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Projet de maîtrise
Hiver 2001

Développement d'auxiliaires
pouvant engendrer des cycloalcènes chiraux
par métathèse

remis au

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Faculté des Sciences
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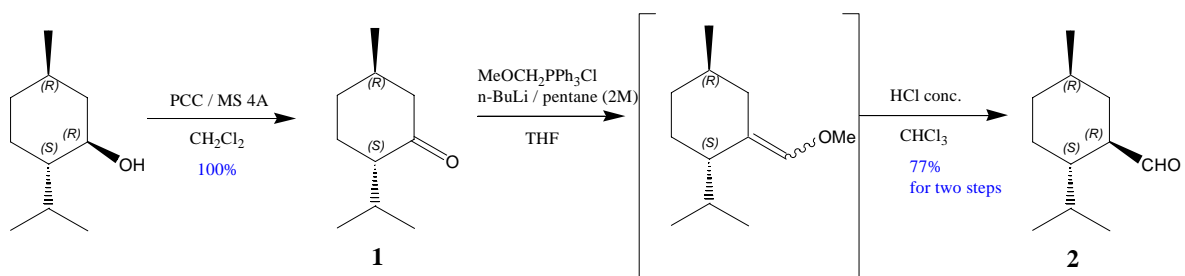
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INTRODUCTION

The objective of this project was the development of an auxiliary that could lead to chiral cycloalkene by ring closing metathesis. With the methodology recently developed in the Spino group^{1,2,3}, we could investigate the feasibility of the formation of cycloalkene bearing a quaternary center in *alpha* position. This study will demonstrate that the strategy has proven itself to be very efficient and promising for the future.

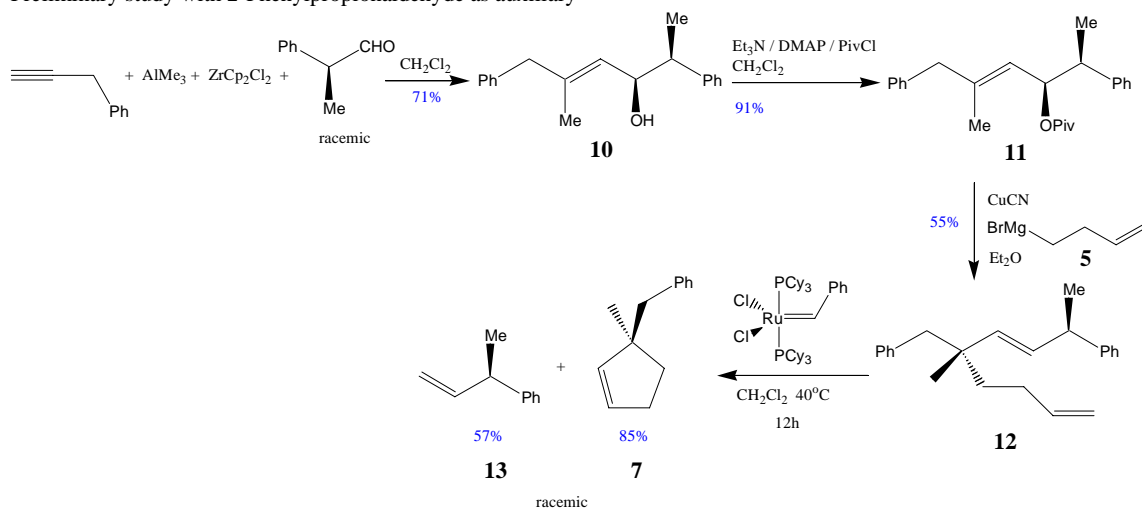
Scheme 1

Synthesis of menthylaldehyde



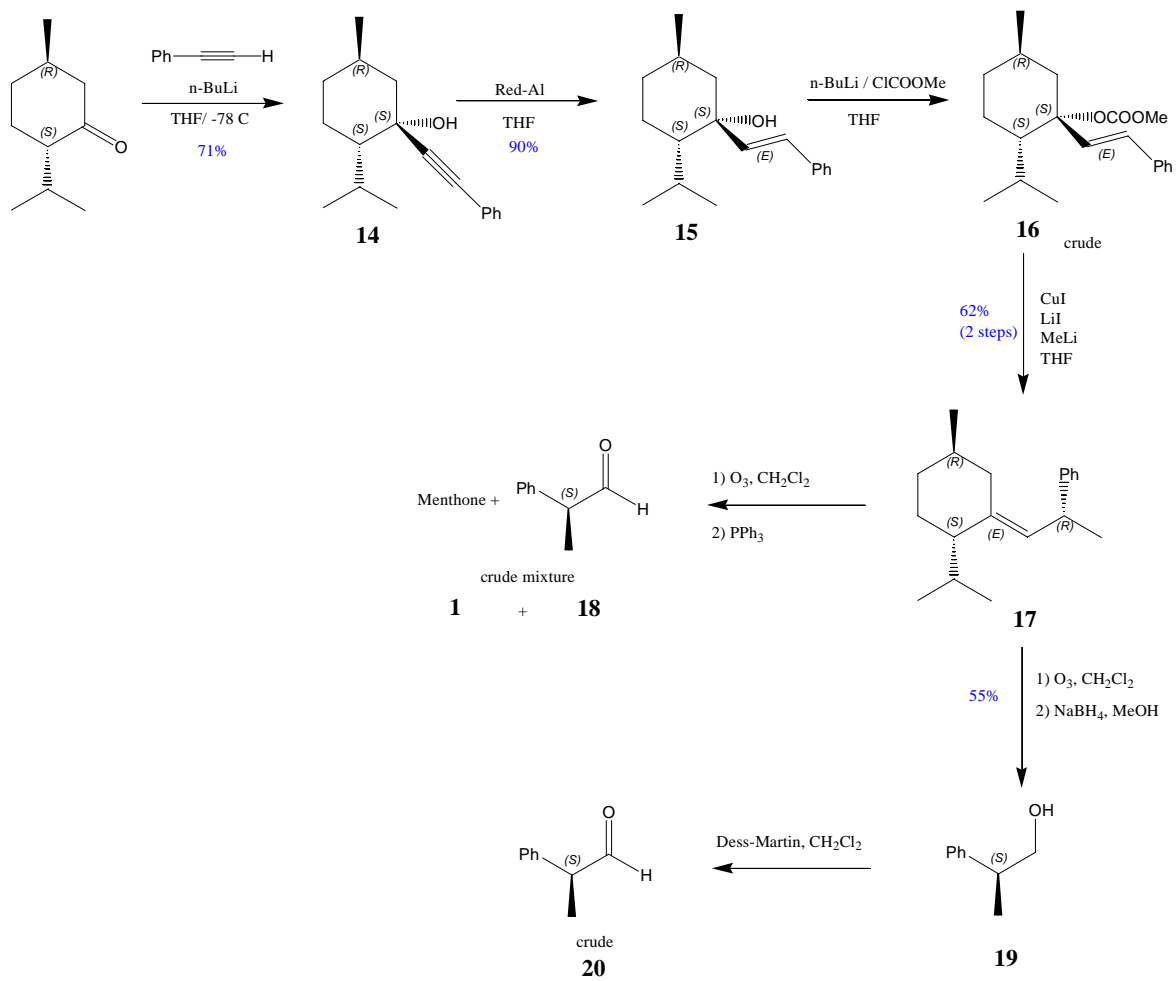
Scheme 3

Preliminary study with 2-Phenylpropionaldehyde as auxiliary



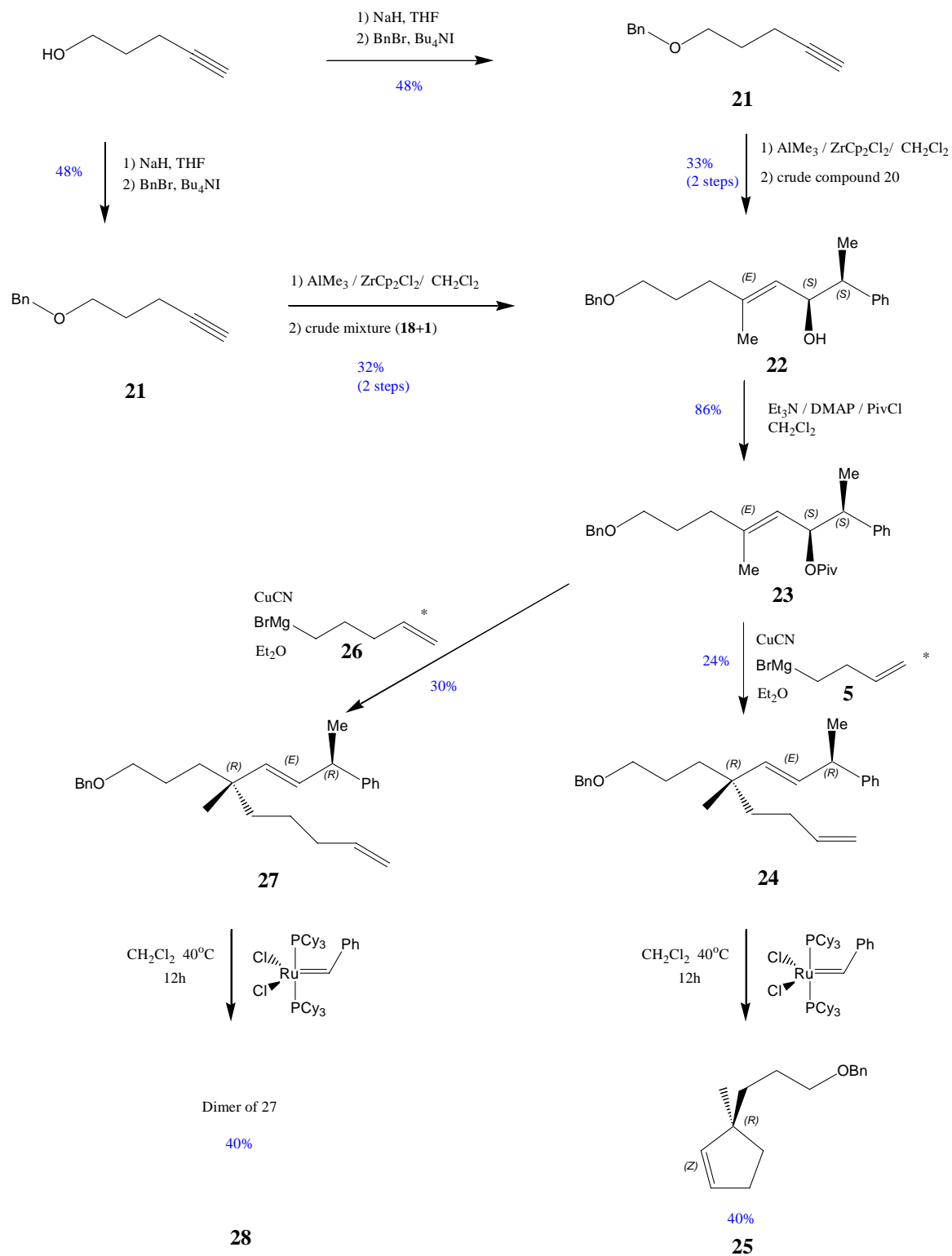
Scheme 4

Synthesis of (S)-2-Phenylpropionaldehyde



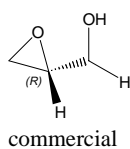
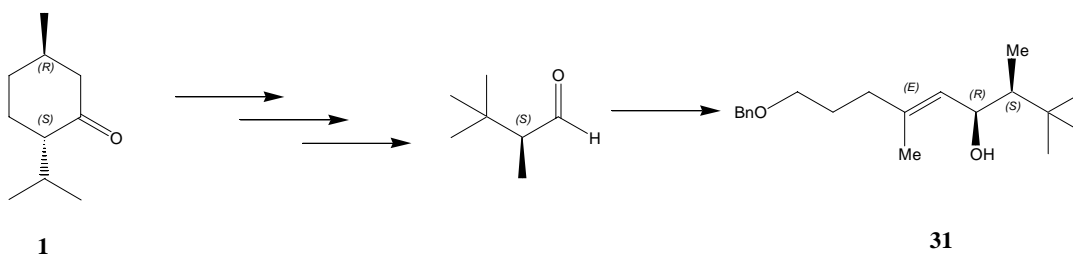
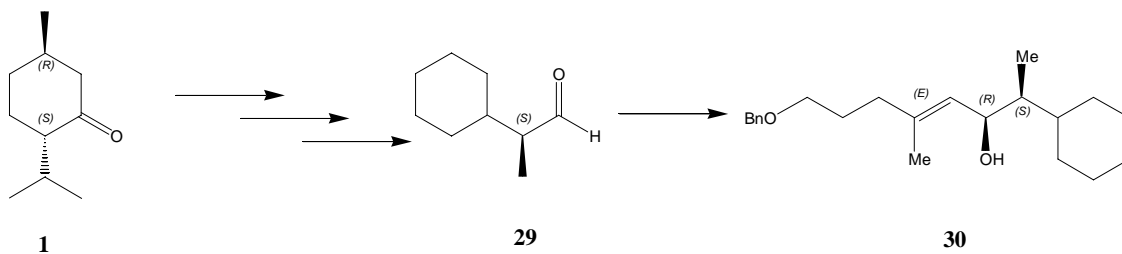
Scheme 5

Study of (S)-2-Phenylpropionaldehyde as auxiliary

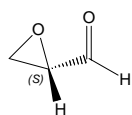


FUTURE WORK

- Investigate another catalyst (new Grubb's⁴ or Schrock) that could reduce the dimer adduct's formation
- Develop a new auxiliary that will not racemize upon flash chromatography or find a way to purify the (S)-2-Phenylpropionaldehyde (distillation, neutral column)

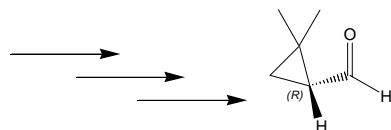


Dess-Martin



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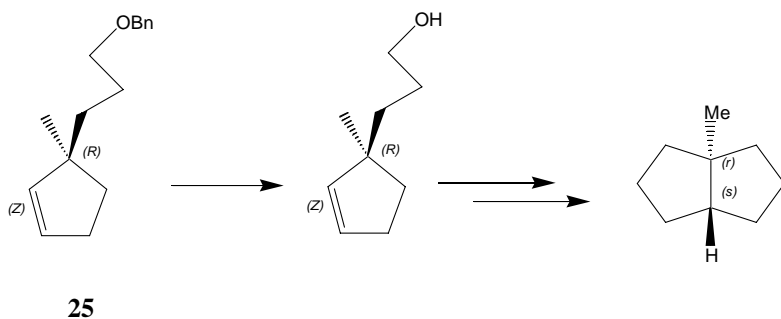
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ref.: 7

- Introduce an heteroatom in the cycle
- Try to form 6,7 and 8 member rings

- Perform the RCM with bulkies quaternary centers
- Demonstrate the utility of the method with significant examples



EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 spectrometer, and only the major bands are reported. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-300 instrument. The following abbreviations were used: s, singlet; d, doublet; dd, doublet of doublets; q, quadruplet; m, multiplet. Chemical shifts are reported relative to chloroform. Proton decoupled carbon NMR spectra used chloroform (77.0 ppm) as internal standard. Mass spectra (MS) were obtained on a VG Micromass ZAB-2F instrument.

Scheme 1. Synthesis of menthylaldehyde

Procedure for the oxidation of menthol. Anhydrous Molecular Sieves 4°A were heated with heat gun 4X and purged with argon when cooled. DCM (0.5M) and (-)-menthol (1 eq) were then added at 0°C followed by PCC (1.4eq). The mixture was stirred for 18h then activated carbon was added. The resulting mixture was filtered on a plug of silica gel, washed several times with DCM which was evaporated to give (-)-menthone **1** (100%)

Procedure for the Wittig olefination of (-)-menthone and for the hydrolysis of the resulting adduct. To a suspension of 9.33g (19.45 mmol) of dry (methoxymethyl)triphenylphosphonium chloride in 60 mL of dry THF, cooled to 0 °C, 13.61 mL (27.22 mmol) of a 2M solution of n-BuLi in hexanes was added via syringe over 10 min. The red solution was stirred 30 min at 0°C and 3g (19.45 mmol) of (-)-menthone (**1**) was added over 5 min. The reaction mixture was stirred for 10 hrs at r.t. then quenched with 1N HCl, extracted with diethyl ether (3X), dried over anhydrous magnesium sulfate and concentrated partially under reduced pressure. The residue was filtered to remove the solid triphenyl phosphine oxide and the filtrate was concentrated under reduced pressure. The enol ether obtained was then dissolved in 20 mL of chloroform and 3 mL of 12 N HCl were added. The solution was stirred 4 hrs at r.t. and the chloroform was evaporated. Diethyl ether and water were added and the aqueous phase was extracted with diethyl ether (2X). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate : hexanes (1 : 20) to yield 3.1g (95%) of the desired aldehyde **2**.

Menthyl aldehyde (2) ¹H NMR (CDCl₃, 300 MHz) : 9.49 (d, 1H, J=4.4 Hz), 2.24 (tt, 1H, J=11.5, 4.4 Hz), 1.82-1.63 (m, 4H), 1.54 (tt, 1H, J=11.8, 3.2 Hz), 1.47-1.26 (m, 2H), 1.17-0.88 (m, 2H), 0.92 (d, 6H, J=6.5 Hz), 0.80 (d, 3H, J=7.5 Hz) ; ¹³C NMR (CDCl₃, 75 MHz) : 206.0 (s), 54.1 (d), 43.1 (d), 35.5 (t), 34.9 (t), 32.0 (d), 30.2 (d), 24.5 (t), 22.9 (q), 21.6 (q), 16.8 (q) ; **IR** (neat, cm⁻¹) : 2956, 2871, 1725, 1456 ; **LRMS (m/z(relative intensity))** : 168 (M+, 10), 150 (20), 135 (50), 109(80) ; **Exact Mass** calcd for C₁₁H₂₀O : 168.1514 Found : 168.1511 ; [α]_D = -68.6, CHCl₃, c = 3.82.

Scheme 2. Study with menthylaldehyde as auxiliary

Procedure for the addition of alkenyl alanes to menthylaldehyde. ZrCp₂Cl₂ (0.30 eq) was added to dry dichloromethane (0.08M) followed by addition of trimethyl aluminium (3.9 eq). The solution was cooled to 0°C and the alkyne (1.3 eq) was added dropwise over 5 min. The solution was stirred 19 hrs at r.t. and then cooled to -78 °C. Menthyl aldehyde **2** (1 eq) was added dropwise over 10 min. The reaction was stirred for 9 hrs then a saturated aqueous potassium carbonate solution was carefully added and the white precipitate obtained was dissolved with 1N HCl. The aqueous phase was extracted with dichloromethane (3X) and the combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting oil was purified by flash chromatography eluting with ethyl acetate : hexanes (1:14) to yield (23%) of the allylic alcohol **3**.

Allylic alcohol (3) ¹H NMR (C₆D₆, 300 MHz) : 7.31-7.15 (m,5H), 5.58 (d, 1H, J=7.8 Hz), 4.72-4.66 (m, 1H), 3.35-3.22 (m,2H), 2.38-2.27 (m, 1H), 1.94-1.88 (m, 1H), 1.82-1.72 (m, 2H),1.60 (s, 3H), 1.57-1.31

(m, 3H), 1.22 (t, 1H, J=11.8 Hz), 1.15-0.82 (m, 9H), 0.89 (d, 3H, J=6.8 Hz) ; ^{13}C NMR (C_6D_6 , 75 MHz) : 139.8 (s), 134.7 (s), 130.3 (d), 128.9 (d), 128.4 (d), 126.2 (d), 67.4 (d), 46.3 (t), 45.2 (d), 43.1 (d), 35.3 (t), 34.4 (t), 32.9 (d), 26.2 (d), 24.3 (t), 23.0 (q), 21.6 (q), 16.0 (q), 15.5 (q) ; **IR** (neat, cm^{-1}) : 3363, 3026, 2954, 2870, 1494, 1102; **LRMS**(m/z (relative intensity)) : 209 (M-C₇H₇⁺, 15), 143 (100), 128(25) ; **Exact Mass** calcd for C₁₄H₂₅O : 209.1905 Found : 209.1911 ; $[\alpha]_{\text{D}}$ = -46.9, CHCl₃, c = 1.5.

Procedure for the conversion of allylic alcohol to pivalate ester. To a solution of the allylic alcohol **3** (1 eq) in dry dichloromethane (0.4M) was added freshly distilled triethylamine (4 eq) and a catalytic amount of DMAP. The solution was cooled to 0°C and pivaloyl chloride (3eq) was added slowly over 5 min. The solution was warmed to r.t. and stirred 50 hrs, quenched with an saturated aqueous NH₄Cl solution and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting oil was purified by flash chromatography eluting with ethyl acetate : hexanes (1 : 20) to yield (96%) of the desired pivalate ester **4** as a colorless oil.

Pivalate ester (4) ^1H NMR (C_6D_6 , 300 MHz) : 7.18-7.01 (m, 5H), 5.97 (dd, 1H, J=8.6, 2.1 Hz), 5.46 (d, 1H, J=8.6 Hz), 3.22-3.12 (m, 2H), 2.30-2.18 (m, 1H), 2.01-1.92 (m, 1H), 1.71 (s, 3H), 1.71-1.62 (m, 2H), 1.53 (tt, 1H, J=11.1, 2.6 Hz), 1.36-1.02 (m, 3H), 1.21 (s, 9H), 0.99-0.81 (m, 8H), 0.77 (d, 3H, J=7.2 Hz); ^{13}C NMR (C_6D_6 , 75 MHz) : 176.5 (s), 139.4 (s), 138.0 (s), 128.8 (d), 128.3 (d), 126.1 (d), 125.0 (d), 70.5 (d), 46.1 (t), 44.2 (d), 43.7 (d), 35.9 (t), 35.2 (t), 32.8 (d), 27.1 (q), 26.2 (d), 24.2 (t), 22.8 (q), 22.7 (s), 21.4 (q), 16.4 (q), 15.4 (q), 14.0 (q) ; **IR** (neat, cm^{-1}) : 2957, 2870, 1721, 1601, 1454 ; **LRMS** (m/z (relative intensity)) : 384 (M⁺, 5), 327 (5), 293 (50), 209 (40); **Exact Mass** calcd for C₂₆H₄₀O₂ : 384.3028 Found : 384.3035 ; $[\alpha]_{\text{D}}$ = -31.9, CHCl₃, c = 1.5.

Procedure for the formation of the Grignard reagent. Magnesium (1.2 eq) was heated with heat gun. When cooled, anhydrous diethyl ether (1M) and a catalytic amount of dibromoethane were added followed by 4-bromobutene(1 eq). The solution went to reflux without any help (exothermic). Helped to reflux for 2h then cooled to rt. There's a little amount of Magnesium left. This procedure gave a 1M solution of Grignard reagent **5** in diethyl ether.

Procedure for the addition of cuprate to allylic pivalate esters A suspension of CuCN (0.6eq) in anhydrous diethyl ether (0.05M) was cooled to -40 °C and the freshly prepared Grignard reagent **5** (6eq) in diethyl ether (1M) was added dropwise over 10 min. The mixture was stirred for 10 min and the pivalate ester **4** (1 eq) in diethyl ether (0.16M) was added dropwise over 30 min at -10°C. The reaction was then warmed to r.t. and stirred overnight then quenched with an aqueous solution saturated with NH₄Cl and NH₄OH (9 : 1) and stirred for 30 min. The aqueous layer was separated and extracted with diethyl ether (3X). The combined organic layers were washed once with water, once with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting oil was purified by flash chromatography eluting with 100% hexanes to give the desired cuprate adduct **6** (76%) as a colorless oil. *(The use of a catalytic amount of CuCN may cause a lost in diastereoselectivity although it seems we have 98%de by GC. We have to verify this assumption in further studies (synthetise the opposite diastereoisomer and compare GC of mixture and of pure diastereoisomer)*

Cuprate Adduct(6) ^1H NMR (CDCl₃, 300 MHz) : 7.23 -7.17 (m, 3H), 7.09 (d, 2H, J=6.3 Hz) 5.90-5.70 (m, 1H), 5.29 (d, 1H, J=15.7 Hz), 5.00-4.87(m, 3H) 2.59 (d, 1H, J=13Hz) 2.53 (d, 1H, J=13Hz) 2.05-1.95 (m, 2H), 1.95-1.65 (m, 3H), 1.65 -1.50 (m, 3H), 1.45- 1.25 (m, 4H), 1.00-0.80 (m, 2H), 0.91(s, 3H), 0.88-0.84 (m, 6H) 0.69(d, 3H, J=6.9Hz) ; **IR** (neat, cm^{-1}) : 3066, 3029, 2931, 1811, 1641, 1600, 1449, 1367, 992, 909; **LRMS** (m/z (relative intensity)) : 356 (MNH₄⁺, 5), 339 (MH⁺, 2), 247 ((M-CH₂Ph)⁺, 28), 109 (100); **Exact Mass** calcd for C₂₅H₃₉ : 339.3052 , Found : 339.3057

Procedure for the ring closing metathesis. Cuprate adduct **6** (1eq) in anhydrous DCM (0.01M) was purged 3X with argon. Grubb's catalyst (0.05eq) was added, the solution was purged with argon again and eated to reflux for 12h then cooled to rt, filtered on a plug a silica gel and evaporated under reduced pressure. The resulting oil was purified by flash chromatography eluting with pentane to give the desired

cycloalkene **7** (27%), adduct **8** (27%) and the dimer adduct **9^I** (55%). This dimer can be recycled using the same procedure as above (48h at reflux) to give 18% of the desired cycloalkene **7** (could be more with a less volatile product), the dimer **9^{II}** (60%) and 40% of the starting dimer **9^I**.

Cycloalkene (7) ¹H NMR (CDCl₃, 300 MHz) : 7.30 -7.10 (m, 5H), 5.65-5.60 (m, 1H), 5.55-5.50 (m, 1H), 2.66 (s, 2H) 2.35-2.25 (m, 1H) 2.20 -2.10 (m, 1H) 1.90-1.80 (m, 1H) 1.61-1.50 (m, 1H), 1.05 (s, 3H); **IR** (neat, cm⁻¹) : 3034, 2951, 2846, 1605, 1491, 1449, 1376, 1097; **LRMS (m/z(relative intensity))** : 172 (M+,1), 81(100)

Adduct (8) ¹H NMR (CDCl₃, 300 MHz) : 5.60 (dt, 1H, J=18 et 9.5 Hz), 4.95 (dd, 1H, J=18 et 2.2 Hz), 4.90 (dd, 1H, J=12Hz et 2.2 Hz) 2.00-1.55 (m, 6H) 1.40-1.30 (m, 1H) 1.10 -0.80 (m, 3H) 0.87 (d, 6H, J=6.7Hz) 0.71 (d, 3H, J=6.8Hz); ¹³C NMR (CDCl₃, 75 MHz) : 144.03, 113.17, 46.98, 46.05, 43.03, 35.22, 32.49, 27.96, 24.07, 22.64, 21.48, 15.27; **IR** (neat, cm⁻¹) : 2958, 2913, 1647, 1557, 901 ; **LRMS (m/z(relative intensity))** : 166 (M+, 16), 81(100); **Exact Mass** calcd for C₁₂H₂₂ : 166.1721 Found : 166.1715

Dimer (9^I) ¹H NMR (CDCl₃, 300 MHz) : 7.30 -7.10 (m, 10H), 5.40-5.30 (m, 4H), 5.00-4.90 (m, 2H), 2.62 (d,2H, J=13Hz) 2.58 (d, 2H, J=13Hz) 2.00 -1.20 (m, 18H) 1.05-0.85 (m, 22H) 0.73 (d, 6H, J=6.9Hz); **IR** (neat, cm⁻¹) : 3026, 2964, 1661, 1532, 1217, 777 ; **Exact Mass** calcd for C₄₁H₆₅ : 557.5086 Found:557.5076

Dimer (9^{II}) ¹H NMR (CDCl₃, 300 MHz) : 7.30 -7.20 (m, 3H), 7.12-7.05 (m,2H) 5.40-5.27 (m, 2H), 5.12 (dd, 1H, J=17 et 10Hz), 4.90 (dd, 1H, J=17 et 10Hz) 2.60 (d, 1H, J=13Hz) 2.52 (d, 1H, J=13Hz) 2.00-1.25 (m, 19H) 1.05-0.75 (m, 20H) 0.69 (d, 6H, J=7Hz); **IR** (CHCl₃, cm⁻¹) : 3026, 2964, 1540, 1201, 794 ; **LRMS (m/z(relative intensity))** : 385 ((M-C₇H₇)⁺,50) 123(100) ; **Exact Mass** calcd for C₂₈H₄₉ : 385.3834 Found:385.3831

Scheme 3. Preliminary study with 2-Phenylpropionaldehyde as auxiliary

Procedure for the addition of alkenyl alane to 2-Phenylpropionaldehyde. ZrCp₂Cl₂ (0.30 eq) was added to dry dichloromethane (0.08M) followed by addition of trimethyl aluminium (3.9 eq). The solution was cooled to 0°C and the alkyne (1.3 eq) was added dropwise over 5 min. The solution was stirred 19 hrs at r.t. and then cooled to -78 °C. 2-Phenylpropionaldehyde **2** (1 eq) was added dropwise over 10 min. The reaction was stirred for 6hrs then a saturated aqueous potassium carbonate solution was carefully added and the white precipitate obtained was dissolved with 1N HCl. The aqueous phase was extracted with dichloromethane (3X) and the combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting oil was purified by flash chromatography eluting with ethyl acetate : hexanes (1:9) to yield (71%) of the allylic alcohol **10** as the major isomer (20 :1).

Allylic alcohol (10) ¹H NMR (CDCl₃, 300 MHz) : 7.35-7.15 (m,8H), 6.90 (d, 2H,J=7Hz) 5.20 (d, 1H, J=8.9Hz), 4.46 (dd,1H,J=8.9 et 7Hz), 3.25 (d,1H, J=14.6Hz), 3.17 (d, 1H, J=14.6Hz), 2.88 (quintuplet, 1H, J=7Hz), 1.47 (s, 3H),1.37 (d, 3H, J=7Hz)

Procedure for the conversion of alcohol to pivalate. To a solution of the allylic alcohol **10** (1 eq) in dry dichloromethane (0.4M) was added freshly distilled triethylamine (4 eq). The solution was cooled to 0°C and pivaloyl chloride (2eq) was added slowly over 5 min. The solution was warmed to r.t. and stirred 72hrs. To help the reaction completion, DMAP (catalytic amount) was added then 12hrs later the solution was quenched with an saturated aqueous NH₄Cl solution and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting oil was purified by flash chromatography eluting with ethyl acetate : hexanes (1 : 20) to yield (91%) of the desired pivalate ester **11** as a colorless oil.

Pivalate (11) ¹H NMR (CDCl₃, 300 MHz) : 7.35-7.12 (m,8H), 6.80 (dm, 2H,J=6Hz) 5.55 (dd, 1H, J=9.1Hz), 5.05 (d,1H,J=9.2Hz), 3.20 (d,1H, J=14.6Hz), 3.12 (d, 1H, J=14.6Hz), 3.01 (quintuplet, 1H, J=7.4Hz), 1.47 (s, 3H),1.31 (d, 3H, J=7Hz) 1.21(s,9H)

Procedure for the addition of cuprates to allylic pivalate esters A suspension of CuCN (2eq) in diethyl ether (0.2M) was cooled at -10°C and the freshly prepared Grignard reagent **5** (1.5eq) in diethyl ether (1M)

was added dropwise over 10 min. The mixture was stirred for 10 min and the pivalate ester (1eq) in diethyl ether (0.5M) was added dropwise over 5 min. The reaction was then warmed to r.t., stirred for 20hrs and then quenched with an aqueous solution of saturated NH_4Cl and NH_4OH (9 : 1) and stirred for 30 min. The aqueous layer was separated and extracted with diethyl ether (3X). The combined organic layers were washed once with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting oil was purified by flash chromatography eluting with ethyl acetate:hexanes (1 : 50) to give the desired cuprate **12** (55%) as a colorless oil and SM.

Cuprate Adduct(12) $^1\text{H NMR}$ (CDCl_3 , 300 MHz): 7.34-7.09 (m, 10H), 5.87-5.77 (m, 1H), 5.45-5.30 (m, 2H) 5.02-4.91(m, 2H) 3.48-3.36 (m, 1H), 2.67-2.57 (m, 2H), 2.08-1.98 (m, 2H), 1.54-1.36 (m, 2H), 1.34 (d, 3H, $J=7\text{Hz}$), 0.96 (s, 3H)

Procedure for the ring closing metathesis. Cuprate adduct **12** (1eq) in anhydrous DCM (0.02M) was purged 3X with argon. Grubb's catalyst (0.05eq) was added, the solution was purged with argon again and heated to reflux for 12h. When completed, the solution was cooled to rt. filtered on a plug a silica gel and evaporated under reduced pressure. The resulting oil was purified by flash chromatography eluting with pentane to give the desired cycloalkene **7** (85%) and the adduct **13** (57%).

Cycloalkene (7) $^1\text{H NMR}$ (CDCl_3 , 300 MHz) : 7.30 -7.10 (m, 5H), 5.65-5.60 (m, 1H), 5.55-5.50 (m, 1H), 2.66 (s, 2H) 2.35-2.25 (m, 1H) 2.20 -2.10 (m, 1H) 1.90-1.80 (m, 1H) 1.61-1.50 (m, 1H), 1.05 (s, 3H) ; **IR** (neat, cm^{-1}) : 3034, 2951, 2846, 1605, 1491, 1449, 1376, 1097; **LRMS (m/z(relative intensity))** : 172 (M^+ ,1), 81(100)

Adduct (13) $^1\text{H NMR}$ (CDCl_3 , 300 MHz) : 7.30 -7.10 (m, 5H), 6.10-5.95 (m, 1H), 5.10-5.00 (m, 2H), 3.52-3.45 (m, 1H) 1.37(d, 3H, $J=7\text{Hz}$)

Scheme 4. Synthesis of (S)-2-Phenylpropionaldehyde

Procedure for the Addition of Alkynyl to Menthone. The alkyne (1.2 equiv) was dissolved in dry THF (0.7M) at -78°C and $n\text{-BuLi}$ (1.2 equiv) was slowly added. (-)-menthone (1.0 equiv) was added over 5 min. The reaction mixture was stirred at -78°C for 1 h after which time saturated sodium chloride was poured into the cold solution. The aqueous phase was separated and extracted with ether, the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography on silica gel (hexanes-EtOAc 9:1) to give the axial alcohol compound **14** (71%).

Propargyl alcohol (14). $^1\text{H NMR}$ (CDCl_3 , 300MHz): 7.44-7.39 (m, 2H), 7.31-7.28 (m, 3H), 2.53-2.44 (m, 1H), 2.06 (dt, 1H, J) 13.7, 2.7 Hz), 1.85-1.73 (m, 2H), 1.71-1.65 (m, 1H), 1.58-1.41 (m, 5H), 1.01 (d, 3H, J) 9.9 Hz), 0.98 (d, 3H, J) 9.9 Hz), 0.90 (d, 3H, J) 5.9 Hz); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): 131.6 (s), 128.2 (s), 123.0 (s), 94.0 (s), 83.5 (s), 72.1 (s), 50.6 (d), 50.1 (t), 34.8 (t), 28.5 (d), 27.3 (d), 23.9 (q), 21.9 (q), 20.7 (t), 18.8 (q); **IR** (neat, cm^{-1}): 3474, 3015, 2943, 2863, 1491, 1451; **LRMS (m/z (relative intensity))**: 256 (M^+ , 10), 241 (15), 213 (20), 171 (100); **Exact mass** calcd for $\text{C}_{18}\text{H}_{24}\text{O}$: 256.1827. Found: 256.1825. $[\alpha]_D^{20}$: +11.5 (c 0.88, CHCl_3).

Procedure for the Reduction of the Propargyl Alcohol to the Corresponding Allyl Alcohol. The alkyne was dissolved in THF (0.3 M) and Red-Al (1.5 equiv) dissolved in THF (0.6 M) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 22h after which time H_2SO_4 (10%) was poured slowly into the solution precooled at 0°C . The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with sat. sodium carbonate solution, dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography on silica gel (hexanes-EtOAc 20:1) to give allyl alcohol **15** (90%).

Allyl alcohol (15). $^1\text{H NMR}$ (CDCl_3 , 300 MHz): 7.41-7.19 (m, 5H), 6.64 (d, 1H, $J = 16.2\text{ Hz}$), 6.22 (d, 1H, $J=16.2\text{ Hz}$), 2.05-1.94 (m, 1H), 1.87-1.72 (m, 2H), 1.62-1.37 (m, 4H), 1.31-1.07 (m, 3H), 0.98-0.87 (m, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): 138.2 (d), 137.2 (s), 128.4 (d), 127.0 (d), 126.5 (d), 126.2 (d), 76.6 (s), 49.7 (d), 49.2 (t), 35.0 (t), 27.8 (d), 27.1 (d), 23.8 (q), 22.0 (q), 20.9 (t), 18.6 (q); **IR** (neat, cm^{-1}) : 3594,

3494, 3014, 2943, 2863, 1496, 1446, 1171; **LRMS (m/z (relative intensity))**: 258 (M + , 20), 223 (5), 202 (20), 173 (100); **Exact mass** calcd for C₁₈H₂₆O: 258.1984. Found: 258.1989. [α]²⁰_D: -51.5 (c 3.06, CHCl₃)

Procedure for the Conversion of the Alcohol to Carbonate. The allyl alcohol **15** was dissolved in dry cold (-78 °C) THF (0.1 M), n-BuLi (1.2 eq) was added dropwise, and the yellow solution was stirred at -78°C for 90 min. Methylchloroformate (1.8 eq) was added and the reaction mixture was stirred at -78°C to 0°C for 6hrs after which time sat. ammonium chloride was poured into the cold solution. The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give the carbonate **16** which were used crude in the next reaction.

Carbonate (16) ¹H NMR (CDCl₃, 300 MHz): 7.40-7.28 (m, 5H), 6.48 (d, 1H, *J* = 16.2 Hz), 6.35 (d, 1H, *J* = 16.2 Hz), 3.75 (d, 3H), 2.83 (dm, 1H, *J* = 15.3 Hz), 2.25-2.16 (m, 1H), 1.90-1.75 (m, 2H), 1.69-1.15 (m, 5H), 0.98-0.83 (m, 9H).

Procedure for the Addition of Cuprates to Allyl Carbonates. The cuprates were prepared by adding 4eq of the organolithium to a suspension of purified copper iodide (2 eq) and lithium iodide (2 eq) in dry THF (0.1 M) at -78°C. After the second equivalent of organolithium was added, the solution was stirred 4hrs at -78°C then the crude carbonate **16** (1 eq) dissolved in THF(0.6M) was added dropwise. The reaction mixture was stirred at -78°C to r.t. overnight after which time a solution of sat. ammonium chloride and ammonium hydroxide (9:1) was poured into the cooled solution (0°C). The aqueous phase was separated and extracted with ether and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography on silica gel (100% pentane) to give the anti SN2' diastereomer **17** (62% for two steps) resulting from addition.

Adduct (17) ¹H NMR (CDCl₃, 300 MHz): 7.28-7.12 (m, 5H), 5.24 (d, 1H, *J* = 9.2 Hz), 3.77-3.68 (m, 1H), 2.36 (dd, 1H, *J* = 13.3, 4.2 Hz), 1.94 (octet, 1H, *J* = 7.8 Hz), 1.82-1.54 (m, 5H), 1.45-1.35 (m, 1H), 1.32 (d, 3H, *J* = 7.3 Hz), 1.18-1.07 (m, 1H), 0.95-0.80 (m, 9H). [R]²⁰_D: -102.9 (c 0.99, CHCl₃)

Procedure for the Ozonolysis of the Cuprate Adduct to Alcohol. The alkene **17** was dissolved in dichloromethane (0.1 M), the solution was cooled to -78 °C, and ozone was bubbled through. When the solution remained light blue, indicating an ozone excess, the ozone flow was stopped and N₂ was bubbled to remove excess of ozone. Dichloromethane was then evaporated and the ozonide was dissolved in MeOH (0.1M) followed by the addition of sodium borohydride (5 eq) at -20°C. The resulting slurry was stirred at room temperature for 12h. 1N HCl was slowly added to the mixture cooled at 0°C to destroy the excess reagent. The mixture was concentrated to vacuo, water and ether were added, the aqueous phase was separated and extracted with ether and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered, concentrated in vacuo and purified by flash chromatography on silica gel (hexanes- EtOAc 20:1) to give the desired alcohol **19** (55%).

(S)-2-Phenylpropanol (19) ¹H NMR (CDCl₃, 300 MHz): 7.40-7.30 (m, 3H), 7.28-7.20 (m, 2H), 3.68 (d, 1H, *J* = 6.9Hz), 2.94 (sextuplet, 1H, *J* = 6.9 Hz), 1.78 (s, 1H) 1.28 (d, 3H, *J* = 7Hz)

Procedure for the Oxidation of the Alcohol to Aldehyde. To a stirred solution of alcohol (19) in DCM at rt was added Dess-Martin periodinane. After 1h ethyl ether was added to the reaction mixture, followed by a 10% solution of Na₂S₂O₃ in saturated aqueous NaHCO₃. The mixture was stirred for 45 minutes until all the solids were dissolved. The layers were separated and the aqueous extracted with ethyl ether (3X). The etheric layer was washed with saturated aqueous NaHCO₃, water, then dried over MgSO₄, filtered and concentrated to give aldehyde **20** as an oil that was used in the next step without further purification (Product racemize upon flash chromatography on silica gel)

(S)-2-Phenylpropanaldehyde (20) ¹H NMR (CDCl₃, 300 MHz): 9.70 (s, 1H) 7.41-7.30 (m, 3H), 7.24-7.20 (m, 2H), 3.65 (q, 1H, *J* = 6.9Hz) 1.46 (d, 3H, *J* = 6.9Hz)

Procedure for the Ozonolysis of the Cuprate Adduct to Aldehyde. The alkene **17** was dissolved in dichloromethane (0.1 M), the solution was cooled to -78°C, and ozone was bubbled through. When the

solution remained light blue, indicating an ozone excess, the ozone flow was stopped and N₂ was bubbled to remove the excess of ozone. Triphenylphosphine was added (1.1 eq) at -78°C and the resulting solution was stirred at room temperature for 12 h. Dichloromethane was evaporated, the residue was triturated with hexane to remove the excess of triphenylphosphine. The concentrated oil **18+1** (aldehyde + menthone) was used in the next step without further purification.

(S)-2-Phenylpropanaldehyde (18) ¹H NMR (CDCl₃, 300 MHz): 9.70 (s,1H) 7.41-7.30 (m, 3H), 7.24-7.20 (m, 2H), 3.65 (q,1H, J=6.9Hz) 1.46 (d, 3H, J=6.9Hz)

Scheme 5. Study with (S)-2-Phenylpropionaldehyde as auxiliary

Procedure for the protection of the alcohol. To a suspension of NaH (1eq) in THF (0.4M) at 0°C was added the alcohol (1eq). The mixture was stirred 10 min then warmed to rt and stirred 3hrs. BnBr (1eq) and Bu₄NI were then added to the precooled mixture at 0°C. The mixture was warmed to rt and stirred 60hrs then quenched with a saturated aqueous NH₄Cl solution and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting oil was purified by flash chromatography eluting with ethyl acetate : hexanes (1 : 20) to yield the desired alkyne **21** (48% + alkyne not yet repurified) as a colorless oil.

Alkyne (21) ¹H NMR (CDCl₃, 300 MHz) 7.35-7.28 (m,5H) 4.52 (s,2H) 3.58 (t,2H, J=6.1Hz) 2.33 (td,2H, J=7.1 and 2.7Hz) 1.94 (t, 1H,J=2.7Hz) 1.84 (tt,2H, J=6Hz) ; **IR** (neat, cm⁻¹): 3295, 3029, 2859, 2360, 1453, 1104, 736, 697; **LRMS (m/z (relative intensity))**: 173 ((M-H)+, 25), 105 (25), 91(100); **Exact mass** calcd for C₁₂H₁₃O: 173.0966 Found: 173.0969

Procedure for the addition of alkenyl alane to 2-Phenylpropionaldehyde. ZrCp₂Cl₂ (0.30 eq) was added to dry dichloromethane (0.08M) followed by addition of trimethyl aluminium (3.9 eq). The solution was cooled to 0°C and the alkyne **21** (1.3 eq) was added dropwise over 5 min. The solution was stirred 19hrs at r.t. and then cooled to -78 °C. 2-Phenylpropionaldehyde **20 or 18+1** (1 eq) was added dropwise over 10 min. The reaction was stirred for 3hrs then a saturated aqueous potassium carbonate solution was carefully added and the white precipitate obtained was dissolved with 1N HCl. The aqueous phase was extracted with dichloromethane (3X) and the combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting oil was purified by flash chromatography eluting with ethyl acetate : hexanes (1:9) to yield (32% for two steps) the allylic alcohol **22** as the major isomer (20 :1).

Allylic alcohol (22) ¹H NMR (CDCl₃, 300 MHz) : 7.38-7.17 (m, 10H), 5.08 (d, 1H, J=8.5 Hz), 4.45 (s, 2H), 4.42 (dd, 2H, J=8.5, 6.5Hz) 3.33 (t, 2H, J=6.5Hz) 2.85(quintuplet, 1H, J=6.9Hz) 2.00(t, 2H, J=7.4Hz) 1.70-1.60 (m, 2H), 1.53 (s, 3H), 1.33 (d, 3H, J=7 Hz) ; **IR** (neat, cm⁻¹): 3409, 3032, 2935, 2858, 1671, 1605, 1498, 1457, 1371, 1098, 1003; **LRMS (m/z (relative intensity))**: 342 ((MNH₄)+, 5) 307((M-H₂O)H+, 60), 219(100), 91(100); **Exact mass** calcd for C₂₂H₃₂NO₂: 342.2433 Found: 342.2425

Procedure for the conversion of allylic alcohol to pivalate ester. To a solution of the allylic alcohol **22** (1 eq) in dry dichloromethane (0.4M) was added freshly distilled triethylamine (4 eq) and a catalytic amount of DMAP. The solution was cooled to 0°C and pivaloyl chloride (3eq) was added slowly over 5 min. The solution was warmed to r.t.and stirred 60hrs. The rxn was then quenched with a saturated aqueous NH₄Cl solution and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting oil was purified by flash chromatography eluting with ethyl acetate : hexanes (1 : 20) to yield (86%) the desired pivalate ester **23** as a colorless oil.

Pivalate (23) ¹H NMR (CDCl₃, 300 MHz) : 7.34-7.14 (m,10H) 5.51 (dd, 1H, J=9.3, 7.6Hz) 4.95 (d, 1H, J=9.3 Hz) 4.42(s, 2H) 3.28 (t, 2H, J=6.6Hz) 2.96 (quintuplet, 1H, J=7.2Hz) 1.95 (t, 2H, J=7.6Hz) 1.59-1.50 (m, 2H) 1.52 (s, 3H), 1.29 (d, 3H, J=7Hz) 1.18(s,9H); **IR** (neat, cm⁻¹): 3029, 2987, 2919, 2874, 1721, 1449, 1274, 1150; **LRMS (m/z (relative intensity))**: 408 (M+, 5) 303(M-C₈H₉, 15), 105(100); **Exact mass** calcd for C₁₉H₂₇O₃: 303.1960 Found: 303.1967

Procedure for the formation of the Grignard reagent. Magnesium (1.2 eq) was heated with heat gun. When cooled, anhydrous diethyl ether (1M) and a catalytic amount of dibromoethane were added followed by 5-bromopentene(1 eq). The solution reached reflux without any help (exothermic) and then helped to reflux for 2h then cooled to rt. There's a little amount of Magnesium left. This procedure give a 1M solution of Grignard reagent **26** in diethyl ether.

Procedure for the addition of cuprates to allylic pivalate esters A suspension of CuCN (2eq) in diethyl ether (0.2M) was cooled to -40°C and the freshly prepared Grignard reagent **5** or **26** (6 eq) in diethyl ether (1M) was added dropwise over 10 min. The mixture was stirred for 10 min and the pivalate ester **23** (1eq) in diethyl ether (0.5M) was added dropwise over 5 min. The reaction was then stirred for 2hrs and then quenched with a saturated aqueous NH₄Cl and NH₄OH (9:1) solution and stirred for 30 min. The aqueous layer was separated and extracted with diethyl ether (3X). The combined organic layers were washed once with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to an oil. The resulting oil was purified by flash chromatography eluting with ethyl acetate:hexanes (1 : 50) to give the desired cuprate **24** (24%+SM) or **27**(30%+SM). *This procedure have to be optimized.*

Cuprate Adduct (24) ¹H NMR (CDCl₃, 300 MHz) : 7.40 -7.15 (m, 10H) 5.90-5.70 (m,1H) 5.47(dd, 1H, J=18, 7.8Hz), 5.32 (d, 1H, J=18Hz), 5.03-4.88 (m, 2H) 4.50 (s, 2H) 3.50-3.40 (m, 3H) 2.10-1.90 (m, 2H), 1.70-1.30 (m, 6H), 1.35 (d, 3H, J=7.5Hz), 0.96 (s, 3H)

Cuprate Adduct (27) ¹H NMR (CDCl₃, 300 MHz) : 7.40 -7.15 (m, 10H) 5.90-5.70 (m,1H) 5.47(dd, 1H, J=18, 7.8Hz), 5.32 (d, 1H, J=18Hz), 5.03-4.90 (m, 2H) 4.50 (s, 2H) 3.50-3.40 (m, 3H) 2.10-1.90 (m, 2H), 1.70-1.30 (m, 8H), 1.35 (d, 3H, J=7.5Hz), 0.96 (s, 3H) **LRMS (m/z (relative intensity))**: 376 (M+, 4) 348(17) 285(40) 105(100); **Exact mass** calcd for C₂₇H₃₆O: 376.2766 Found: 376.2758

Procedure for the ring closing metathesis. Cuprate adduct **24** or **27** (1eq) in anhydrous DCM (0.01M) was purged 3X with argon. Grubb's catalyst (0.05eq) was added, the solution was purged with argon again and heated to reflux for 12h then cooled to rt, filtered on a plug a silica gel and evaporated under reduced pressure. The resulting oil was purified by flash chromatography eluting with hexanes to give the desired cycloalkene **25** (40%) in the first case and the dimer adduct **28**(40%) + SM in the second. *(this experiment has been done on a scale too small to gave a representative yield)*

Cycloalkene (25) ¹H NMR (CDCl₃, 300 MHz) : 7.35 -7.25 (m, 5H), 5.62-5.58 (m, 1H) 5.50-5.46 (m, 1H), 4.50 (s, 2H) 3.45 (t, 2H, J=6.7Hz) 2.33 -2.30 (m, 2H) 1.75-1.30 (m, 6H) 1.03 (s, 3H) ; **IR** (neat, cm⁻¹): 3054, 2930, 2840, 2790, 1449, 1353, 1093, 737; **LRMS (m/z (relative intensity))**: 248 (MNH₄⁺, 15) 231(MH⁺, 20), 213(25) 81(100); **Exact mass** calcd for C₁₆H₂₃O: 231.1749 Found: 231.1743

Dimer adduct (28) ¹H NMR (CDCl₃, 300 MHz) : 7.40 -7.15 (m, 20H) 5.50-5.25 (m,6H) 4.50 (s, 4H) 3.50-3.40 (m, 6H) 2.00-1.90 (m, 4H), 1.70-1.30 (m, 16H), 1.35 (dm, 6H, J=7.5Hz), 0.96 (m, 6H) **LRMS (m/z (relative intensity))**: 724 (M+, 1) 696(1) 633(7) 605(13) 181(100)

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