Supporting information

Palladium-catalyzed [3+2] Intramolecular Cycloaddition of Alk-5-enylidenecyclopropanes*

Moisés Gulías, Rebeca García, Alejandro Delgado, Luis Castedo, and José L. Mascareñas**

Departamento de Química Orgánica y Unidad Asociada al CSIC,
Universidad de Santiago de Compostela, 15782 Santiago de
Compostela, (Spain).

EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

General procedures. All dry solvents were freshly distilled under argon from an appropriate drying agent before use. Toluene and THF were distilled from sodium/benzophenone, CH_2Cl_2 and Et_3N were distilled from CaH_2 , and dioxane was distilled from sodium. $\text{Pd}_2(\text{dba})_3$, triisopropyl phosphite, triphenylphosphite and triphenylphosphine were purchased from Aldrich and tris(2,4-*t*-butylphenyl)phosphite from Strem. All reactions were conducted in dry solvents under argon atmosphere unless otherwise stated. External bath temperatures were used to record all reaction temperatures. Thin-layer chromatography (TLC) was performed on silica gel plates and components were visualised by observation under UV light, or by treating the plates with either p-anisaldehyde or cerium nitrate followed by heating. Flash chromatography was carried out on silica gel unless otherwise stated. Drying was performed with anhydrous Na_2SO_4 . Concentration refers to the removal of volatile solvents via distillation using a Buchi rotary evaporator at water aspirator pressure, followed by residual solvent removal at high vacuum (approx. 0.5 mmHg).

^1H and ^{13}C NMR spectra were recorded in CDCl_3 , at 250 MHz and 62.9 MHz, respectively, and 300 and 500 MHz (75.5 and 125.7 for ^{13}C) for cycloadducts. Carbon types were determined from DEPT-NMR experiments. The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were acquired using chemical ionization techniques.

SUBSTRATES

2-(2-Cyclopropylideneethyl)malonic acid diethyl ester (13)

To a suspension of NaH (1.02 g, 25.5 mmol) in THF (20 mL) cooled at 0°C was added diethyl malonate (4.03 g, 15.2 mmol) dropwise. After stirring for 15 min, a solution containing allylcyclopropyl tosylate¹ (2.00 g, 8.40 mmol), $\text{Pd}_2(\text{dba})_3$ (77 mg, 0.085 mmol) and dppe (34 mg, 0.085 mmol) in THF (20 mL), that had been previously stirred for 20 min, was added “via cannula”. The reaction mixture was stirred for 3h at rt, poured into water and extracted with Et_2O (3x10 mL). The combined organic phases were dried, filtered and concentrated, and the crude residue was purified by flash chromatography (0.5-1 % Et_2O /hexanes) to give **13** (1.21 g, 63%) and **9** (369 mg, 30%) as colorless oils.

¹ (a) Racauchot, S.; Silvestre, I.; Olliver, J.; Kozyrkov, Y.; Pukin, A.; Kulinkovich, O.; Salaün, J. *Eur. J. Org. Chem.* **2002**, 2160. (b) Silvestre, I.; Olliver, J.; Salaün, J. *Tetrahedron. Lett.* **2001**, 42, 1991

Physical data for 13:

¹H-NMR δ (ppm): 5.73 (1H, m), 4.15 (4H, q, *J* = 7.2 Hz), 3.49 (1H, t, *J* = 7.6 Hz), 2.74 (2H, m), 1.22 (6H, t, *J* = 7.2 Hz), 1.00 (4H, s).

¹³C-NMR δ (ppm): 169.1 (C), 124.5 (CH), 113.7 (C), 61.2 (CH₂), 51.7 (CH), 31.0 (CH₂), 14.0 (CH₃), 2.2 (CH₂), 1.9 (CH₂).

MS (*m/z*, %): 227 ([M+1], 15), 215 (19), 197 (18), 181 (62), 153 (98), 135 (100), 107 (96).

HRMS calculated for C₁₂H₁₉O₄ 227.1283, found 227.1279.

Physical data for 9:

¹H-NMR δ (ppm): 5.64 (2H, m), 4.13 (4H, q, *J* = 7.1 Hz), 2.77 (4H, d, *J* = 7.4 Hz), 1.22 (6H, t, *J* = 7.1 Hz), 0.97 (4H, m).

¹³C-NMR δ (ppm): 171.2 (C), 125.9 (CH), 112.2 (CH), 61.0 (CH₂), 57.8 (C), 34.9 (CH₂), 14.0 (CH₃), 2.82 (CH₂), 1.8 (CH₂).

MS (*m/z*, %): 293 ([M+1], 59), 247 (19), 219 (70), 201 (70), 191 (54), 173 (89), 145 (100).

HRMS calculated for C₁₇H₂₅O₄ 293.1753, found 293.1759.

General procedure of alkylation of 13; exemplified for the synthesis of 1a-E
Synthesis of 1a-E, 1c, 1d-Z, 1e and 1f-E.

To a suspension of NaH (142 mg, 3.55 mmol) in THF (10 mL) cooled at 0°C was added dropwise a solution of **13** (800 mg, 3.51 mmol) in THF (10 mL). After stirring for 30 min, *E*-ethyl 4-bromocrotonate (0.49 mL, 3.51 mmol) was slowly added, leading to the appearance of a white precipitate. The mixture was stirred overnight at rt, poured into water and extracted with Et₂O (3x20 mL). The organic phases were dried, filtered and concentrated to give a crude oily residue that was purified by flash chromatography (5 % Et₂O/hexanes) to yield 908 mg of **1a-E** as a yellow oil (81 %).

¹H-NMR δ (ppm): 6.80 (1H, m), 5.80 (1H, d, *J* = 15.7 Hz), 5.59 (1H, m), 4.17-4.10 (6H, m), 2.78-2.73 (4H, m), 1.27-1.21 (9H, m), 1.08-0.97 (4H, m).

¹³C-NMR δ (ppm): 170.4 (C), 165.8 (C), 142.9 (CH), 126.9 (C), 124.8 (CH), 111.5 (CH), 61.4 (CH₂), 60.3 (CH₂), 57.3 (C), 35.3 (CH₂), 35.3 (CH₂), 14.2 (CH₃), 14.0 (CH₃), 2.9 (CH₂), 1.9 (CH₂).

MS (*m/z*, %): 339 ([M+1], 72), 293 (66), 265 (72), 247 (58), 219 (100), 201 (74), 191 (98), 173 (69), 145 (48).

HRMS calculated for C₁₈H₂₇O₆ 339.1808, found 339.1799.

Physical data for 1c:

(Yellow oil, *E:Z* = 3:5:1)

(75 % yield). **¹H-NMR** δ (ppm): 6.65 (1H, m), 6.49 (0.28H, m), 5.59-5.53 (1.23H, m), 5.35 (1.23H, d, *J* = 16.2 Hz), 4.21-4.14 (5.2H, m), 2.93 (0.63H, dd, *J*=7.6 and 1.3 Hz), 2.78-2.69 (4.72 H, m), 1.23 (6H, t, *J* = 7.1 Hz), 1.09-0.95 (4H, m).

¹³C-NMR δ (ppm): 170.1 (C), 170.0 (C), 150.6 (C), 149.5 (C), 127.4 (C), 116.8 (C), 111.2 (CH), 102.7 (CH), 102.0 (CH), 61.7 (CH₂), 57.2 (C), 36.6 (CH₂), 35.8 (CH₂), 34.9 (CH₂), 13.98 (CH₃), 13.94 (CH₃), 3.0 (CH₂), 2.0 (CH₂), 1.9 (CH₂).

MS (*m/z*, %): 293 (19), 292, ([*M*+1], 100), 264 (14), 246 (21), 218 (28), 172 (19).

HRMS calculated for C₁₆H₂₂O₄N 292.1549, found 292.1554

Physical data for 1d-Z:

(Yellow oil, 60 % yield). **¹H-NMR** δ (ppm): 5.62 (1H, s), 5.58 (1H, m), 4.19-4.07 (6H, m), 2.78-2.75 (4H, m), 2.06 (3H, d, *J* = 0.9 Hz), 1.25-1.20 (9H, m), 1.05-0.91 (4H, m).

¹³C-NMR δ (ppm): 171.8 (C), 166.1 (C), 154.1 (CH), 126.5 (C), 120.1 (CH), 111.8 (CH), 61.4 (CH₂), 59.6 (CH₂), 57.3 (C), 43.0 (CH₂), 35.1 (CH₂), 19.2 (CH₃), 14.2 (CH₃), 13.9 (CH₃), 2.8 (CH₂), 2.0 (CH₂).

MS (*m/z*, %): 353 ([*M*+1], 3), 307 (8), 306 (7), 261 (3), 233 (4), 108 (16).

HRMS calculated for C₁₉H₂₉O₆ 353.1964, found 353.1962.

Physical data for 1e:

(Colorless oil, 85 % yield). **¹H-NMR** δ (ppm): 5.73-5.61 (2H, m), 5.09 (1H, s), 5.06 (1H, s), 4.31 (4H, q, *J* = 7.2 Hz), 2.77 (2H, d, *J* = 7.4 Hz), 2.63 (2H, d, *J* = 7.4 Hz), 1.25 (6H, t, *J* = 7.2 Hz), 1.09-0.97 (4H, m).

¹³C-NMR δ (ppm): 170.8 (C), 132.5 (C), 126.0 (CH), 118.6 (CH₂), 111.8 (CH), 61.0 (CH₂), 57.5 (C), 36.6 (CH₂), 34.7 (CH₂), 13.9 (CH₃), 2.7 (CH₂), 1.8 (CH₂).

MS (*m/z*, %): 267 ([*M*+1], 0.5), 192 (13), 147 (15), 119 (32), 91 (34).

HRMS calculated for C₁₅H₂₃O₄ 267.1596, found 267.1584.

Physical data for 1f-E:

(Colorless oil, 85 % yield). **¹H-NMR** δ (ppm): 7.32-7.19 (5H, m), 6.41 (1H, d, *J* = 15.7 Hz), 6.01 (1H, m), 5.67 (1H, m), 4.24-4.15 (4H, m), 2.84 (2H, d, *J* = 7.4 Hz), 2.79 (2H, d, *J* = 7.4 Hz), 1.24 (6H, t, *J* = 7.1 Hz), 1.13-0.96 (4H, m).

¹³C-NMR δ (ppm): 171.0 (CO), 137.2 (C), 133.7 (CH), 128.4 (CH), 127.3 (CH), 126.3 (C), 126.1 (CH), 124.3 (CH), 112.0 (CH), 61.2 (CH₂), 57.9 (C), 36.2 (CH₂), 35.2 (CH₂), 14.1 (CH₃), 2.9 (CH₂), 1.9 (CH₂).

MS (*m/z*, %): 343 ([*M*+1], 40), 314 (44), 269 (49), 268 (479), 241 (26), 223 (23), 195 (61), 117(100).

HRMS calculated for C₂₁H₂₇O₄ 343.1909, found 343.1914.

Synthesis of 1a-Z:

To a solution of 5-(2-cyclopropylideneethyl)-5-ethoxycarbonyl-hex-2-ynedioic acid diethyl ester² (200 mg, 0.59 mmol) in EtOAc (12 mL) was added Pd Lindlar (68 mg, 10 %) and quinoline (68 μL). This solution was flushed with H₂ and stirred for 1h under atmosphere of H₂ (1 bar). The resulting suspension was filtered through celite and the filtrate concentrated to give a crude product which was purified by flash chromatography (2-3% Et₂O/hexanes) to yield 195 mg of **1a-Z** (97 %) as a colorless oil.

¹H-NMR δ (ppm): 6.20 (1H, m), 5.84 (1H, d, *J* = 11.7 Hz), 5.67 (1H, m), 4.19-4.12 (6H, m), 3.31 (2H, dd, *J* = 7.2 and 1.8 Hz), 2.83 (2H, d, *J* = 7.3 Hz), 1.26-1.20 (9H, m), 1.09-0.92 (4H, m).

¹³C-NMR δ (ppm): 170.5 (CO), 165.6 (CO), 143.6 (CH), 126.4(C), 121.6 (CH), 111.6 (CH), 61.2 (CH₂), 59.8 (CH₂), 57.2 (C), 36.0 (CH₂), 32.1 (CH₂), 14.2 (CH₃) 14.0 (CH₃), 2.9 (CH₂), 1.8 (CH₂).

MS (*m/z*, %): 339 ([*M*+1], 2), 267 (4), 219 (20), 191 (18), 173 (20), 145 (23), 147 (44).

HRMS calculated for C₁₈H₂₇O₆ 339.1808, found 339.1805.

² Delgado, A.; Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2003**, 125, 9282

Synthesis of 1b-Z

2-(2-Cyclopropylideneethyl)-2-(4-hydroxypent-2-ynyl)malonic acid diethyl ester.

To a solution of 2-(2-cyclopropylideneethyl)-2-prop-2-ynyl-malonic acid diethyl ester² (380 mg, 1.43 mmol) in THF (30 mL) cooled -78 °C, was added dropwise n-BuLi (0.75 mL, 2.29 M, 1.72 mmol). After stirring for 1h at -78° C, acetaldehyde (0.40 mL, 7.13 mmol) was added and the resulting solution was stirred at the same temperature for 1h and then warmed to room temperature. After pouring into water the mixture was extracted with Et₂O, and the residue obtained after drying and concentration was purified by flash column chromatography (15% EtOAc/hexanes) to give 250 mg of 2-(2-cyclopropylideneethyl)-2-(4-hydroxypent-2-ynyl)-malonic acid diethyl ester (yellow oil, 57%).

¹H-NMR (δ, ppm): 5.54 (1H, m), 4.53 (1H, q, *J* = 6.5 Hz), 4.15 (4H, q, *J* = 7.4 Hz), 2.89 (2H, m), 2.75 (2H, d, *J* = 1.8 Hz), 2.30 (1H, br s), 1.38 (3H, d, *J* = 6.0 Hz), 1.21 (6H, t, *J* = 7.0 Hz), 1.01 (4H, m).

¹³C-NMR (δ, ppm): 170.0 (CO), 127.1 (C), 111.3 (CH), 85.3 (C), 79.1 (C), 71.0 (C), 61.5 (CH₂), 58.1 (CH), 57.0 (C), 34.5 (CH₂), 24.4 (CH), 22.7 (CH₃), 14.0 (CH₃), 2.9 (CH₂), 1.9 (CH₂).

MS (*m/z*, %): 309.3 ([*M*+1], 6), 291 (28), 217 (81), 189 (13), 145 (18).

HRMS calculated for C₁₇H₂₅O₅ 309.1702, found 309.1708

2-(2-Cyclopropylideneethyl)-2-(4-oxopent-2-ynyl)malonic acid diethyl ester

To a solution of 2-(2-cyclopropylideneethyl)-2-(4-hydroxypent-2-ynyl)malonic acid diethyl ester (250 mg, 0.81 mmol) in CH₂Cl₂ (60 mL) was added PCC (522 mg, 2.43 mmol) and NaOAc (133 mg, 1.62 mmol) at rt. The mixture was stirred at rt for 3h and filtered through a short column of silica gel with Et₂O washings. After removing the solvent, the oily residue was purified by flash column chromatography (10 % Et₂O/hexanes) to afford 2-(2-cyclopropylideneethyl)-2-(4-oxopent-2-ynyl)malonic acid diethyl ester (220 mg, 89 %) as a yellow oil.

¹H-NMR (δ, ppm): 5.54 (1H, m), 4.20 (4H, q, *J* = 7.0 Hz), 2.92-2.89 (4H, m), 2.29 (3H, s), 1.25 (6H, t, *J* = 7.3 Hz), 1.05 (4H, m).

¹³C-NMR (δ, ppm): 184.1 (CO), 169.5 (CO), 127.9 (C), 110.9 (CH), 88.5 (C), 83.1 (C), 61.8 (CH₂), 56.7 (C), 34.9 (CH₂), 32.8 (CH₃), 23.1 (CH₂), 14.0 (CH₃), 3.0 (CH₂), 1.9 (CH₂).

MS (m/z, %): 307 ([M+1], 80), 289 (23), 233 (100), 187 (13).

HRMS calculated for C₁₇H₂₃O₅ 307.1545, found 307.1547

Hydrogenation of 2-(2-cyclopropylideneethyl)-2-(4-oxopent-2-ynyl)malonic acid diethyl ester to give **1b-Z**

To a solution of 2-(2-cyclopropylideneethyl)-2-(4-oxopent-2-ynyl)malonic acid diethyl ester (130 mg, 0.42 mmol) in EtOAc (10 mL) was added Pd Lindlar (50 mg, 10 %) and quinoline (50 μ L). This solution was flushed with H₂ and stirred for 3h under a H₂ atmosphere (balloon). The resulting suspension was filtered through celite and the filtrate concentrated to give a crude product which was purified by flash chromatography (10% Et₂O/hexanes) to yield 125 mg of **1b-Z** (96%) as slightly yellow oil.

¹H-NMR (δ , ppm): 6.16 (1H, d, J = 11.6 Hz), 6.01 (1H, m), 5.58 (1H, m), 4.12 (4H, q, J = 7.0 Hz), 3.15 (2H, dd, J = 6.5 and 1.8 Hz), 2.74 (2H, d, J = 7.3 Hz), 2.15 (3H, s), 1.19 (6H, t, J = 7.3 Hz), 1.05-0.89 (4H, m).

¹³C-NMR (δ , ppm): 198.7 (CO), 170.7 (CO), 141.9 (CH), 128.5 (CH), 126.6 (C), 111.7(CH), 61.2 (CH₂), 57.3 (C), 36.0 (CH₂), 32.4 (CH₂), 31.4 (CH₃), 13.9 (CH₃), 2.8 (CH₂), 1.8 (CH₂).

MS (m/z, %): 309 (M, 100), 263 (30), 235 (25), 189 (19), 161 (13).

HRMS calculated for C₁₇H₂₅O₅ 309.1702, found 309.1698.

General procedure for synthesis of **3e** and **3g**, exemplified for **3e**:

To a solution containing Pd₂(dba)₃ (172 mg, 0.19 mmol), PPh₃ (196 mg, 0.75 mmol) and allylcyclopropyltosylate (894 mg, 3.76 mmol) in dioxane (15 mL), stirred for 10 min, was added allylbenzylamine³ (540 mg, 4.08 mmol) dropwise at room temperature and the resulting mixture was stirred for 3 h. After partial removal of the solvent, it was poured into NaHCO₃ (aq) solution and extracted with Et₂O (3x10 mL). The organic phases were dried over sodium sulphate, filtered and concentrated to give a orange crude which was purified by flash chromatography (10 % EtOAc/hexanes) to give **3e** as a yellow oil in a 70% yield

³ Aurrecoechea, J.M.; Fernández, A.; Gorgojo, J.M.; Suero, R. *Synth. Commun.* 693-702, 33, **2003**.

¹H-NMR (δ , ppm): 7.27-7.10 (5H, m), 5.87-5.77 (2H, m), 5.13-5.03 (2H, m), 3.49 (2H, s), 3.13 (2H, d, J = 6.8), 2.99 (2H, m), 1.02-0.92 (4H, m).

¹³C-NMR (δ , ppm): 139.5 (C), 136.1 (CH), 128.9 (CH), 128.8 (CH), 126.7 (CH), 125.0 (C), 117.2 (CH₂), 115.3 (CH), 57.5 (CH₂), 55.5 (CH₂), 54.8 (CH₂), 2.3 (CH₃), 1.9 (CH₃).

Synthesis of **3g-E** (74% yield) ⁴

¹H-NMR (δ , ppm): 7.33-7.20 (5H, m), 5.87 (1H, m), 5.58-5.53 (2H, m), 3.55 (2H, s), 3.20 (2H, d, J = 5.3), 3.01 (2H, m), 1.68 (3H, d, J = 3.9 Hz), 1.05-0.97 (4H, m).

¹³C-NMR (δ , ppm): 139.7 (C), 128.9 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 126.6 (CH), 124.8 (C), 115.4 (CH), 57.5 (CH₂), 55.6 (CH₂), 54.7 (CH₂), 17.81 (CH₃), 2.3 (CH₃), 1.8 (CH₃).

CYCLOADDITION EXPERIMENTS (exemplified for the cycloaddition of substrate **1a-E**)

To a test tube with Pd₂(dba)₃ (14.6 mg, 6 %) was added dioxane (2 mL) and triisopropylphosphite (13.8 μ L, 20 %), or phosphite **8**, according to the table 1 of the main manuscript. After stirring for 5 minutes at room temperature a solution of **1a-E** (90 mg, 0.266 mmol) was added and the reaction mixture was heated under reflux for 6h. The mixture was cooled to room temperature, diluted with Et₂O (8 mL) and filtered through a short pad of silica eluting with Et₂O. The filtrate was concentrated and purified by flash chromatography (60-90 %CH₂Cl₂/hexanes) to afford **4a** as colorless oil (67 mg, 74 %).

¹H-NMR δ (ppm): 4.86 (1H, s), 4.76 (1H, s), 4.17-4.05 (6H, m), 3.09 (1H, m), 2.84 (1H, m), 2.69-2.55 (4H, m), 2.50 (1H, dd, J = 13.6 and 8.4 Hz), 2.05-1.97 (2H, m), 1.22-1.17 (9H, m).

¹³C-NMR δ (ppm): 174.9 (CO), 171.7 (CO), 171.4 (CO), 153.1 (C), 106.7 (CH₂), 62.6 (C), 61.4 (CH₂), 61.3 (CH₂), 60.4 (CH₂), 48.8 (CH), 47.4 (CH), 47.1 (CH), 39.7 (CH₂), 39.5 (CH₂), 37.8 (CH₂), 14.1 (CH₃), 13.90 (CH₃), 13.86 (CH₃).

MS (m/z , %): 339 ([M+1]⁺, 6), 293 (M-OEt, 45), 265 (M-CO₂Et, 66).

HRMS calculated for C₁₈H₂₇O₆ 339.1808, found 339.1799.

⁴ **3e** was prepared from crotylbenzylamine, itself prepared from benzylamine, crotyl chloride and potassium carbonate.

Physical data for 6a:

(Colorless oil, 73% isolated yield). $^1\text{H-NMR}$ δ (ppm): 4.91 (1H, s), 4.81 (1H, s), 4.19-4.13 (6H, m), 3.06 (1H, m), 2.96-2.89 (2H, m), 2.81 (1H, t, J = 13.8 Hz), 2.73 (1H, dd, J = 12.0 and 9.5 Hz), 2.42 (1H, dd, J = 15.7 and 6.7 Hz), 2.27 (1H, dd, J = 12.7 and 7.5 Hz), 1.95 (1H, dd, J = 14.6 and 7.1 Hz), 1.90 (1H, t, J = 12.0 Hz), 1.24-1.16 (9H, m).

$^{13}\text{C-NMR}$ δ (ppm): 173.2 (CO), 171.8 (CO), 171.1 (CO), 153.4 (C), 107.5 (CH_2), 62.0 (C), 61.42 (CH_2), 61.38 (CH_2), 60.4 (CH_2), 47.5 (CH), 45.4 (CH), 45.1 (CH), 41.0 (CH_2), 35.8 (CH_2), 33.1 (CH_2), 14.3 (CH_3), 14.0 (CH_3).

MS (m/z , %): 339 ($[\text{M}+1]^+$, 20), 293 (33), 265 (100), 218 (16), 190 (10).

HRMS calculated for $\text{C}_{18}\text{H}_{27}\text{O}_6$ 339.1808, found 339.1808.

Physical data for 7a:

(Colorless oil). $^1\text{H-NMR}$ δ (ppm): 4.75 (1H, s), 4.70 (1H, d, J = 1.6 Hz), 4.20-4.09 (6H, m), 3.13 (d, J = 16.0 Hz), 2.90 (1H, m), 2.81-2.71 (2H, m), 2.54 (1H, dd, J = 12.8 and 6.5 Hz), 2.46 (1H, J = 12.7 and 6.1 Hz), 2.10 (1H, m), 1.78-1.62 (2H, m), 1.27-1.21 (9H, m).

$^{13}\text{C-NMR}$ δ (ppm): 173.9 (CO), 172.4 (CO), 172.0 (CO), 147.5 (C), 103.6 (CH_2), 64.7 (C), 61.5 (CH_2), 61.4 (CH_2), 60.4 (CH_2), 53.4 (CH), 52.6 (CH), 40.2 (CH), 39.9 (CH_2), 33.4 (CH_2), 32.7 (CH_2), 14.4 (CH_3), 14.0 (CH_3).

Physical data for 4b:

(Colorless oil, 70% isolated yield). $^1\text{H-NMR}$ δ (ppm): 4.89 (1H, d, J = 2.1 Hz), 4.79 (1H, t, J = 1.7 Hz), 4.20-4.08 (4H, m), 3.09 (1H, m), 2.80 (2H, m), 2.70-2.49 (4H, m), 2.16 (3H, s), 2.07-2.01 (2H, m), 1.28-1.19 (6H, m).

$^{13}\text{C-NMR}$ δ (ppm): 209.4 (CO), 171.6 (CO), 171.5 (CO), 153.1 (C), 106.8 (CH), 62.2 (C), 61.5 (CH_2), 57.0 (CH), 47.5 (CH), 45.6 (CH), 40.0 (CH_2), 39.7 (CH_2), 37.1 (CH), 29.0 (CH_3), 14.0 (CH_3).

MS (m/z , %): 309 ($[\text{M}+1]$, 17), 308 (17), 291 (33), 262 (100), 235 (11), 188 (13).

HRMS calculated for $C_{17}H_{25}O_5$ 309.1702, found 309.1707.

Physical data for 4c:

(Slightly yellow oil, 75% isolated yield). **1H -NMR** δ (ppm): 4.99 (1H, d, J = 1.8 Hz), 4.79 (1H, t, J = 1.7 Hz), 4.20-4.10 (4H, m), 3.18 (1H, m), 2.96 (1H, m), 2.80 (1H, m), 2.72 (1H, m), 2.66-2.62 (2H, m), 2.55 (1H, m), 1.27-1.21 (6H, m).

^{13}C -NMR δ (ppm): 171.2 (CO), 150.3 (C), 121.9 (CN), 108.9 (CH₂), 62.2 (C), 61.72 (CH₂), 61.68 (CH₂), 48.5 (CH), 46.9 (CH), 39.7 (CH), 38.9 (CH₂), 38.2 (CH₂), 33.1 (CH₂), 29.0 (CH), 14.0 (CH₃).

MS (m/z , I): 292 ([M+1], 87), 245 (100), 217 (52), 143 (11).

HRMS calculated for $C_{16}H_{22}O_4N$ 292.1549, found 292.1549.

Physical data for 4d:

(Slightly yellow oil, 70% isolated yield). **1H -NMR** δ (ppm): 4.84 (1H, s), 4.77 (1H, s), 4.11-4.02 (6H, m), 2.80-2.76 (2H, m), 2.67 (1H, d, J = 14.6 Hz), 2.63 (1H, t, J = 9.7 Hz), 2.55-2.51 (2H, m), 2.17 (1H, d, J = 14.6 Hz), 2.11 (1H, dd, J = 13.4 and 9.5 Hz), 1.21-1.15 (9H, m), 0.94 (3H, s).

^{13}C -NMR δ (ppm): 173.4 (CO), 172.2 (CO), 171.9 (CO), 151.3 (C), 107.3 (CH₂), 61.6 (C), 61.4 (CH₂), 60.1 (CH₂), 56.8 (CH), 52.1 (CH), 46.1 (CH₂), 40.4 (CH₂), 34.9 (CH), 22.5 (CH₃), 14.3 (CH₃), 14.0 (CH₃).

MS (m/z , I): 353 ([M+1]⁺, 17), 306 (21), 279 (100), 205 (23).

HRMS calculated for $C_{19}H_{29}O_6$ 353.1964, found 353.1962.

Physical data for 4e:

(Colorless oil, 32% isolated yield). **1H -NMR** δ (ppm): 4.84 (1H, s), 4.76 (1H, s), 4.21-4.12 (4H, m), 2.96 (1H, m), 2.68-2.61 (2H, m), 2.49-2.42 (2H, m), 2.26 (1H, m), 1.95-1.73 (4H, m), 1.48 (1H, m), 1.27-1.20 (6H, m).

^{13}C -NMR δ (ppm): 172.1, (CO), 171.7 (CO), 156.3 (C), 105.6 (CH₂), 62.7 (C), 61.3 (CH₂), 47.6 (CH), 43.1 (CH), 40.8 (CH₂), 40.2 (CH₂), 32.6 (CH₂), 30.6 (CH₂), 14.0 (CH₃).

Physical data for 7e:

(Yellow oil, 51% isolated yield). **¹H-NMR** δ (ppm): 4.68 (1H, s), 4.65 (1H, s), 4.19-4.12 (4H, m), 2.73 (1H, m), 2.67-2.45 (3H, m), 2.31 (1H, m), 1.85-1.58 (5H, m), 1.24-1.20 (6H, m).

¹³C-NMR δ (ppm): 172.5 (CO), 149.5 (C), 102.9 (CH₂), 65.5 (C), 61.3 (CH₂), 57.3 (CH), 51.8 (CH), 36.6 (CH₂), 36.3 (CH₂), 33.2 (CH₂), 26.0 (CH₂), 14.0 (CH₃).

Physical data for 5e:

(Yellow oil, 82% isolated yield). **¹H-NMR** δ (ppm): 7.32-7.23 (5H, m), 4.85 (1H, s), 4.73 (1H, s), 3.60 (1H, d, J = 13.0 Hz), 3.51 (1H, d, J = 13.0 Hz), 3.00 (1H, m), 2.80 (1H, t, J = 8.6 Hz), 2.75-2.68 (2H, m), 2.47 (1H, m), 2.36 (1H, dd, J = 9.1 and 5.0 Hz), 2.28-2.20 (2H, m), 1.78 (1H, m), 1.51 (1H, m).

¹³C-NMR δ (ppm): 157.0 (C), 139.3 (C), 128.7 (CH), 128.1 (CH), 126.7 (CH), 104.9 (CH₂), 61.7 (CH₂), 61.2 (CH₂), 60.1 (CH₂), 47.4 (CH), 42.7 (CH), 33.8 (CH₂), 31.2 (CH₂).

MS (m/z , I): 214 ([M+1], 13), 212 (4), 191 (1), 175 (1).

Physical data for 5g:

(Yellow oil, 57% isolated yield). **¹H-NMR** δ (ppm): 7.32-7.23 (5H, m), 4.86 (1H, m), 4.73 (1H, m), 3.60 (1H, d, J = 13.0 Hz), 3.51 (1H, d, J = 13.0 Hz), 3.04 (1H, m), 2.63 (1H, dd, J = 16.1 and 7.8 Hz), 2.58-2.47 (3H, m), 2.39 (1H, dd, J = 9.1 and 4.0 Hz), 2.21 (1H, m), 1.99-1.79 (1H, m), 0.92 (3H, d, J = 6.6 Hz).

¹³C-NMR δ (ppm): 156.3 (C), 139.3 (C), 128.6 (CH), 128.1 (CH), 126.7 (CH), 105.3 (CH₂), 61.1 (CH₂), 60.1 (CH₂), 60.0 (CH₂), 51.1 (CH), 47.0 (CH), 42.7 (CH₂), 38.9 (CH), 20.1 (CH₃).

157.0 (C), 139.3 (C), 128.7 (CH), 128.1 (CH), 126.7 (CH), 104.9 (CH₂), 61.7 (CH₂), 61.2 (CH₂), 60.1 (CH₂), 47.4 (CH), 42.7 (CH), 33.8 (CH₂), 31.2 (CH₂).

Physical data for 1-benzyl-3-(prop-1-en-2-yl)-4-vinylpyrrolidine.

(Yellow oil, 25% isolated yield). **¹H-NMR** δ (ppm): 7.34-7.23 (5H, m), 7.25 (1H, M), 5.71 (1H, ddd, $J = 16.9, 10.2$ and 9.5 Hz), 4.95 (1H, m), 4.90 (1H, s), 4.79 (1H, s), 4.69 (1H, s), 3.66 (s, 2H), 3.11 (1H, dd, $J = 9.2$ and 7.1 Hz) 2.97-2.88 (3H, m), 2.52 (1H, m), 2.26 (1H, dd, $J = 9.5$ and 5.5 Hz), 1.68 (3H, s).

¹³C-NMR δ (ppm): 144.2 (C), 139.1 (C), 138.7 (CH), 128.7 (CH), 128.2 (CH), 126.9 (CH), 114.4 (CH₂), 110.7 (CH₂), 60.7 (CH), 60.1 (CH), 56.7 (CH₂), 48.4 (CH), 44.7(CH), 23.3 (CH₃).

Physical data for 4f:

(Yellow oil, 70% isolated yield). **¹H-NMR** δ (ppm): 7.37-7.18 (5H, m), 4.94 (1H, s), 4.85 (1H, s), 4.23-4.16 (4H, m), 3.25-3.21 (1H, m), 2.96-2.91 (1H, m), 2.87-2.82 (1H, m), 2.77-2.66 (2H, m), 2.61-2.49 (2H, m), 2.14-2.08 (2H, m), 1.26-1.23 (6H, m).

¹³C-NMR δ (ppm): 172.0 (CO), 171.7 (CO), 154.6 (C), 144.4 (C), 128.4 (CH), 127.1 (CH), 126.8 (C), 126.2 (CH), 106.3 (CH₂), 63.0 (C), 61.4 (CH₂), 51.7 (CH), 50.6 (CH), 48.0 (CH), 43.1 (CH₂), 40.2 (CH₂), 39.5 (CH₂), 14.0 (CH₃).

MS (m/z , I): 343 ([M+1], 2), 297 (8), 269 (2).

Procedure for the tandem addition-cyclization reaction of diethylmalonate and allyl cyclopropyltosylate:

To a suspension of NaH (60 mg, 1.50 mmol) in dry dioxane (10 mL) was added dropwise, diethyl malonate (105 μ L, 0.69 mmol). After stirring for 10 min at rt, to this mixture was added other solution containing Pd₂(dba)₃ (37.9 mg, 0.041 mmol), P(O^{*i*}Pr)₃ (35.8 μ L, 0.138 mmol) and allylcyclopropyltosylate (3.90 mg, 1.64 mmol) in dioxane (4 mL), previously stirred for 20 minutes. The resulting mixture was stirred for 1h at rt and refluxed for 5h. The solution was filtered through a short pad of silica, concentrated and purified (EtOAC/hexanes 3 %) to give a **10** and **11** as a colorless oils in 44% and 35% yields, respectively.

Physical data for 10:

(Colorless oil). $^1\text{H-NMR}$ δ (ppm): 4.79 (2H, t, J = 0.8 Hz), 4.20-4.11 (4H, m), 3.15 (1H, m), 2.76 (1H, dd, J = 15.8 and 1.9 Hz), 2.66 (1H, ddd, J = 13.4, 8.8 and 1.8 Hz), 2.31 (1H, ddd, J = 12.9, 7.9 and 1.4 Hz), 2.13 (1H, q, J = 9.2 Hz), 1.98 (2H, m), 1.83 (1H, d, J = 15.8 Hz), 1.26-1.20 (6H, m), 0.52-0.38 (4H, m).

$^{13}\text{C-NMR}$ δ (ppm): 172.1 (CO), 171.5 (CO), 155.2 (C), 106.4 (CH_2), 62.6 (C), 61.70 (CH_2), 61.68 (CH_2), 51.3 (CH), 48.9 (CH), 41.5 (CH_2), 41.3 (CH_2), 38.9 (CH_2), 25.5 (CH_2), 15.8 (CH_2), 14.4 (CH_3), 7.5 (CH_2).

MS (m/z , %): 293 ($[\text{M}+1]^+$, 100), 247 (85), 219 (95), 173 (29), 145 (26).

HRMS calculated for $\text{C}_{17}\text{H}_{25}\text{O}_4$ 293.1753, found 293.1744.

Physical data for 11:

(Colorless oil). $^1\text{H-NMR}$ δ (ppm): 4.69 (2H, s), 4.21-4.12 (4H, m), 2.89 (1H, d, J = 17.1 Hz), 2.65 (1H, m), 2.56 (1H, dd, J = 12.4 and 6.3 Hz), 2.41 (1H, d, J = 17.1 Hz), 2.14-2.08 (2H, m), 1.81 (1H, t, J = 12.2 Hz), 1.43 (1H, m), 1.26-1.21 (m, 6H), 0.62 (1H, m), 0.48 (2H, t, J = 7.5 Hz), 0.19 (1H, m).

$^{13}\text{C-NMR}$ δ (ppm): 172.5 (CO), 172.4 (CO), 149.5 (C), 103.0 (CH_2), 64.5 (C), 61.4 (CH_2), 56.8 (CH), 54.1 (CH), 46.6 (CH_2), 33.5 (CH_2), 32.7 (CH_2), 14.0 (CH_3), 9.1 (CH_2), 7.2 (CH_2).

MS (m/z , %): 293 ($[\text{M}+1]^+$, 100), 247 (82), 219 (81), 173 (21), 145 (20).

HRMS calculated for $\text{C}_{17}\text{H}_{24}\text{O}_4$ 292.1675, found 292.1664.

General procedure for acid-induced isomerizations to the endocyclic alkenes:⁵

A solution of **4a** (34 mg, 0.10 mmol) in 0.5 mL of CDCl_3 (NMR tube) with a few crystals of *p*-toluenesulfonic acid monohydrate was heated at 55 °C. The reaction was monitored by $^1\text{H-RMN}$ until observation of a complete rearrangement (5h). The solution was filtered through a short pad of silica eluting with ether, and the filtrate was concentrated in vacuo to give **14** (28 mg, 84 %).

⁵ Trost, B. M.; Greese, T. A.; Chan D. M. T. *J. Am. Chem. Soc.* **1991**, *113*, 7350.

Physical data for 14:

(Slightly yellow oil). **¹H-NMR** δ (ppm): 5.15 (1H, m), 4.20-4.05 (6H, m), 3.25 (1H, t, J = 2.2 Hz), 3.20 (1H, m), 3.07 (1H, m), 2.50 (1H, dd, J = 13.3 and 9.3 Hz), 2.43 (1H, dd, J = 12.9 and 8.9 Hz), 2.06-2.00 (2H, m), 1.68 (3H d, J = 0.8 Hz), 1.25-1.21 (9H, m).

¹³C-NMR δ (ppm): 174.7 (CO), 171.8 (CO), 171.3 (CO), 145.2 (C), 121.5 (CH), 61.50 (C), 61.47 (CH₂), 61.3 (CH₂), 60.5 (CH₂), 57.2 (CH), 52.8 (CH), 44.1 (CH₂), 41.0 (CH₂), 37.1 (CH₂), 14.9 (CH₃), 14.2 (CH₃), 13.99 (CH₃), 13.93 (CH₃).

MS (m/z , %): 339 ([M+1]⁺, 17), 293 (14), 265 (30).

HRMS calculated for C₁₈H₂₇O₆ 339.1808, found 339.1803.

Physical data for 15:

(Slightly yellow oil, 82% yield). **¹H-NMR** δ (ppm): 5.12 (1H, s), 4.18 (2H, q, J = 7.0 Hz), 4.16-4.08 (4H, m), 3.42 (1H, s), 2.68 (1H, br s), 2.61 (1H, d, J = 14.3 Hz), 2.42 (1H, dd, J = 13.5 and 8.3 Hz), 2.30 (1H, dd, J = 13.5 and 4.5 Hz), 2.25 (1H, d, J = 14.3 Hz), 1.70 (3H, s), 1.28-1.19 (9H, m), 1.10 (3H, s).

¹³C-NMR δ (ppm): 173.8 (CO), 172.3 (CO), 171.5 (CO), 144.9 (C), 122.1 (CH), 61.5 (CH₂), 61.4 (CH), 61.2 (CH), 60.2 (CH₂), 53.1 (C), 49.0 (CH₂), 36.4 (CH₂), 23.9 (CH₃), 15.3 (CH₃), 14.0 (CH₃), 13.9 (CH₃).

EMBR (m/z , %): 353 ([M+1], 41), 307 (48), 306 (46), 280 (100).

EMAR calculated for C₁₉H₂₉O₆ 353.1964, founded 353.1969.

Procedure for the ozonolysis of 4a:

Ozone was bubbled through a solution of **4a** (40 mg, 0.118 mmol) in CH₂Cl₂ (5 mL), at -78°C for 5 min until the solution gets a dark blue color. The consumption of the starting material was easily monitored by TLC. After removing the O₃ source, argon was bubbled through for 10 min to remove excess of O₃. PPh₃ (45mg, 0.17 mmol) was added at -78 °C and the reaction mixture was allowed to slowly reach rt. After aqueous workup and column chromatography (15 % Et₂O/hexanes) **16** was obtained as a colorless oil (38 mg, 95 %).

Physical data for 16:

¹H-NMR δ (ppm): 4.21-4.12 (6H, m), 3.00 (1H, m), 2.93-2.85 (2H, m), 2.67-2.53 (4H, m), 2.32 (1H, dd, $J = 14.3$ and $J = 5.6$ Hz), 2.11 (1H, m), 1.27-1.20 (9H, m).

¹³C-NMR δ (ppm): 217.1 (CO), 174.4 (CO), 171.2 (CO), 171.1 (CO), 61.7(CH₂), 61.26 (C), 61.12 (CH₂), 50.8 (CH), 44.1 (CH), 43.7 (CH), 40.1 (CH₂), 40.0 (CH₂), 35.7 (CH₂), 14.1 (CH₃), 13.9 (CH₃), 13.8 (CH₃).

MS (m/z , %): 341 ([M+1], 100), 295 (90), 267 (30).

HRMS calculated for C₁₇H₂₅O₇ 341.1600, found 341.1611.

STEREOCHEMICAL ANALYSIS OF THE PRODUCTS

The structure of the cycloadducts was determined on the basis of two dimensional NMR experiments (COSY, NOESY, HMBC and HMQC), in addition to standard ^1H , ^{13}C and DEPT experiments. The stereochemistry of the cycloadducts and derivatives was confirmed by NOESY and NOE experiments.

Stereochemistry of 4a:

The *cis*-stereochemistry of the ring-junction was deduced from the observation of NOE between H1 and H5 in **4a**, **14** and **16**. The relative stereochemistry of the carbon alpha to the ester group was assigned upon the observation of NOE between H4 and H6-endo in **14** and NOE (NOESY) between H4 and H8-endo in **16**, as well as the absence of coupling ($J = 0$ Hz) between H4 and H5 in **14**.

Stereochemistry of 6a:

Observation of NOE between H1 and H5 confirms a *cis*-fusion between the rings. NOE between H3-endo and H6-endo confirms that H4-H5 are in *cis*.

Stereochemistry of 7a:

The absence of NOE between H1-H5 and the observation of secondary NOEs indicates *trans* fusion of the ring junction; NOE between H4 and H5 suggests that both hydrogens are in *cis*.

Stereochemistry of 4b:

NOE between H1 and H5 confirms the *cis* fusion of the ring junction and NOE between H4_{endo} and H6_{endo} strongly suggest that both H4 and H5 are in *trans*.

Stereochemistry of 4c:

NOE between H1-H5 show the *cis* fusion of ring junction of this compound. Strong NOE between H4 and H6_{endo} indicates that H4-H5 are in *trans*.

Stereochemistry of 4d:

NOE between H1 and the methyl group in 4d and in the isomerized product 15, confirm the *cis* fusion at the ring junction. The absence of NOE between H4 and Me, and the observation of a strong NOE between H4 and H6_{endo} in the isomerized product 15 confirms the relative stereochemistry of C-4.

Stereochemistry of 6d:

It was not possible to directly determine the stereochemistry of **6d**, but we could do it indirectly on the isomerized product shown below. NOE between H1 and the methyl group confirmed the *cis* fusion of ring junction whereas NOE between H4 and methyl group confirms the relative stereochemistry of C-4 and C-5.

Stereochemistry of 10 and 11:

Both products show a very weak NOE signal between H1-H5 (aprox. 1 %), but observation of NOEs (NOESY) between H1 and H6 β , H5 and H3 α and H5 and H8 α confirmed the *trans* fusion of compound **11**.

Stereochemistry of 4e and 7e:

The stereochemistry of these compounds was assigned by comparison of the spectra with those of other *cis* and *trans*-cycloadducts. The *trans* fusion of **7e** was confirmed by the observation of a NOE (NOESY) between H1 and H6 β .

Stereochemistry of 5e.

Stereochemistry was determined by observation of NOE (NOESY) between H1-H5.

Stereochemistry of 4f.

Stereochemistry was determined by NOE (NOESY) between H1-H5 and the absence of NOE between H4-H5.

Stereochemistry of 5g.

NOE between H1 and H5 confirm the *cis* fusion at the ring junction. NOE (NOESY) between H5-Me and absence of NOE between H5-H4 indicate H5-H4 are in *trans*.

THEORETICAL RESULTS

Calculations were performed with the GAUSSIAN 98 series of programs.⁶ The geometries of all complexes here reported were optimized using density functional theory (DFT) at the generalized gradient approximation using the B3LYP hybrid functional.⁷ The standard 6-31G(d) basis set was used for C, H, O and P. For Pd we used the standard LANL2DZ basis set, which includes a relativistic effective core potential (ECP) and the explicit description of 18 valence electrons by a double- ξ basis set. Harmonic frequencies were calculated at B3LYP level to characterize the stationary points and to determine the zero-point energies (ZPE). The starting approximate geometries for the transition states (TSs) were located graphically. Intrinsic reaction coordinate calculations (IRC) showed that the calculated TSs connect the reagents and the products.

To determine the reaction profile for substrates **1**, we performed density functional calculations (DFT) on 7-cyclopropylidene-2-methylheptenoate (**12**) as a model compound.

Several pathways could be envisaged, but a survey based on computational data showed that paths 1, 2 and 3 are the more favourable ones. All of them involve as initial step the distal insertion of the metal in the cyclopropane to give palladacyclobutane **A**.

Calculations performed on *trans*-alkene **A-(E)** led to a concerted pallada-ene transition state (**TS**₂) which connects intermediates **A-(E)** and **C** and lies 16.4 kcal mol⁻¹ above **A-(E)** (pathway 2, figure 1). Formation of **C** is exothermic (-13.0 kcal mol⁻¹) and the transition state **TS**₂ shows a relatively short distance (2.053 Å) for the C-C bond that is being formed and a larger one for the Pd-C bond that is being formed in the same step (3.208 Å). Initial coordination of Pd with C4 in complex **A-(E)** is also present in intermediate **C**, but previous coordination of Pd to C6 is exchanged by a new coordination Pd-C11 at the same time than the double bond C3-C6 is being formed. Reductive elimination through transition state **TS**₄, which lies 11.0 kcal mol⁻¹ above **A-(E)**, furnishes the cycloadduct **E**, whose stereochemistry is similar to that of the experimental product obtained from **3a-E**.

⁶ M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, N. Rega, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian 98, Revision A.11.3, Gaussian, Inc., Pittsburgh PA, 2002.

⁷ (a) Stephens, P.J.; Devlin, F.J.; Chabalowski, C.F.; Frisch, M.J. *J. Phys. Chem* **1994**, *98*, 11623. (b) Kohn, W.; Becke, A.D.; Parr, R.G. *J. Phys. Chem.*, **1996**, *100*, 12974.

Figure 1. Reaction coordinate for *pathway 2*. Energies are ZPE-corrected energies given in kcal mol⁻¹ and are referred to **A-(E)**. Distances are given in Å.

Remarkably, when the same calculations were performed on the *cis*-alkene **A-(Z)**, we found a more favourable stepwise process (*pathway 3*, figure 2) involving the initial formation of zwitterionic intermediate **D**. The transition state corresponding to the rate determining step (**TS₃**) is only 14.5 kcal mol⁻¹ above **A**, and geometrically it is not very different from **TS₂**. Intermediate **D**, which is 10.4 kcal mol⁻¹ less stable than **A-(Z)**, presents a π-allylic type of coordination on the palladium. This intermediate **D** might evolve to the more stable conformer **F**, in which the Pd atom is coordinated to the oxygen of the enolate. This intermediate is easily converted to the cycloadduct through a barrierless process via the low-energy **TS₅**.

Figure 2. Reaction coordinate for **pathway 3**. Energies are ZPE-corrected energies given in kcal mol^{-1} and are referred to **A-(Z)**. Distances are given in Å.

In addition to *pathways 2* and *3*, an alternative energetic profile was also examined (*pathway 1*, Figure 3). In this pathway, initial distal insertion of the metal into the cyclopropane is followed by isomerization to **G** via a TMM-type transition state (TS_1), which lies $21.4 \text{ kcal mol}^{-1}$ above **A**. Coordination of the double bond to Pd and loss of one of the ligands produces **B**, which could evolve to **H** by way of TS_6 . The considerable activation barrier [$28.7 \text{ kcal mol}^{-1}$ above **A-(Z)**] required for this carbametallation step together with the fact that this mechanism can not justify the stereochemical inversion experimentally observed with *Z*-alkenes, discards this mechanistic hypothesis in favour of those described in *pathways 2* and *3*, in the case of alkenes bearing electron withdrawing groups (**12**).

Figure 3. Reaction coordinate for **pathway 1**. Energies are ZPE-corrected energies given in kcal mol⁻¹ and are referred to **A-(Z)**. Distances are given in Å.

Calculations performed in the case of non-activated alkenes (model **13**), led to a concerted palladaene transition state (**TS_{2,H}**) which connects intermediates **A_H** and **C_H** and lies 27.1 kcal mol⁻¹ above **A_H** (*pathway 2 for non-activated alkenes*, Figure 4). Formation of **C_H** is exothermic (-15.8 kcal mol⁻¹) and the transition state **TS_{2,H}** shows a relatively short distance (2.108 Å) for the C-C bond that is being formed and a larger one for the Pd-C bond that is being formed in the same step (2.469 Å), although this distance is shorter than the observed in the case of activated alkenes [3.184 Å for **A-(Z)** and 3.208 for **A-(E)**]. Reductive elimination from intermediate **C_H** will furnish the final cycloadduct.

Figure 4. Reaction coordinate for *pathway 2 for non-activated alkenes*. Energies are ZPE-corrected energies given in kcal mol⁻¹ and are referred to **A_H**. Distances are given in Å.

An alternative energetic profile was also examined (*pathway 1 for non-activated alkenes*, Figure 5). In this pathway, initial distal insertion of the metal into the cyclopropane is followed by isomerization to **G_H** via a TMM-type transition state (**TS_{1,H}**), which lies 21.0 kcal mol⁻¹ above **A_H**. Coordination of the double bond to Pd and loss of one of the ligands produces **B_H**, which could evolve to **H_H** by way of **TS_{6,H}**. The activation barrier [29.8 kcal mol⁻¹ above **A_H**] required for this carbametallation step is a bit bigger than the rate limiting step for the metallo-ene pathway (27.1 kcal mol⁻¹ above **A_H**), so these data suggest pathways 2 and 1 are competitive, being a little more preferred path 2, the metallo-ene one.

Figure 5. Reaction coordinate for *pathway 1 for non-activated alkenes*. Energies are ZPE-corrected energies given in kcal mol⁻¹ and are referred to A_H. Distances are given in Å.

Remarkably, a stepwise process similar to that founded for the activated alkene (*pathway 3*, figure 2) involving the initial formation of zwitterionic intermediate **D** was not founded for non-activated alkenes which confirms that the presence of the ester group is determining for the formation of these kinds of intermediates.

The energies of the rate-limiting steps of the found pathways for non-activated alkenes [27.1 kcal mol⁻¹ (TS_{2,H}) and 29.8 kcal mol⁻¹ (TS_{6,H}) for A_H] are higher than those found for activated alkenes [16.4 kcal mol⁻¹ for A-(E) and 14.5 kcal mol⁻¹ for A-(Z)], which could explain why non-activated alkenes don't react with the catalytic system Pd₂dba₃/P(OⁱPr)₃ and need another kind of ligand (**8**), which could lower the activation barrier of the rate limiting step of some of these mechanisms.