Creation of highly congested quarternary centers via Cu catalyzed conjugate addition of alkenyl alanates to β -substituted cyclic enones

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SUPPORTING INFORMATION

Table of Contents

General	3					
Reagents	3					
Synthesis of substrates	4					
Representative Experimental Procedure for Preparing Aluminum Reagents						
Representative Experimental Procedure for the Cu-catalyzed Reactions						
Analytical Data of Alkenyl-addition products	6-9					

General. ¹H (400 MHz or 300 MHz) and ¹³C (100 MHz or 75 MHz) NMR spectra were recorded in CDCl₃ and chemical shifts are given in ppm relative to residual CHCl₃. Evolution of reaction was followed by GC-MS Hewlett Packard (EI mode) HP6890-5973. Flash chromatographies were performed using silica gel 32-63 μ m, 60 Å and a pentane-diethylether mixture as eluent. All reactions were carried out under inert atmosphere. All solvents were dried on alumina columns.

Reagents

Reagents used for alane and alanate synthesis:

Methyllithium: was purchased from ACROS (1.6 M solution in ether)

n-Butyllithium: was purchased from ACROS (1.6 M solution in hexane)

tert-Butyllithium: was purchased from ACROS (1.9 M solution in pentane)

2-Bromopropene was purchased from Sigma-Aldrich (99%) and used as received.

cis-1-Bromo-1-propene was purchased from Sigma-Aldrich (97%) and used as received.

1-Bromo-2-methyl-1-propene was purchased from Sigma-Aldrich (98%) and used as received.

2-Bromo-3-methyl-2-butene was purchased from Sigma-Aldrich (96%) and used as received. **Me₃Al** was purchased from Sigma-Aldrich (2.0 M in heptane) and used as received.

DIBAL-H was purchased from ACROS (ACROSEAL, 1.0M solution in heptane) and used as received.

5-Chloro-1-pentyne was purchased from ACROS (98%) and used as received.

Reagents used for Catalysis

3-methylcyclohex-2-enone was purchased from Sigma-Aldrich (98%)

isophorone: was purchased from ACROS (98%)

CuTC was purchased from Frontier Scientific and used as received.

Copper(II)naphtenate, 77% in mineral spirits (8% Cu) was purchased from Strem (CAS: 1338-02-9) and used as a solution in pentane (3.2 g of the fir green viscous oil was dissolved in pentane (50 mL)).

Dichlorobis(triphenylphosphine)nickel(II) was purchased from Fluka (98%) and used as received. (CAS: 14264-16-5).

Synthesis of Enones

General Procedure A:

A flame-dried flask was charged with Grignard or lithium reagent (2.0 eq.), cooled to 0 °C and ethoxycyclohex-2-en-1-one (50 mmol) in THF (40mL) was added dropwise. Once the addition was complete the reaction mixture was left at rt until complete disappearance of the starting material. The reaction mixture poured into 1M aqueous HCl (50 mL). Diethyl ether (50 mL) was added and the aqueous phase was separated and extracted further with diethyl ether (2 \times 50 mL). The combined organic fractions were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The oily residue was purified by distillation under reduced pressure or trituration with pentane.

3-isobutylcyclohex-2-enone (2)^[1]



The crude oil was obtained according to *General Procedure E* and purified by distillation (150 °C at 30 mbar) to afford 4.47 as a pale yellow oil (53% yield). ¹**H-NMR** (400.13 MHz, CDCl₃): δ = 5.90 (brs, 1H), 2.44-2.37 (m, 2H), 2.31 (t, J = 5.7 Hz, 2H), 2.13 (d, J = 7.2 Hz, 2H), 2.08-1.99 (m, 2H), 1.98-1.87 (m, 1H), 0.96 (dt, J = 6.4, 3.1 Hz, 6H).

3-phenylcyclohex-2-enone (3)^[2]



The crude product was obtained according to General Procedure E and was triturated in Pentane / $Et_2O = 5:1$ to afford **4.46** as beige crystals (72% yield). ¹**H-NMR** (400.13 MHz, CDCl₃): δ = 7.65-7.51 (m, 2H), 7.45-7.38 (m, 3H), 6.43 (brs, 1H), 2.82-2.75 (m, 1H), 2.52-2.47 (m, 1H), 2.21-2.12 (m, 1H).

Preparation of alkenylalanates from the corresponding alkenyl bromides; exemplified for 4.103

General Procedure B:



To a solution of 1-bromo-2-methylprop-1-ene 4 (166 μ L, 243 g, 1.8 mmol, 1.0 eq.) in Et₂O (1.8 mL) was added under inert atmosphere t-BuLi (1.9 mL, 3.6 mmol, 1.9 M in pentane, 2.0 eq.) at -78 °C. The reaction was stirred for 30 min at this temperature. Then Me₃AI (0.9 mL, 1.8 mmol, 2.0 M in heptane, 1.0 eq.) was added and the reaction mixture was stirred for 30 min maintaining the temperature at -78 °C. The cooling bath was removed and the reaction vessel was immediately submerged in a water bath (20 °C). The alanate was stirred over 5 h at 20 °C and A1 was used without purification.

Preparation of alkenyaluminums by Ni-catalyzed hydroalumination from alkynes^[3]

General Procedure C:



Commercial grade 1,3-bis(diphenylphosphino)propane nickel(II) chloride (Ni(dppp)Cl₂, 57 mg, 0.10 mmol, 3 mol %) is placed in an oven-dried round bottom flask equipped with a stir bar. The flask was sealed with a septum and purged with N₂. THF (3.5 mL) is added through a syringe, followed by dropwise addition of DIBAL-H (3.8 mL, 3.8 mmol, 1.1 eq. 1.0 M in heptane) at rt. The resulting black solution was allowed to cool to 0 °C before 5-chloropent-1-yne (0.37 mL, 0.36 g, 3.5 mmol, 1.0 eq.) was added slowly over five minutes. The resulting black solution was allowed to warm to 20 °C and stirred for an additional two hours. Then the reaction mixture was cooled to 0 °C and MeLi (2.9 mL, 3.5 mmol, 1.2 M solution in Et_2O) was added. The reaction was stirred for another 10 min at 0 °C and then for 5 h at 20 °C.^[a]

[a] The reaction was stirred for another 5 h to ensure complete equilibration of alane and alanate species.

■ Cu-catalyzed conjugate addition employing alkenylalanates generated from the alkenylbromides; exemplified for the synthesis of 4.31

General Procedure D:



A flame-dried Schlenk tube was charged with Copper(II)naphthenate solution in pentane (1.17 mL, 0.09 mmol Cu(II), 10 mol %) and and ether (3.0 mL).^[a] The solution of the Cu-salt was cooled to -10° C and a solution of the alanate (4.8 mL, 1.8 mmol, 2.0 eq., 0.38 M solution in ether; prepared according to *General Procedure B*) was added slowly. After 5 min neat 3-methylcyclohex-2-enone **5** (102 µl, 99 mg, 0.9 mmol, 1.0 eq.) was added at once and the solution was allowed to stir at -10° C for another 14 h after which the reaction was quenched by slow addition of MeOH (0.1 mL; CAUTION: gas evolution) at -10° C. When the gas evolution stopped aq. 1 M HCl (3 mL) was added slowly (CAUTION: gas evolution) and stirred vigorously for 30 min at room temperature.^[b] The aqueous layer was extracted with Et₂O (3 × 10 mL), the combined organic phases were dried over Na₂SO₄ and the solvents removed under reduced pressure to yield the crude product as a brownish oil. Purification by column chromatography over silica gel (Pentane / Et₂O = 10:1) afforded **1b** as a colourless viscous oil (89 mg, 0.54 mmol, 60% yield).

[a] Alternatively the Cu(II)naphthenate solution can be directly added to the cooled suspension of the alante (-10 °C) without addition of diethyl ether. The neat 3-methylcyclohex-2-enone is then added directly to the black solution.

[b] For reactions on a **larger scale** it is highly recommended to slowly pour the black solution into a mixture of ice and HCl (aq.; 5%) in order to quench the reaction mixture!

■ Cu-catalyzed conjugate addition employing alkenylalanates generated from the corresponding alkyne via Ni-catalyzed hydroalumination.

General Procedure E:



A flame-dried Schlenk tube was charged with Copper(II)naphthenate solution in pentane (2.3 mL, 0.18 mmol Cu(II), 10 mol %) and and ether (6.0 mL).^[a] The solution of the Cu-salt was cooled to – 10°C and a solution of the alanate (10.6 mL, 3.5 mmol, 2.0 eq., 0.33 M solution in THF; prepared according to *General Procedure C*) was added slowly. After 5 min neat 3-methylcyclohex-2-enone **5** (198 µl, 193 mg, 1.75 mmol, 1.0 eq.) was added followed by Me₃Al (0.9 mL, 1.75 mmol, 2.0 M in heptane, 1.0 eq.). After 14 h the reaction mixture was slowly poured onto a slush of ice and HCl (aq.; 5%; 30 mL) in an Erlenmeyer flask. Once the gas evolution ceased (careful shaking of the Erlenmeyer flask) the mixture was transferred into a separatory funnel and vigorously shaken for 5 min. Then the organic phase was separated and the aqueous layer was extracted with Et₂O (3 × 20 mL), the combined organic phases were dried over Na₂SO₄ and the solvents removed under reduced pressure to yield the crude product as a brownish oil. Purification by column chromatography over silica gel (Pentane / Et₂O = 8:1) afforded **1b** as a brownish viscous oil (250 mg, 1.17 mmol, 67% yield).

[a] Alternatively the Cu(II)naphthenate solution can be directly added to the cooled suspension of the alante (-10 °C) without addition of diethyl ether. The neat 3-methylcyclohex-2-enone is then added directly to the black solution.

Analytical Data of Addition Products

3-methyl-3-(3-methylbut-2-en-2-yl)cyclohexanone (1a)



1a was prepared according to *General Procedure D*. Purification of the crude mixture by flash chromatography on silica gel (Pentane / $Et_2O = 10:1$; $R_f = 0.23$ in pentane / $Et_2O = 10:1$) gave **1a** in 81% yield as a colourless oil. Product was revealed with anisaldehyde to give brown stains. ¹H-NMR (400.13 MHz, CDCl₃): $\delta = 2.72$ (d, J = 14.1 Hz, 1H), 2.29-2.20 (m, 5H), 1.86-1.81 (m, 1H), 1.78 (d, J = 1.1 Hz, 3H), 1.72-1.66 (m, 1H), 1.64 (s, 3H), 1.59 (s, 3H), 1.14 (s, 3H).

¹³C-NMR (100.61 MHz, CDCl₃): δ =212.7, 132.4, 126.2, 54.6, 44.3, 40.9, 36.4, 26.2, 24.5, 23.5,

22.2, 17.4. **EI-MSHR**: $[M]^+$ calculated for: $C_{12}H_{20}O$: 180.15087, found 180.15099. **IR**: v $[cm^{-1}] =$ 2934, 1707, 1454, 1078.

3-methyl-3-(2-methylprop-1-enyl)cyclohexanone (1b)^[4]



1b was prepared according to General Procedure D. Purification of the crude mixture by flash chromatography on silica gel (Pentane / $Et_2O = 10:1$; $R_f =$ 0.33 in pentane / $Et_2O = 10:1$) gave **1b** in 60% yield as a colourless oil. Product was revealed with anisaldehyde to give purple stains. ¹H-NMR $(400.13 \text{ MHz}, \text{CDCl}_3)$: $\delta = 4.99 \text{ (s, 1H)}, 2.42 \text{ (d, } J = 13.4 \text{ Hz}, 1\text{H}), 2.27-2.11 \text{ (m, III)}$

3H), 1.97-1.75 (m, 3H), 1.66 (d, J = 0.8 Hz, 3H), 1.63 (d, J = 1.0 Hz, 3H), 1.59-1.51 (m, 1H), 1.12 (s, 3H). ¹³**C-NMR** (100.61 MHz, CDCl₃): δ = 211.8, 133.1, 130.3, 55.1, 40.9, 40.4, 37.7, 28.0, 27.3, 22.5, 19.1.

(Z)-3-methyl-3-(prop-1-enyl)cyclohexanone (1c)^[5]

1c was prepared according to General Procedure D. Purification of the crude mixture by flash chromatography on silica gel (Pentane / $Et_2O = 10:1$, $R_f = 0.22$ in pentane / $Et_2O = 10:1$) gave **4.30** in 66% yield as colourless viscous oil. Product was revealed with anisaldehyde to give yellow stains. ¹H-NMR (400.13) MHz, $CDCl_3$): δ = 5.42 (dq, J = 12.0, 7.2 Hz, 1H), 5.23 (dd, J = 12.0, 1.6 Hz, 1H), 2.52 (d, J = 13.5 Hz, 1H), 2.32-2.20 (m, 3H), 2.01-1.82 (m, 3H), 1.72 (dd, J = 7.2, 1.6 Hz, 3H), 1.69-1.59 (m, 1H), 1.20 (s, 3H). ¹³**C-NMR** (100.61 MHz, CDCl₃): δ = 211.7, 136.3, 125.2, 54.6,

41.2, 40.9, 37.6, 27.2, 22.5, 14.5. **IR**: v [cm⁻¹] = 2953, 1707, 1454, 1227, 709.

3-methyl-3-vinylcyclohexanone (1d)^[6]



1d was prepared according to *General Procedure D*.^[a] Purification of the crude mixture by flash chromatography on silica gel (Pentane / $Et_2O = 7:1$; $R_f = 0.29$ in pentane / $Et_2O = 7:1$) gave 4.29 in 83% yield as a colourless oil. Product was revealed with anisaldehyde to give yellow stains. ¹H-NMR (400.13 MHz, $CDCl_3$): δ = 5.65 (dd, J = 17.5, 10.9 Hz, 1H), 5.01-4.84 (m, 2H), 2.38 (d, J = 14.0 Hz, 1H), 2.25-2.03 (m, 3H), 1.84-1.73 (m, 2H), 1.70-1.51 (m, 2H), 1.00 (s, 3H). ¹³C-NMR (100.61 MHz, CDCl₃, 298 K): δ = 211.2, 145.7, 112.6, 51.6, 41.5, 40.8, 36.5, 27.2, 22.0.

[a] Due to the low boiling point of vinyl bromide (15 °C) the handling of it requires a special technique which is shown in the picture below.



3-isobutyl-3-(prop-1-en-2-yl)cyclohexanone (2a)

2a was prepared according to General Procedure K. Purification of the crude mixture by flash chromatography on silica gel (Pentane / $Et_2O = 10:1$; $R_f = 0.29$ in Pentane / $Et_2O = 10:1$) gave **2a** in 65% yield as a pale yellow viscous oil.

Product was revealed with anisaldehyde to give brown stains. ¹H-NMR (400.13 MHz, CDCl₃): δ = 4.93 (s, 1H), 4.74 (s, 1H), 2.73 (d, *J* = 14.5 Hz, 1H), 2.35-2.09 (m, 3H), 1.90-1.73 (m, 2H), 1.65 (d, *J* = 0.4 Hz, 3H), 1.53 (ddd, *J* = 19.5, 13.5, 5.4 Hz, 3H), 1.25-1.17 (m, 2H), 0.85 (td, *J* = 6.7, 2.8 Hz, 6H). ¹³C-NMR (100.61 MHz, CDCl₃): δ = 211.8, 147.6, 114.8, 51.3, 48.3, 47.6, 41.0, 34.9, 25.1, 24.7, 24.1, 21.2, 19.3. **EI-MSHR**: [M-C₃H₇]⁺ calculated for: C₁₃H₂₂O: 151.11174, found 151.11183. **IR**: v [cm⁻¹] = 2952, 1710, 1447, 1233, 902.

3-phenyl-3-(prop-1-en-2-yl)cyclohexanone (3a)



3a was prepared according to *General Procedure D*. Purification of the crude mixture by flash chromatography on silica gel (Pentane / $Et_2O = 10:1$; $R_f = 0.21$ in pentane / $Et_2O = 10:1$) gave **3a** in 44% yield as a colourless viscous oil. Product was revealed with anisaldehyde to give brown stains. ¹H-NMR (400.13 MHz, CDCl₃): $\delta = 7.35-7.28$ (m, 4H), 7.24-7.18 (m, 1H), 5.06 (s, 1H), 4.99 (s, 1H), 2.78 (d, J = 15.1 Hz, 1H), 2.62 (d, J = 15.1 Hz, 1H), 2.44-2.17 (m, 4H), 1.82-1.73 (m, 2H), 1.44 (s, 3H). ¹³C-NMR (100.61 MHz, CDCl₃): $\delta = 210.9$, 148.7, 145.1,

128.5, 126.5, 126.2, 113.5, 52.5, 51.3, 40.8, 32.4, 21.0, 19.6. **EI-MSHR**: $[M]^+$ calculated for: C₁₅H₁₈O: 214.13522, found 214.13523. **IR**: v [cm⁻¹] = 2945, 1710, 1447, 1233, 902, 755.

3,3,5-trimethyl-5-(prop-1-en-2-yl)cyclohexanone (6a)^[7]



6a was prepared according to *General Procedure D*. Purification of the crude mixture by flash chromatography on silica gel (Pentane / $Et_2O = 9:1$; $R_f = 0.38$ in Pentane / $Et_2O = 7:1$) gave **6a** in 77% yield as a colourless oil. Product was revealed with KMnO₄ to give yellow stains. ¹H-NMR (400.13 MHz, CDCl₃, 298 K): $\delta = 4.85$ (s, 1H), 4.76 (s, 1H), 2.74 (d, J = 13.7 Hz, 1H), 2.19 (d, J = 13.4 Hz, 1H), 2.15-2.12 (m, 2H), 1.97 (d, J = 14.3 Hz, 1H), 1.76 (s,

3H), 1.55 (d, *J* = 14.3 Hz, 1H), 1.13 (s, 3H), 1.03 (s, 3H), 0.98 (s, 3H). ¹³**C-NMR** (100.61 MHz, CDCl₃): δ = 211.6, 150.9, 111.4, 54.5, 51.3, 47.3, 43.7, 36.1, 33.1, 30.8, 27.5, 19.8.

3-methyl-3-(prop-1-en-2-yl)cyclopentanone (7a) [8]



7a was prepared according to *General Procedure D*. Purification of the crude mixture by flash chromatography on silica gel (Pentane / $Et_2O = 10:1$; $R_f = 0.22$ in pentane / $Et_2O = 10:1$) gave **7a** in 30% yield as a colourless oil. Product was revealed with anisaldehyde to give brown stains. ¹H-NMR (400.13 MHz, CDCl₃, 298 K): $\delta = 4.80-4.75$ (m, 1H), 4.73-4.68 (m, 1H), 2.41 (dd, J = 17.6, 4.1 Hz, 1H), 2.34-2.24 (m, 2H), 2.17-1.98 (m, 2H), 1.93-1.81 (m, 1H), 1.77 (s, 3H), 1.17 (s, 3H).

¹³**C-NMR** (100.61 MHz, CDCl₃, 298 K): δ = 219.0, 150.5, 109.5, 51.2, 44.8, 36.6, 33.7, 25.6, 19.5. **IR**: v [cm⁻¹] = 2923, 1703, 1457, 1164, 893.

3-(5-chloropent-1-en-2-yl)-3-methylcyclohexanone (1e)^[9]



1e was prepared according to *General Procedure E*. Purification of the crude mixture by flash chromatography on silica gel (Pentane / $Et_2O = 8:1$; $R_f = 0.162$ in pentane / $Et_2O = 10:1$) gave **1e** in 67% yield as a brownish viscous oil. Product was revealed with anisaldehyde to give brown stains which later on turned with $L_{2}O = 10.12$ ($L_{2}O = 10.12$) as $L_{2}O = 10.12$ ($L_{2}O = 10.12$) as $L_{2}O = 10.12$ ($L_{2}O = 10.12$) as $L_{2}O = 10.12$ ($L_{2}O = 10.12$) as $L_{2}O = 10.12$ ($L_{2}O = 10.12$) by $L_{2}O = 10.12$ ($L_{2}O = 10.12$) as $L_{2}O = 10.12$ ($L_{2}O = 10.12$) ($L_{2}O = 10$

Me|| pink. ¹H-NMR (400.13 MHz, CDCl₃, 298 K): δ = 4.92 (s, 1H), 4.86 (s, 1H), 3.58 (t, J = 6.4 Hz, 2H), 2.61 (d, J = 14.2 Hz, 1H), 2.36 – 2.22 (m, 3H), 2.18 – 2.10 (m, 2H), 2.02 – 1.80 (m, 4H), 1.77 – 1.58 (m, 2H), 1.10 (s, 3H). ¹³C-NMR (100.61 MHz, CDCl₃, 298 K): δ = 211.4, 152.5, 110.3, 52.6, 44.8, 44.3, 40.7, 34.8, 31.7, 27.6, 26.7, 21.8.

Cyclization of **1e** to yield cis-decaline derivative is described in ref. 9.

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NMR-data









150 140 130 120 110 100 90 f1 (ppm) 200 190 . 40 -10





240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 f1 (ppm)



240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 f1 (ppm)





(Product obtained by Cu-catalyzed conjuagate addition with alanate A7; Table 4, Entry 7)



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210	200	190	180	170	160	150	140	130	120	110	100 f1 (ppm)	90	80	70	60	50	40	30	20	10	0	-10