (m, 2H), 2.08-1.97 (m, 1H), 1.38-1.27 (m, 1H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.14-1.06 (m, 1H), 0.81 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR δ 174.1 (C), 145.6 (C), 128.2 (CH), 127.7 (CH), 126.0 (CH), 51.4 (CH_3), 42.8 (CH), 41.4 (CH), 35.3 (CH_2), 24.4 (CH_2), 17.1 (CH_3), 11.1 (CH_3); LRMS (EI) *m/z* 220 (M^+, 20), 189 (11), 146 (43), 105 (100) 57 (21); HRMS Calcd. for $C_{14}H_{20}O_2$ 220.14632, found 220.14572. Diastereoselectivity determined by Chiraldex G-TA column (30 m x 0.25 mm), 100 ºC, retention times (min): 59.6 (minor: *3R,4S and 3S,4R*) and 62.4 (major, *3S,4S*). Alternatively ,the diastereoselectivity could also be determined by ^{1}H-NMR, by integration of the 3.5 ppm signals corresponding to the methyl ester group.

(+)-(*3R,4S*)-methyl 3-ethyl-4-phenylpentanoate (8): Same procedure as above but using (*S,R*)-**1b** instead of (*R,S*)-**1b**. [84% yield, 92% de, $[\alpha]_D$ = + 6 (*c* 0.6, $CHCl_3$)]; ^{1}H-NMR δ 7.24-7.20 (m, 2H), 7.14-7.11 (m, 3H), 3.53 (s, 3H), 2.71-2.67 (m, 1H), 2.16-2.01 (m, 3H), 1.44-1.29 (m, 2H), 1.19 (d, *J* = 7.2 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR δ 174.0 (C), 145.6 (C), 128.2 (CH), 127.8 (CH), 126.1 (CH), 51.3 (CH_3), 42.5 (CH), 41.8 (CH), 36.3 (CH_2), 23.1 (CH_2), 18.2 (CH_3), 10.4 (CH_3); LRMS (EI) *m/z* 220 (M^+, 18), 189 (12), 146 (58), 105 (100); HRMS Calcd. for $C_{14}H_{20}O_2$ 220.14632, found 220.14621. Diastereoselectivity determined by Chiraldex G-TA column (30 m x 0.25 mm), 100 ºC, retention times (min): 59.6 (major: *3R,4S*), 62.4 (minor: *3S,4S*) and 63.3 (minor: *3R*, *4R*). Alternatively ,the de could also be determined by ^{1}H-NMR, by integration of the 3.57 and 3.53 ppm signals corresponding to the methyl ester groups of **7** and **8**.

Note: The conjugate addition of EtMgBr to **(*S*)-6**, following the procedure described above, but using ***racemic*-1b** instead of (*R,S*)-**1b** led to a 84 : 16 mixture of **7** and **8**, as deduced by GC [Chiraldex G-TA column (30 m x 0.25 mm), 100 ºC, retention times (min): 59.6 (minor: *3R,4S and 3S,4R*) and 62.4 (major, *3S,4S*)] and ^{1}H-NMR [by integration of the 3.57 and 3.53 ppm signals corresponding to the methyl ester groups of **7** and **8** respectively], indicating a strong preference for the formation of the 1,2-*anti* product **7**.

Influence of the copper source and Grignard halide in the enantioselective allylic alkylation of cinnamyl halides catalyzed by Taniaphos 2.



3 **4** **5**

Entry	EtMgX	[Cu]	**4** : **5**	ee
1	EtMgBr	$CuBr{\cdot}SMe_2$	82 : 18	96
2	EtMgBr	CuTC	82 : 18	96
3	EtMgBr	$Cu(CH_3CN)_4PF_6$	83 : 17	96
4	EtMgBr	CuCl	82 : 18	95
5	EtMgCl	$CuBr{\cdot}SMe_2$	80 : 20	94
6	EtMgBr	$CuBr{\cdot}SMe_2$	81 : 19	95