Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Aminocyclopropanes as precursors of endoperoxides with antimalarial activity

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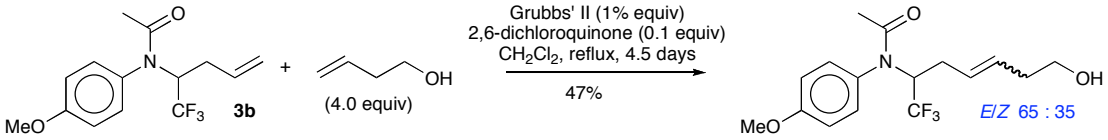
Supplementary Information

Part 1: Preparation of the starting amides **3c–j** and **3m**; method used for the analysis, by NMR spectroscopy, of the crude products of the intramolecular Kulinkovich-de Meijere reactions, as well as the crude oxidation products obtained from the bicyclic aminocyclopropanes; mechanistic considerations; additional results.

I. Preparation of the starting alkenyl amides 3c–j and 3m

• *N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoro-7-hydroxyhept-4-en-2-yl)acetamide

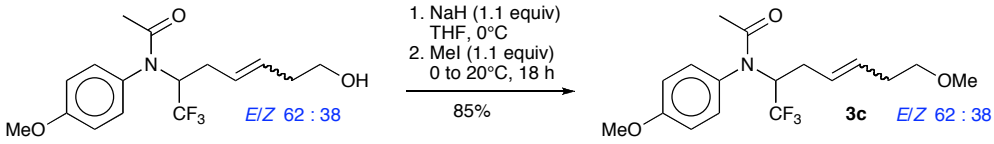


2,6-Dichloro-1,4-benzoquinone (10.0% equiv, 533 μmol, 94.3 mg) and Grubbs II catalyst (1.00% equiv, 53.3 μmol, 45.3 mg) were added to a solution of alkenyl amide **3b** (1.00 equiv, 5.33 mmol, 1.53 g) and but-3-en-1-ol (4.00 equiv, 21.3 mmol, 1.82 mL) in freshly distilled CH_2Cl_2 (27 mL). The mixture was heated at reflux for 4.5 days. After cooling, the reaction medium was concentrated under reduced pressure to afford a green oil. Analysis of the crude product by ^{13}C NMR spectroscopy gave a 65 : 35 estimation for the *E*/*Z* ratio of the diastereoisomeric cross-metathesis products. Purification by flash column chromatography (silica gel, AcOEt/heptane, gradient from 10% to 50%) led to the isolation of pure **3b** (769 mg, 50%), pure *N*-(4-methoxyphenyl)-*N*-(1,1,1-trifluoro-7-hydroxyhept-4-en-2-yl)acetamide (*E*/*Z* 62 : 38, 675 mg, 2.04 mmol, 38%), and a 27 : 73 mixture of *N*-(4-methoxyphenyl)-*N*-(1,1,1-trifluoro-7-hydroxyhept-4-en-2-yl)acetamide and hex-3-ene-1,6-diol (317 mg, 49.1 (9% yield) and 1.33 μmol respectively). In a separate experiment where the same procedure was repeated, the (*E*) and (*Z*) diastereoisomers of the desired cross-coupled product could be separated by a further flash column chromatography (silica gel, AcOEt/heptane, gradient from 40% to 100%).

(*E*)–*N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoro-7-hydroxyhept-4-en-2-yl)acetamide. Pale green oil; ν_{max}/cm^{-1} 3426 (br), 2936, 1659, 1511, 1373, 1292, 1251, 1164, 1129, 1108, 1031, 838, 731; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.80 (3 H, s), 2.16–2.47 (2 H, m), 2.33 (2 H, dt, *J* 7.0, 6.5), 2.72 (1 H, br s, O*H*), 3.67 (2 H, t, *J* 6.5), 3.84 (3 H, s), 5.46–5.70 (3 H, m), 6.84–7.04 (2 H, m), 7.05–7.26 (2 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 22.8, 28.7, 35.8, 54.1 (q, J^2 28.5), 55.3, 61.6, 114.1, 114.6, 124.8 (q, J^1 283.0), 126.5, 130.3, 130.6, 130.8, 131.0, 159.6, 172.6; *m/z* (ES$^+$) 354 (MNa$^+$), 355; *m/z* (ES$^+$) 354.1296 (MNa$^+$ $C_{16}F_3H_{20}NNaO_3$ requires 354.1293).

(*Z*)–*N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoro-7-hydroxyhept-4-en-2-yl)acetamide. Pale green oil; ν_{max}/cm^{-1} 3418 (br), 2934, 1657, 1510, 1372, 1292, 1250, 1164, 1129, 1108, 1030, 838; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.80 (3 H, s), 2.25 (2 H, q, *J* 6.5), 2.26–2.50 (2 H, m), 2.79 (1 H, br s, O*H*), 3.65 (2 H, t, *J* 6.5), 3.84 (3 H, s), 5.45–5.73 (3 H, m), 6.81–7.03 (2 H, m), 7.09 (1 H, m), 7.17 (1 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 22.8, 24.1, 31.1, 54.6 (q, J^2 28.5), 55.2, 61.5, 114.3, 114.6, 124.8 (q, J^1 283.0), 125.9, 129.8, 130.2, 130.7, 131.1, 159.7, 172.6; *m/z* (ES$^+$) 354 (MNa$^+$), 355; *m/z* (ES$^+$) 354.1294 (MNa$^+$ $C_{16}F_3H_{20}NNaO_3$ requires 354.1293).

• *N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoro-7-methoxyhept-4-en-2-yl)acetamide (3c)

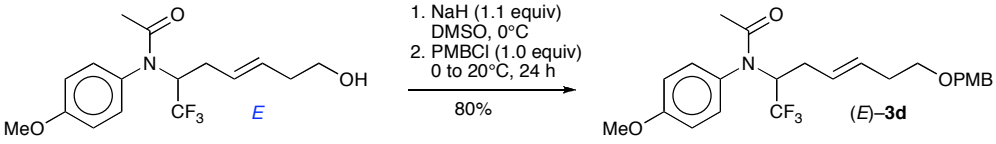


Sodium hydride (60% in oil, 1.10 equiv, 2.24 mmol, 89.6 mg) was carefully added to a solution of *N*-(4-methoxyphenyl)-*N*-(1,1,1-trifluoro-7-hydroxyhept-4-en-2-yl)acetamide (*E*/*Z* 62 : 38, 1.00 equiv, 2.04 mmol, 675 mg) in THF (2.0 mL), at 0°C. Methyl iodide (1.10 equiv, 2.24 mmol, 140 µL) was then added at 0°C, and the mixture was allowed to warm to 20°C and stirred for 18 h. The reaction medium was diluted with Et_2O (15 mL), and 0.3 N HCl aq. soln (15 mL) was added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford a brown oil (686 mg). Analysis of the crude product by ^{13}C NMR spectroscopy gave a 62 : 38 estimation for the *E*/*Z* ratio of the diastereoisomeric products **3c**. Purification by flash column chromatography (silica gel, AcOEt/heptane, gradient from 5% to 50%) allowed the isolation of pure (*Z*)–**3c** (105 mg, 304 µmol, 15%), a mixture of the (*E*) and (*Z*) diastereoisomers of **3c** (363 mg, 1.05 mmol, 52%), and pure (*E*)–**3c** (128 mg, 371 µmol, 18%).

(*E*)–3c. Pale yellow oil; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.80 (3 H, s), 2.13–2.47 (2 H, m), 2.33 (2 H, dt, *J* 7.0, 6.5), 3.34 (3 H, s), 3.43 (2 H, t, *J* 6.5), 3.84 (3 H, s), 5.40–5.75 (3 H, m), 6.80–7.03 (2 H, m), 7.07–7.26 (2 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 22.8, 28.8, 32.8, 53.9 (q, J^2 28.5), 55.2, 58.3, 72.0, 114.1, 114.5, 124.9 (q, J^1 283.0), 125.9, 130.5 (br), 130.7, 131.1, 159.6, 172.2; *m/z* (ES$^+$) 326, 346 (MH$^+$), 368 (MNa$^+$), 369; *m/z* (ES$^+$) 368.1468 (MNa$^+$ $C_{17}F_3H_{22}NNaO_3$ requires 368.1449).

(*Z*)–3c. Pale yellow oil; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.80 (3 H, s), 2.25 (2 H, dt, *J* 7.0 and 6.5), 2.27–2.47 (2 H, m), 3.34 (3 H, s), 3.40 (2 H, t, *J* 6.5), 3.84 (3 H, s), 5.42–5.72 (3 H, m), 6.79–7.03 (2 H, m), 7.08 (1 H, m), 7.17 (1 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 22.9, 24.2, 28.2, 54.4 (q, J^2 29.5), 55.3, 58.5, 71.6, 114.3, 114.6, 124.9 (q, J^1 283.0), 125.6, 129.8, 130.4, 130.9, 131.2, 159.7, 172.3; *m/z* (ES$^+$) 326, 346 (MH$^+$), 365, 368 (MNa$^+$), 369, 567; *m/z* (ES$^+$) 368.1462 (MNa$^+$ $C_{17}F_3H_{22}NNaO_3$ requires 368.1449).

• (*E*)–*N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoro-7-(4-methoxybenzyloxy)hept-4-en-2-yl)acetamide [(*E*)–3d]

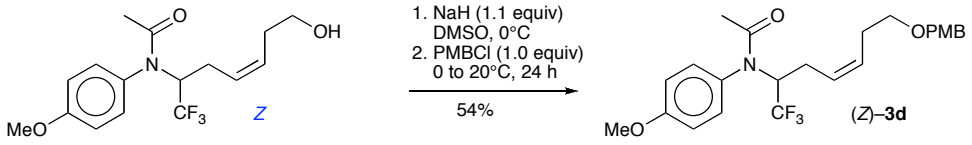


Sodium hydride (60% in oil, 1.10 equiv, 767 µmol, 30.7 mg) was carefully added to a solution of (*E*)–*N*-(4-methoxyphenyl)-*N*-(1,1,1-trifluoro-7-hydroxyhept-4-en-2-yl)acetamide (1.00 equiv, 697 µmol, 231 mg) in DMSO (5.0 mL), at 0°C. *p*-Methoxybenzyl chloride (1.00 equiv, 697 µmol, 94.5 µL) was then added at 20°C, and the mixture was stirred for 24 h. The reaction medium was diluted with Et_2O (50 mL), and water (30 mL) was added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford a yellow oil (313 mg). Purification by flash column chromatography (silica gel, AcOEt/heptane, gradient from 10% to 50%) allowed the isolation of pure (*E*)–**3d** (251 mg, 556 µmol, 80%).

(*E*)–3d. Pale yellow oil; ν_{max}/cm^{-1} 2954, 2926, 2853, 1672, 1510, 1371, 1299, 1247, 1166, 1136, 1107, 1031, 837, 819; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.76 (3 H, s), 2.18 (1 H, ddd, *J* 15.5, 10.5 and 7.0), 2.25–2.46 (1 H, m), 2.36 (2 H, td, *J* 6.5, 6.0), 3.50 (2 H, t, *J* 6.5), 3.79 (3 H, s), 3.81 (3 H, s), 4.44 (2 H, s), 5.40–5.69 (3 H, m), 6.68–6.97 (4 H, m), 7.02–7.19 (2 H, m), 7.19–7.33 (2 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 22.9,

28.8, 33.0, 53.9 (q, J^2 28.5), 55.1, 55.3, 69.5, 72.5, 113.7, 114.1, 114.6, 125.0 (q, J^1 283.0), 125.9, 129.2, 130.4, 130.5, 130.8, 131.1, 159.1, 159.6, 172.3; *m/z* (ES^+) 474 (MNa^+); *m/z* (ES^+) 474.1870 (MNa^+ $C_{24}F_3H_{28}NNaO_4$ requires 474.1868).

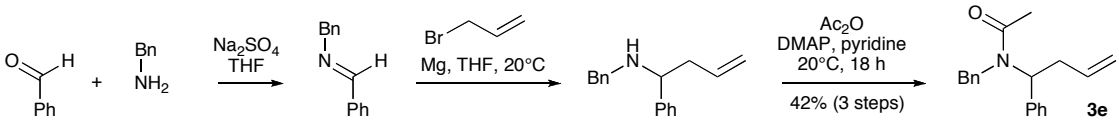
• (*Z*)–*N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoro-7-(4-methoxybenzyloxy)hept-4-en-2-yl)acetamide [(*Z*)–3d]



Sodium hydride (60% in oil, 1.10 equiv, 674 µmol, 27.0 mg) was carefully added to a solution of (*Z*)–*N*-(4-methoxyphenyl)-*N*-(1,1,1-trifluoro-7-hydroxyhept-4-en-2-yl)acetamide (1.00 equiv, 613 µmol, 203 mg) in DMSO (5.0 mL), at 0°C. *p*-Methoxybenzyl chloride (1.00 equiv, 613 µmol, 83.1 µL) was then added at 20°C, and the mixture was stirred for 24 h. The reaction medium was diluted with Et_2O (50 mL), and water (30 mL) was added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford an orange oil (298 mg). Purification by flash column chromatography (silica gel, AcOEt/heptane, gradient from 10% to 50%) allowed the isolation of pure (*Z*)–**3d** (149 mg, 330 µmol, 54%) and starting alcohol (53.4 mg, 161 µmol, 26%).

(*Z*)–3d. Yellow oil; ν_{max}/cm^{-1} 2953, 2923, 2852, 1673, 1510, 1370, 1299, 1247, 1207, 1167, 1134, 1107, 1032, 837, 820; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.79 (3 H, s), 2.26 (2 H, dt, *J* 7.0 and 6.5), 2.26–2.46 (2 H, m), 3.46 (2 H, t, *J* 6.5), 3.78 (3 H, s), 3.80 (3 H, s), 4.44 (2 H, s), 5.48 (1 H, ddd, *J* 11.0, 6.5 and 5.5), 5.53–5.73 (2 H, m), 6.73–6.97 (4 H, m), 7.05 (1 H, m), 7.15 (1 H, m), 7.19–7.30 (2 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 22.9, 24.2, 28.4, 54.3 (q, J^2 30.5), 55.1, 55.3, 68.9, 72.6, 113.7, 114.3, 114.6, 124.9 (q, J^1 284.5), 125.5, 129.1, 129.9, 130.3, 130.9, 131.2, 159.1, 159.6, 172.3; *m/z* (ES^+) 474 (MNa^+); *m/z* (ES^+) 474.1873 (MNa^+ $C_{24}F_3H_{28}NNaO_4$ requires 474.1868).

• *N*-Benzyl-*N*-(1-phenylbut-3-enyl)acetamide (3e)[1]



a) Benzaldehyde (1.00 equiv, 20.0 mmol, 2.03 mL) was added dropwise to a solution of benzylamine (1.00 equiv, 20.0 mmol, 2.18 mL) in THF (50 mL) at 20°C. Na_2SO_4 (about 1 g) was then added. The mixture was stirred for 10 min, and then kept under argon overnight.

b) Activated magnesium turnings[2] (2.00 equiv, 40.0 mmol, 972 mg) were placed in a flask that was flushed with argon, with stirring, for 20 min. Dry THF (50 mL) was added. The solution of imine prepared above was then introduced dropwise via a double-ended needle, at the same time as allyl bromide (1.50 equiv, 30.0 mmol, 2.60 mL), for 6 h. Stirring was continued for 45 h. The mixture was then filtered and cooled to 0°C. 2 N HCl aqueous solution (40 mL) was added. The aqueous phase was separated, and the organic layer was extracted with 2 N HCl aqueous solution (2 x 40 mL). The combined aqueous phases were basified with NaOH pellets until pH ≈ 10, then extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford an orange oil (2.95 g).

c) This crude product was dissolved in pyridine (20 mL). 4-Dimethylaminopyridine (10.0% equiv, 2.00 mmol, 244 mg) was added, and the solution was cooled to 0°C. Acetic anhydride (1.00 equiv, 20.0 mmol, 1.89 mL) was added dropwise, and the mixture was allowed to warm to 20°C after 40 minutes. After 18 h of stirring at 20°C, 1 N NaOH aq. solution (100 mL) and diethyl ether (100 mL) were added. The aqueous layer was separated, and the organic phase was washed successively with water (100 mL), 2 N HCl aq.solution (100 mL) and 1 N HCl aq. solution (100 mL). It was then dried over Na_2SO_4, filtered and concentrated to afford an orange oil (2.56 g)

1– The preparation of this compound was performed by Dr Andrea K. Buzas.

2– Magnesium turnings were activated by several washings with 0.1 N HCl aqueous solution, then with distilled water several times, then with ethanol, and finally with diethyl ether. The turnings were then dried in a dessicator under vacuum, overnight.

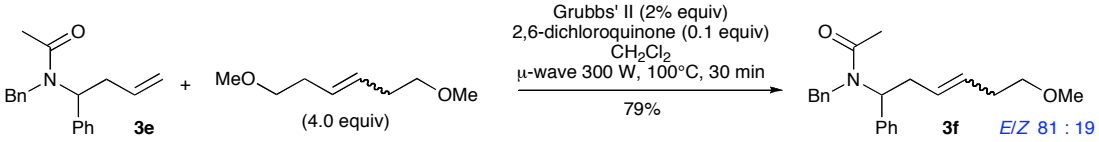
Purification by flash column chromatography (silica gel, AcOEt/heptane, gradient from 2% to 30%) allowed the isolation of pure **3e** (2.36 g, 8.45 mmol, 42%).

3e (2 rotamers 70 : 30). Pale yellow oil (Found: C, 81.7; H, 7.7. Calc. For $C_{19}H_{21}NO$: C, 81.7; H, 7.6%); ν_{max}/cm^{-1} 3029, 1639, 1494, 1451, 1406, 1361, 1326, 1232, 977, 916, 749, 726, 696; *m/z* (ES$^+$) 295, 302 (MNa^+), 303, 348, 438.

3e (major rotamer). δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.00 (3 H, s), 2.66 (2 H, ddt, *J* 8.0, 6.5 and 1.5), 4.33 (2 H, AB system, δ_A 4.27, δ_B 4.39, J_{AB} 17.5), 5.02 (1 H, dq, *J* 10.5 and 1.5), 5.07 (1 H, dq, *J* 17.0 and 1.5), 5.76 (1 H, ddt, *J* 17.0, 10.5 and 6.5), 6.10 (1 H, t, *J* 8.0), 6.85–7.45 (10 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 22.6, 35.1, 47.9, 56.0, 117.2, 126.0, 126.9, 127.6, 128.0, 128.3, 128.5, 134.9, 137.7, 139.1, 171.8.

3e (minor rotamer). δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 2.34 (3 H, s), 4.38 (2 H, AB system, δ_A 3.98, δ_B 4.78, J_{AB} 15.5), 5.65 (1 H, ddt, *J* 17.0, 10.5, 6.5); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) characteristic signals 22.6, 36.1, 45.6, 61.6, 118.2, 126.6, 127.5, 127.8, 134.1, 138.8, 138.9, 171.1.

• ***N*-Benzyl-*N*-(6-methoxy-1-phenylhex-3-enyl)acetamide (3f)**



2,6-Dichloro-1,4-benzoquinone (10.0% equiv, 50.0 μmol, 8.85 mg) and Grubbs II catalyst (2.00% equiv, 10.0 μmol, 8.49 mg) were added to a solution of alkenyl amide **3e** (1.00 equiv, 500 μmol, 140 mg) and 1,6-dimethoxyhex-3-ene[3] (*E*/*Z* 81 : 19, 4.00 equiv, 2.00 mmol, 288 mg) in freshly distilled CH_2Cl_2 (2.5 mL). The mixture was submitted to microwave irradiation using a CEM Discover Microwave Synthesis System (T 100°C, W_{max} 300 W, t 30 min). After cooling, the green reaction medium was concentrated under reduced pressure to afford a green oil (403 mg). Analysis of the crude product by GC/MS gave a 81 : 19 estimation for the *E*/*Z* ratio of the diastereoisomeric products. Purification by flash column chromatography (silica gel, AcOEt/heptane, gradient from 0% to 100%) led to the isolation of pure (*Z*)–**3f** (14.7 mg, 43.5 μmol, 9%), a mixture of both diastereoisomers of **3f** (*E*/*Z* 79 : 21, 41.9 mg, 124 μmol, 25%), and pure (*E*)–**3f** (75.6 mg, 224 μmol, 45%).

(*E*)–3f (2 rotamers 70 : 30). Pale green oil; ν_{max}/cm^{-1} 3028, 2924, 2856, 1643, 1495, 1451, 1407, 1361, 1325, 1114, 1028, 968, 750, 726, 697; *m/z* (ES$^+$) 338 (MH^+), 360 (MNa^+), 361; *m/z* (ES$^+$) 360.1947 (MNa^+ $C_{22}H_{27}NNaO_2$ requires 360.1939).

(*E*)–3f (major rotamer). δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.00 (3 H, s), 2.22 (2 H, td, *J* 6.5 and 6.0), 2.49–2.72 (2 H, m), 3.29 (3 H, s), 3.33 (2 H, t, *J* 6.5), 4.32 (2 H, AB system, δ_A 4.27, δ_B 4.38, J_{AB} 17.5), 5.46 (2 H, AB part of an ABX_2Y_2 system, δ_A 5.44, δ_B 5.48, J_{AB} 15.5, J_{AX} 6.0, J_{AY} 0, J_{BX} 0, J_{BY} 5.5), 6.03 (1 H, t, *J* 8.0), 6.83–7.46 (10 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 22.6, 32.8, 34.1, 48.0, 56.4, 58.4, 72.2, 126.1, 126.9, 127.5, 128.0, 128.2, 128.3, 128.5, 129.5, 137.8, 139.3, 171.8.

(*E*)–3f (minor rotamer). δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 2.33 (3 H, s), 3.33 (2 H, t, *J* 6.5), 4.37 (2 H, AB system, δ_A 3.97, δ_B 4.76, J_{AB} 15.5), 5.01 (1 H, dd, *J* 8.0 and 7.0), 5.33 (2 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) characteristic signals 31.8, 35.0, 45.7, 62.0, 71.9, 126.6, 127.7, 127.9, 130.5, 139.0, 171.2.

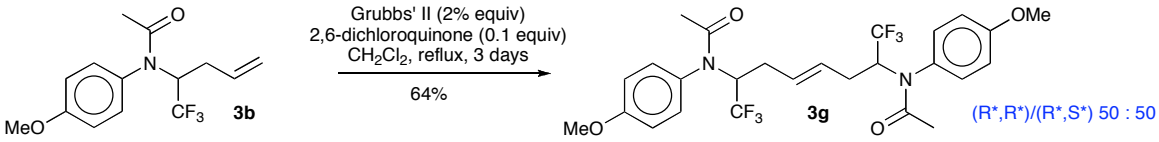
(*Z*)–3f (2 rotamers 70 : 30). Colourless oil; ν_{max}/cm^{-1} 3027, 2924, 2856, 1643, 1495, 1452, 1407, 1362, 1326, 1113, 1028, 974, 750, 727, 697; *m/z* (ES$^+$) 338 (MH^+), 357, 360 (MNa^+), 361, 374; *m/z* (ES$^+$) 360.1944 (MNa^+ $C_{22}H_{27}NNaO_2$ requires 360.1939).

(*Z*)–3f (major rotamer). δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.02 (3 H, s), 2.29 (2 H, td, *J* 6.5 and 5.5), 2.49–2.82 (2 H, m), 3.32 (3 H, s), 3.34 (2 H, t, *J* 6.5), 4.34 (2 H, AB system, δ_A 4.29, δ_B 4.40, J_{AB} 17.5), 5.25–5.55 (2 H, m), 6.01 (1 H, t, *J* 8.0), 6.87–7.45 (10 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 22.7, 28.1, 29.0, 48.2, 56.7, 58.6, 72.0, 126.0, 127.0, 127.6, 127.8, 128.0, 128.4, 128.4, 128.6, 137.8, 139.3, 172.0.

(*Z*)–3f (minor rotamer). δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 2.35 (3 H, s), 4.40 (2 H, AB system, δ_A 4.04, δ_B 4.77, J_{AB} 15.5), 5.04 (1 H, t, *J* 7.0); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) characteristic signals 22.6, 29.6, 45.7, 61.7, 71.8, 126.6, 127.7, 128.0, 128.9, 138.9, 171.3.

3– 1,6-Dimethoxyhex-3-ene was obtained as a side-product in the synthesis of **3h**. See the preparation of this compound for details.

• (*E*)-*N*,*N*'-(1,1,1,8,8,8-Hexafluorooct-4-ene-2,7-diyl)bis(*N*-(4-methoxyphenyl)acetamide) (3g)

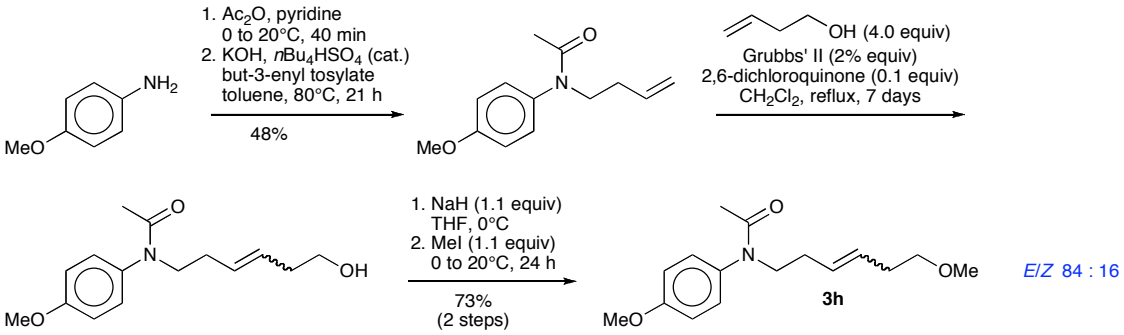


2,6-Dichloro-1,4-benzoquinone (10.0% equiv, 34.8 µmol, 6.2 mg) and Grubbs II catalyst (2.00% equiv, 6.96 µmol, 5.9 mg) were added to a solution of alkenyl amide **3b** (1.00 equiv, 348 µmol, 100 mg) in freshly distilled CH_2Cl_2 (1.8 mL). The mixture was heated at reflux for 3 days. After cooling, the reaction medium was concentrated under reduced pressure to afford a green oil. Purification by flash column chromatography (silica gel, AcOEt/heptane, gradient from 10% to 100%) led to the isolation of pure (*R**,*R**)–**3g** (30.8 mg, 56.3 µmol, 32%) and pure (*R**,*S**)–**3g** (30.6 mg, 55.9 µmol, 32%), as the (*E*) diastereoisomers exclusively.

(*R,*R**)–3g.** Yellowish crystals; ν_{max}/cm^{-1} 2976, 2943, 1666, 1510, 1372, 1295, 1254, 1178, 1144, 1119, 1030, 838, 704; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.79 (6 H, s), 2.34 (4 H, AB part of an ABXY system, δ_A 2.26, δ_B 2.42, J_{AB} 15.5, J_{AX} 11.5, J_{AY} 3.5, J_{BX} 3.0, J_{BY} 3.0), 3.85 (6 H, s), 5.63 (2 H, dd, *J* 3.5 and 3.0), 5.71 (2 H, dqd, *J* 11.5, 8.0 and 3.0), 6.88–7.04 (4 H, m), 7.07–7.23 (4 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 23.1, 28.9, 53.7 (q, J^2 29.5), 55.5, 114.3, 115.1, 124.9 (q, J^1 283.0), 128.1, 130.1, 131.0, 159.9, 172.6; *m/z* (ES^+) 569 (MNa^+), 570; *m/z* (ES^+) 569.1855 (MNa^+ $C_{26}F_6H_{28}N_2NaO_4$ requires 569.1851).

(*R,*S**)–3g.** Colourless crystals; ν_{max}/cm^{-1} 2960, 1667, 1509, 1372, 1302, 1292, 1251, 1192, 1169, 1158, 1128, 1109, 1027, 840; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.82 (6 H, s), 2.35 (4 H, AB part of an ABXY system, δ_A 2.28, δ_B 2.42, J_{AB} 15.5, J_{AX} 10.0, J_{AY} 3.5, J_{BX} 4.5, J_{BY} 3.0), 3.85 (6 H, s), 5.58 (2 H, dd, *J* 3.5 and 3.0), 5.64 (2 H, dqd, *J* 10.0, 8.5 and 4.5), 6.87–6.99 (4 H, m), 6.99–7.10 (2 H, m), 7.11–7.23 (2 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 23.0, 29.2, 53.9 (q, J^2 29.5), 55.5, 114.3, 114.9, 124.9 (q, J^1 283.0), 128.1, 130.3, 130.9, 131.2, 159.8, 172.4; *m/z* (ES^+) 569 (MNa^+), 570; *m/z* (ES^+) 569.1846 (MNa^+ $C_{26}F_6H_{28}N_2NaO_4$ requires 569.1851).

• *N*-(6-Methoxyhex-3-enyl)-*N*-(4-methoxyphenyl)acetamide (3h)



a) Acetic anhydride (1.20 equiv, 7.20 mmol, 681 µL) was added dropwise to a solution of 4-methoxyaniline (1.00 equiv, 6.00 mmol, 739 mg) in pyridine (4.5 mL) at 0°C. The reaction mixture was stirred at 20°C for 40 min, then diluted with diethyl ether (20 mL). The solution was washed successively with 1 N HCl aq. soln (20 mL) and 1 M NaOH aq. soln (20 mL), then dried over Na_2SO_4, filtered and concentrated to afford the crude *N*-(4-methoxyphenyl)acetamide (766 mg, 4.64 mmol, 77%) as a brown solid.

b) Potassium hydroxide (powdered, 2.00 equiv, 7.58 mmol, 425 mg) and tetra-*n*-butylammonium hydrogenosulfate (5.00% equiv, 190 µmol, 64.3 mg) were added successively to a suspension of crude *N*-(4-methoxyphenyl)acetamide prepared as described above (1.00 equiv, 3.79 mmol, 625 mg) in toluene (10 mL). The mixture was stirred at 20°C for 1 h, then heated to 80°C. After 10 min, but-3-enyl benzenesulfonate (1.00 equiv, 3.79 mmol, 626 mg) was added and the reaction medium was stirred for 21 h at 80°C. After cooling, the mixture was diluted with Et_2O (20 mL) and 1 N HCl aq. soln (20 mL). The organic layer was seprated, and the aqueous phase extracted with Et_2O (2 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford a purple oil (705 mg). Purification by flash column chromatography (EtOAc / heptane, gradient from 20% to 50%) yielded pure *N*-(but-3-enyl)-*N*-(4-methoxyphenyl)acetamide (522 mg, 2.38 mmol, 63%)

***N*-(But-3-enyl)-*N*-(4-methoxyphenyl)acetamide.** Yellow oil; ν_{max}/cm^{-1} 2961, 2932, 1651, 1508, 1442, 1394, 1290, 1244, 1212, 1181, 1169, 1030, 914, 837; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.81 (3 H, s), 2.27 (2 H,

tdt *J* 7.5, 7.0 and 1.5), 3.74 (2 H, t, *J* 7.5), 3.83 (3 H, s), 5.02 (1 H, dq, *J* 10.0 and 1.5), 5.05 (1 H, dq, *J* 17.0 and 1.5), 5.76 (1 H, ddt, *J* 17.0, 10.0 and 7.0), 7.01 (4 H, AA'BB' system,[4] δ_A 6.93, δ_B 7.08, *N* 9.0, *L* 8.5, *K* 5.5 (*M* could not be measured accurately)); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 22.6, 32.0, 48.1, 55.3, 114.6, 116.4, 129.1, 135.3, 135.6, 158.8, 170.5; *m/z* (ES^+) 242 (MNa^+), 255, 271; *m/z* (ES^+) 242.1146 (MNa^+ $C_{13}H_{17}NNaO_2$ requires 242.1157).

c) 2,6-Dichloro-1,4-benzoquinone (10.0% equiv, 220 µmol, 38.9 mg) and Grubbs II catalyst (2.00% equiv, 44.0 µmol, 37.4 mg) were added to a solution of *N*-(but-3-enyl)-*N*-(4-methoxyphenyl)acetamide (1.00 equiv, 2.20 mmol, 483 mg) and but-3-en-1-ol (4.00 equiv, 8.81 mmol, 754 µL) in CH_2Cl_2 (11 mL). The mixture was heated at reflux for 7 days. After cooling, the reaction medium was concentrated under reduced pressure to afford a green oil. Purification by flash column chromatography (silica gel, AcOEt/heptane, gradient from 10% to 50%, then MeOH/AcOEt, gradient from 0% to 10%) led to the isolation of starting amide (126 mg, 575 µmol, 26%), and a 72 : 28 mixture of hex-3-en-1,6-diol and *N*-(6-hydroxyhex-3-enyl)-*N*-(4-methoxyphenyl)acetamide (788 mg, 3. 61 and 1.40 mmol respectively).

d) Sodium hydride (60% in oil, 4.31 equiv, 9.48 mmol, 632 mg) was added portion-wise to a solution of the previously obtained mixture of alcohols (788 mg) in THF (9.0 mL), at 0°C. Iodomethane (4.31 equiv, 9.48 mmol, 590 µL) was then added at 0°C, and the mixture was stirred for 23 h. The reaction medium was diluted with Et_2O (20 mL), and 0.3 N HCl aq. soln (20 mL) was added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford a brown oil (1.03 g). Analysis of the crude product by ^{13}C NMR spectroscopy gave a 82 : 18 estimation for the *E*/*Z* ratio of the diastereoisomeric products **3h**. Purification by flash column chromatography (silica gel, AcOEt/heptane, gradient from 30% to 50%) allowed the isolation of pure 1,6-dimethoxyhex-3-ene (*E*/*Z* 81 : 19 as estimated by ^{13}C NMR spectroscopy, 469 mg, 3.25 mmol, 74% over two steps from but-3-en-1-ol) and pure **3h** (*E*/*Z* 84 : 16 as estimated by GC/MS, 446 mg, 1.61 mmol, 74% over two steps from *N*-(but-3-enyl)-*N*-(4-methoxyphenyl)acetamide).

1,6-Dimethoxyhex-3-ene (*E*/*Z* 81 : 19). Yellow oil; ν_{max}/cm^{-1} 2923, 2897, 2859, 2824, 1460, 1451, 1381, 1192, 1114, 1061, 996, 967.

(*E*)–1,6-Dimethoxyhex-3-ene. δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.28 (4 H, tdd, *J* 7.0, 4.0 and 1.5), 3.32 (6 H, s), 3.39 (4 H, t, *J* 7.0), 5.51 (2 H, AB part of an $ABX_2X'_2$ system, δ_A 5.50, δ_B 5.51, J_{AX} 4.0, J_{BX} 1.5 (J_{AB} could not be measured accurately)); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 32.8, 58.3, 72.3, 128.3.

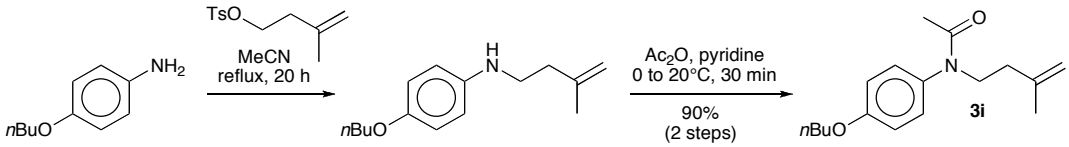
(*Z*)–1,6-Dimethoxyhex-3-ene. δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 2.34 (4 H, tdd, *J* 6.5, 4.5 and 1.0), 3.33 (6 H, s); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 27.7, 58.3, 72.1, 127.5.

3h (*E*/*Z* 84 : 16). Pale green oil; ν_{max}/cm^{-1} 2954, 2923, 2853, 1657, 1509, 1444, 1395, 1291, 1245, 1114, 1031, 968, 837; *m/z* (ES^+) 297, 300 (MNa^+), 301; *m/z* (ES^+) 300.1564 (MNa^+ $C_{16}H_{23}NNaO_3$ requires 300.1576).

(*E*)–3h. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.80 (3 H, s), 2.12–2.36 (4 H, m), 3.31 (3 H, s), 3.37 (2 H, t, *J* 6.5), 3.71 (2 H, t, *J* 7.5), 3.82 (3 H, s), 5.34–5.54 (2 H, m), 7.00 (4 H, AA'BB' system,[4] δ_A 6.92, δ_B 7.08, *N* 8.5, *L* 8.5, *K* 5.5 (*M* could not be measured accurately)); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 22.5, 30.8, 32.7, 48.4, 55.2, 58.2, 72.2, 114.5, 128.5, 128.6, 129.0, 135.6, 158.7, 170.3.

(*Z*)–3h. δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 3.30 (3 H, s), 3.36 (2 H, t, *J* 6.5), 3.69 (2 H, t, *J* 7.5); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) characteristic signals 25.7, 27.7, 72.0, 127.7, 127.8, 129.0.

• *N*-(4-Butoxyphenyl)-*N*-(3-methylbut-3-enyl)acetamide (3i)



a) A solution of *para*-butoxyaniline (3.00 equiv, 15.0 mmol, 2.50 mL) and 3-methylbut-3-enyl 4-methylbenzenesulfonate[5] (1.00 equiv, 5.00 mmol, 1.20 g) in acetonitrile (5.0 mL) was heated at reflux for 20 h. The reaction medium was diluted with Et_2O (0.10 L), and 1 M NaOH aq. soln (40 mL) was added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (50 mL). The combined organic layers were

4– H. Günther, *Angew. Chem.*, 1972, **84**, 907–920; *Angew. Chem. Int. Ed.*, 1972, **11**, 861–874.

5– 3-Methylbut-3-enyl 4-methylbenzenesulfonate was prepared in 82% yield from 3-methylbut-3-en-1ol under standard tosylation conditions (TsCl and pyridin in chloroform). δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.66 (3 H, s), 2.34 (2 H, t, *J* 7.0), 2.44 (3 H, s), 4.12 (2 H, t, *J* 7.0), 4.67 (1 H, br s), 4.78 (1 H, br s), 7.34 (2 H, d, *J* 8.5), 7.78 (2 H, d, *J* 8.5); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 21.5, 22.2, 36.6, 68.4, 113.0, 127.7, 129.7, 133.1, 140.0, 144.6.

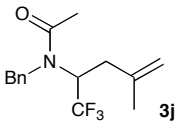
dried over Na_2SO_4, filtered and concentrated to afford a brown oil (2.91 g), containing only starting *para*-butoxyaniline and 4-butoxy-*N*-(3-methylbut-3-enyl)aniline.

4-Butoxy-*N*-(3-methylbut-3-enyl)aniline. δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 0.95 (3 H, t, *J* 7.5), 1.74 (3 H, s), 2.32 (2 H, t, *J* 6.5), 3.16 (2 H, t, *J* 6.5), 3.88 (2 H, t, *J* 6.5), 4.78 (1 H, br s), 4.84 (1 H, br s), 6.67 (4 H, AA'BB' system,[4] δ_A 6.56, δ_B 6.77, *N* 9.0, *L* 8.5, *K* 6.0 (*M* could not be measured accurately)); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 13.8, 19.2, 21.9, 31.5, 37.4, 42.3, 68.4, 112.2, 114.1, 115.7, 142.5, 143.0, 151.6.

b) This crude product (2.91 g) was dissolved in pyridine (12 mL). Acetic anhydride (4.00 equiv, 20.0 mmol, 1.89 mL) was added dropwise at 0°C. The mixture was stirred at 20°C for 30 min, and then diluted with CH_2Cl_2 (0.15 L). The solution was washed successively with 1 M NaOH aq. soln (0.10 L), water (0.10 L), 1 N HCl aq. soln (2 × 0.10 L), and water (0.10 L). The organic layer was separated, and the aqueous phase was extracted with Et_2O (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to afford a brown solid. Purification by flash column chromatography (silica gel, AcOEt/heptane, gradient from 10% to 100%) allowed the isolation of pure amide **3i** (1.24 g, 4.50 mmol, 90% over two steps from the tosylate).

3i. Yellow oil (Found: C, 74.2; H, 9.3. Calc. For $C_{17}H_{25}NO_2$: C, 74.1; H, 9.1%); ν_{max}/cm^{-1} 2958, 2933, 2872, 1657, 1509, 1446, 1395, 1296, 1243, 111191, 1170, 974, 888, 835; δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.99 (3 H, t, *J* 7.5), 1.51 (2 H, sext, *J* 7.5), 1.70 (3 H, s), 1.79 (2 H, tt, *J* 7.5 and 6.5), 1.81 (3 H, s), 2.21 (2 H, t, *J* 7.5), 3.79 (2 H, t, *J* 7.5), 3.98 (2 H, t, *J* 6.5), 4.68 (1 H, s), 4.75 (1 H, s), 6.98 (4 H, AA'BB' system,[4] δ_A 6.91, δ_B 7.06, *N* 9.0, *L* 8.5, *K* 5.5 (*M* could not be measured accurately)); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 13.7, 19.2, 22.4, 22.7, 31.2, 35.6, 47.3, 67.9, 111.5, 115.1, 129.1, 135.5, 142.9, 158.4, 170.5; *m/z* (ES^+) 264, 276 (MH^+), 277, 298 (MNa^+), 573 (M_2Na^+).

• *N*-Benzyl-*N*-(1,1,1-trifluoro-4-methylpent-4-en-2-yl)acetamide (3j)



3j

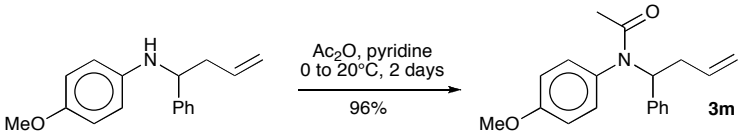
The acetamide **3j** was prepared by acetylating *N*-benzyl-1,1,1-trifluoro-4-methylpent-4-en-2-amine[6] under standard conditions (acetic anhydride at reflux).

3j (2 rotamers 90 : 10). Yellow oil; ν_{max}/cm^{-1} 2975, 1660, 1406, 1290, 1271, 1222, 1180, 1154, 1122, 1099, 967, 899, 729, 695; *m/z* (ES^+) 286 (MH^+), 308 (MNa^+); *m/z* (ES^+) 308.1225 (MNa^+ $C_{15}F_3H_{18}NNaO$ requires 308.1238).

3j (major rotamer). δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.70 (3 H, s), 2.00 (3 H, s), 2.35–2.60 (2 H, m), 4.57 (2 H, AB system, δ_A 4.53, δ_B 4.62, J_{AB} 18.0), 4.83 (1 H, s), 4.88 (1 H, s), 5.80 (1 H, br s), 7.15–7.41 (5 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 21.9, 22.1, 33.8, 47.8, 51.5 (q, J^2 29.5), 113.7, 125.3 (q, J^1 283.0), 125.7, 127.2, 128.6, 136.9, 139.6, 173.3.

3j (minor rotamer). δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 1.64 (3 H, s), 2.28 (3 H, s); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) characteristic signals 20.5, 34.0, 45.6, 58.1 (q, J^2 29.5), 114.6, 126.7, 127.1, 128.1, 137.6, 138.4, 171.9.

• *N*-(4-Methoxyphenyl)-*N*-(1-phenylbut-3-enyl)acetamide (3m)



3m

Acetic anhydride (4.00 equiv, 29.7 mmol, 2.81 mL) was added dropwise at 0°C to a solution of 4-methoxy-*N*-(1-phenylbut-3-enyl)aniline[7] (1.00 equiv, 7.42 mmol, 1.88 g) in pyridine (5.4 mL). The mixture was stirred at 20°C for 2 days, and then diluted with CH_2Cl_2 (50 mL). The solution was washed successively with 1 M NaOH aq. soln (50 mL), water (50 mL), 1 N HCl aq. soln (2 × 50 mL), and water (50 mL). The

6– J. Legros, F. Meyer, M. Coliboeuf, B. Crousse, D. Bonnet-Delpon and J.-P. Bégué, *J. Org. Chem. Soc.*, 2003, **68**, 6444–6446 ; and supporting information.

7– 4-Methoxy-*N*-(1-phenylbut-3-enyl)aniline was prepared in 75% yield, by applying the protocol described in the following paper: R. Fan, D. Pu, L. Qin, F. Wen, G. Yao, J. Wu, *J. Org. Chem.*, 2007, **72**, 3149–3151.

organic layer was dried over Na_2SO_4, filtered and concentrated to afford a yellow oil (2.19 g). Purification by flash column chromatography (silica gel, AcOEt/heptane, gradient from 10% to 50%) allowed the isolation of pure amide **3m** (2.10 g, 7.11 mmol, 96%).

3m.[8] Viscous yellow oil; ν_{max}/cm^{-1} 2957, 2931, 2837, 1650, 1508, 1384, 1315, 1291, 1245, 1030, 913, 834, 733, 699; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.74 (3 H, s), 2.47–2.70 (2 H, m), 3.78 (3 H, s), 5.09 (1 H, dq, *J* 10.5 and 1.5), 5.16 (1 H, dq, *J* 17.0 and 1.5), 5.85 (1 H, ddt, *J* 17.0, 10.5 and 6.5), 6.05 (1 H, br s), 6.27 (1H, t, *J* 8.0), 6.66 (1 H, br s), 6.82, (1 H, br s), 7.00–7.44 (6 H, m); δ_H(300 MHz; CD_3CN; Me_4Si) 1.65 (3 H, s), 2.61 (2 H, m), 3.74 (3 H, s), 5.06 (1 H, dq, *J* 10.5 and 1.5), 5.15 (1 H, dq, *J* 17.5 and 1.5), 5.84 (1 H, ddt, *J* 17.0, 10.5 and 6.5), 6.11 (1H, t, *J* 8.0), 6.77 (4 H, br s), 7.05–7.18 (2 H, m), 7.18–7.32 (3 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 23.2, 35.0, 55.3, 55.9, 113.8, 117.3, 127.5, 128.0, 128.7, 131.2 (br s), 131.4, 135.1, 139.6, 159.0, 170.8; *m/z* (ES^+) 296 (MH^+), 318 (MNa^+), 319, 462, 613 (M_2Na^+), 614; *m/z* (ES^+) 318.1464 (MNa^+ $C_{19}H_{21}NNaO_2$ requires 318.1470).

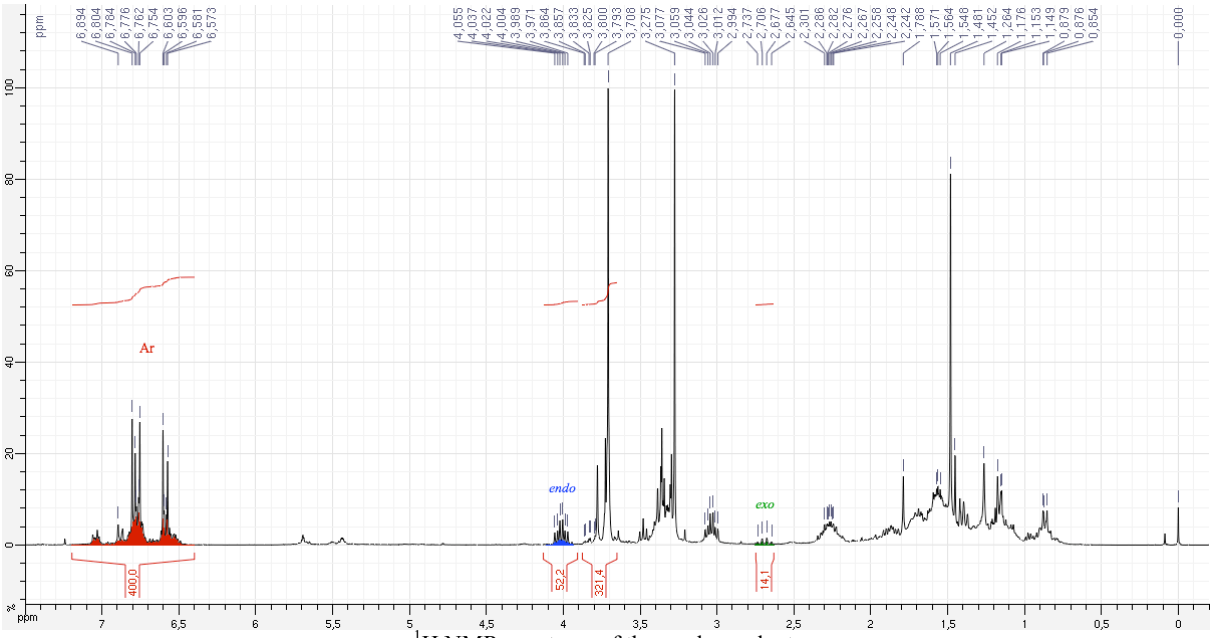
II. Analysis of the crude products by NMR spectroscopy

The following method was used to estimate the yields and the diastereoisomeric ratios of the intramolecular Kulinkovich-de Meijere reactions, as well as the aerobic electrochemical oxidation reactions.

The crude products were analysed by ^{1}H NMR spectroscopy. Proton signals were chosen as internal references. Typically, these signals were associated with functional groups that were common to all the compounds in solution, with the requirement that they did not overlap with the signals of other kinds of protons. The aromatic protons could usually play this role, provided the signal of chloroform was not too intense or did not overlap with them. The amounts of the products could then be assessed by integrating characteristic isolated signals. The values obtained gave access to an estimation of the yields and the diastereoisomeric ratios.

The diastereoisomeric ratios could also be measured by ^{13}C analysis of the crude products: the peak intensities of chosen carbon nuclei were measured for each diastereoisomer.

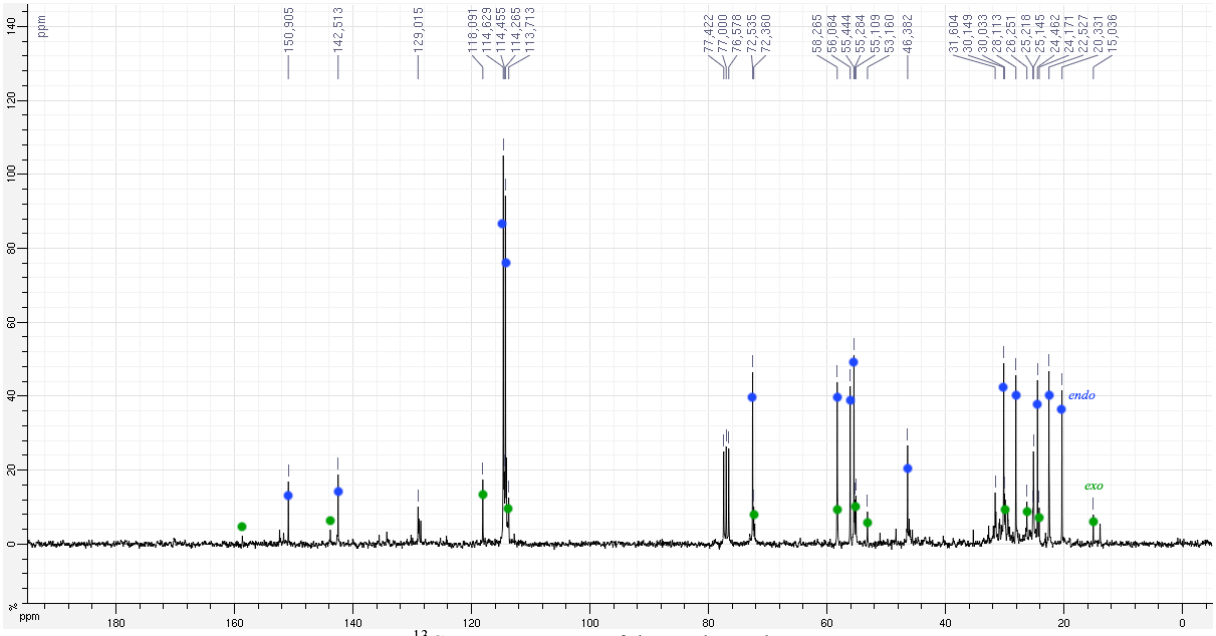
Example 1: Kulinkovich-de Meijere intramolecular cyclopropanation of **3h** (*E*/*Z* 84 : 16).



^{1}H NMR spectrum of the crude product.

8– L. Y. Vargas M., M. V. Castelli, V. V. Kouznetsov, J. M. Urbina G., S. N. López, M. Sortino, R. D. Enriz, J. C. Ribas, S. Zacchino, *Bioorg. Med. Chem.*, 2003, **11**, 1531–1550.

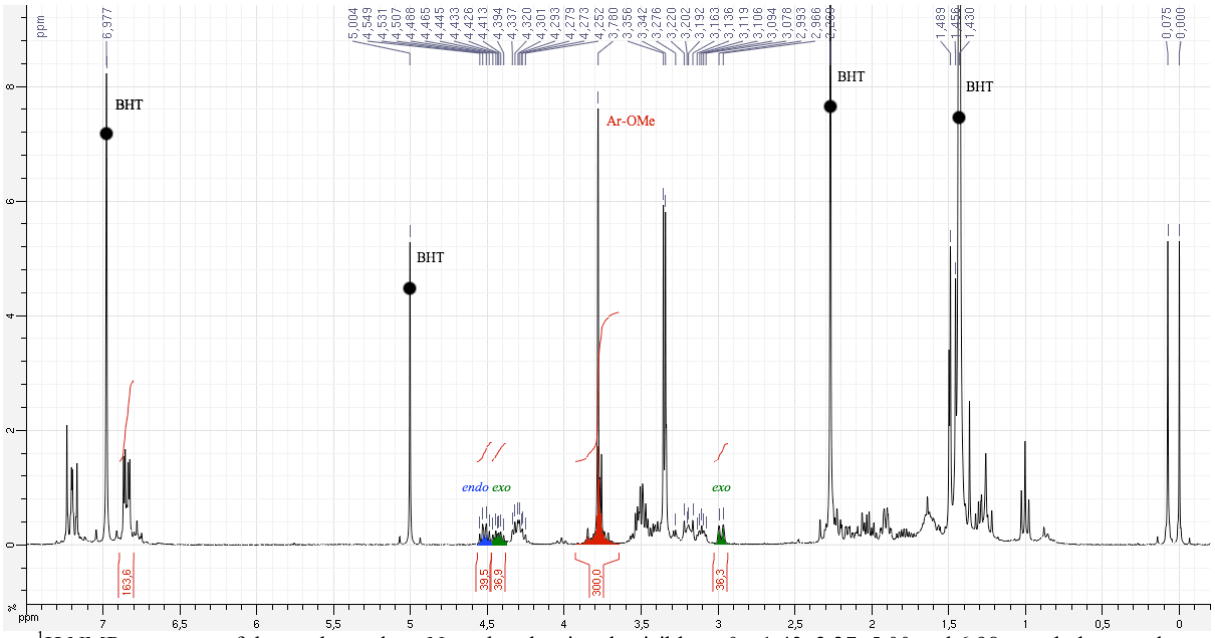
• Integral of the *Ar*-O-CH_3 signals set at 400 (4 protons).
• Integral for one proton of the major *endo* diastereoisomer, measured at the isolated signal displayed in blue: 52.2.
• Integral for one proton of the minor *exo* diastereoisomer, measured at the isolated signal displayed in green: 14.1.
• Estimated yield = 52.2 + 14.1 = **66.3%**. Estimated *endo*/*exo* ratio = **79 : 21**.



^{13}C NMR spectrum of the crude product.

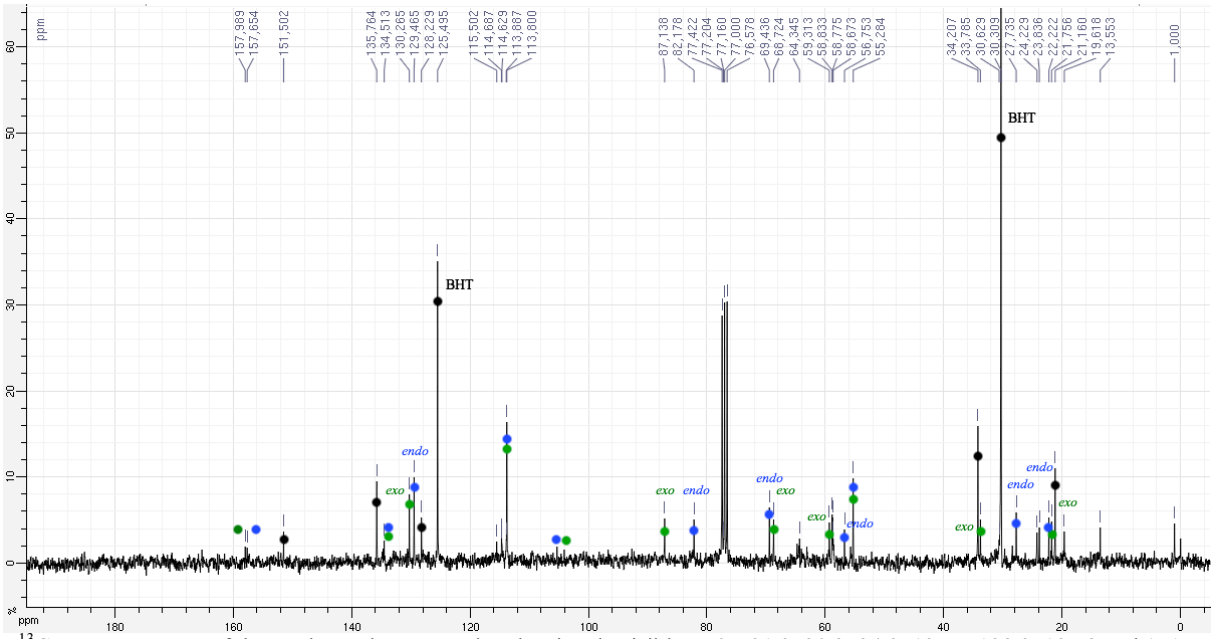
• Estimated *endo*/*exo* ratio, measured at the signals at 20.5 and 15.2 ppm = 84 : 16.
• Estimated *endo*/*exo* ratio, measured at the signals at 142.7 and 144.0 ppm = 82 : 18.
• Mean ratio = **83 : 17**.

Example 2: aerobic electrochemical oxidation of **2c**–*exo* (*cis* / *trans* 92 : 8).



^{1}H NMR spectrum of the crude product. Note that the signals visible at δ = 1.43, 2.27, 5.00 and 6.98 ppm belong to the stabiliser BHT (2,6-di-*tert*-buty-4-methyl-phenol), contained in the diethyl ether used during the work-up.

• Integral of the Ar-O-CH_3 signals set at 300 (3 protons).
• Integral for one proton of the major *endo* diastereoisomer, measured at the isolated signal displayed in blue: 39.5.
• Integral for one proton of the minor *exo* diastereoisomer, measured at the isolated signals displayed in green (mean value): 36.6.
• Estimated yield = 39.5 + 36.6 = **76.1%**. Estimated *endo*/*exo* ratio = **52 : 48**.



^{13}C NMR spectrum of the crude product. Note that the signals visible at δ = 21.2, 30.3, 34.2, 125.5, 128.2, 135.8 and 151.5 ppm belong to the stabiliser BHT (2,6-di-*tert*-buty-4-methyl-phenol), present in the diethyl ether used during the work-up.

• Estimated *endo*/*exo* ratio, measured at the signals at 22.2 and 21.8 ppm = 52 : 48.
• Estimated *endo*/*exo* ratio, measured at the signals at 27.7 and 33.8 ppm = 53 : 47.
• Estimated *endo*/*exo* ratio, measured at the signals at 69.4 and 68.7 ppm = 56 : 44.
• Estimated *endo*/*exo* ratio, measured at the signals at 82.2 and 87.1 ppm = 49 : 51.
• Estimated *endo*/*exo* ratio, measured at the signals at 129.5 and 130.3 ppm = 55 : 45.
• Mean ratio = **53 : 47**.

III. Mechanistic considerations

Molecular mechanics calculations were performed using the Avogadro 0.9.5 software; web-site: http://avogadro.openmolecules.net/

The UFF force field was employed, using the steepest descent or conjugate gradients algorithms. For each round of calculations, the number of iterations was set at 10000, with a convergence criterion of 10^{-7}. During the optimisation process, conformers with lower energy values were systematically looked for, most often by direct manipulation of the structures using the editing tools or, sometimes, *via* the "random conformer search" procedure of the software.

It should be noted that, although we believe the geometries obtained by this crude calculation method provide a reasonably realistic view of the structures of the species involved, the energy values of these optimised geometries cannot be considered reliable at this level of calculation. Nonetheless, they can provide valuable qualitative information, since important differences in energy values can certainly reflect significant differences in ring strain or internal constraints due to steric effects.

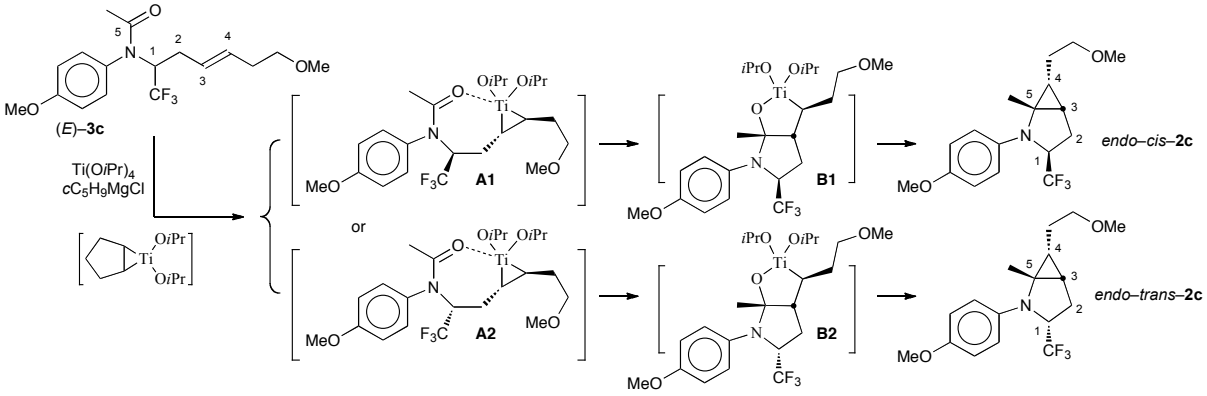
In this preliminary study, the role of the solvent was not considered.

III.1. Diastereoselectivity of the intramolecular Kulinkovich-de Meijere reactions

The case of the transformation of the alkenylamides (*E*)– and (*Z*)–**3c** (R^1 = *p*(OMe)C_6H_4, $R^2 = CF_3$, R^3 = CH_2CH_2OMe) into the corresponding aminocyclopropanes **2c** was chosen as a representative example.

• *Intramolecular cyclopropanation of (E)–**3c***

After coordination of the substrate to the titanium atom by a ligand exchange mechanism, which is assumed to proceed with retention with respect to the original configuration of the olefin moiety, two possible titanacyclopropane diastereoisomers **A1** and **A2** can be formed depending on the face selectivity of this elementary step. It is assumed that these intermediates cyclise irreversibly, with retention of configuration, delivering the oxatitanacyclopentane complexes **B1** and **B2** respectively, that eventually lead to the formation of the aminocyclopropanes *endo–cis–***2c** and *endo–trans–***2c**. The elementary steps of this final transformation are (i) the cleavage of a carbon–oxygen bond, assisted by the lone pair of the nitrogen atom; (ii) the rotation of a carbon–carbon bond in the resulting zwitterionic intermediate, in such a way as to adopt a conformation with a "M" (or "W") shape that is suitable for the cyclopropane ring closure; and (iii) the formation of the three-membered ring *via* a S_E2(back) mechanism.[9] Thus, **A1** is expected to give *endo–cis–***2c** diastereospecifically, and **A2** is expected to give *endo–trans–***2c**.

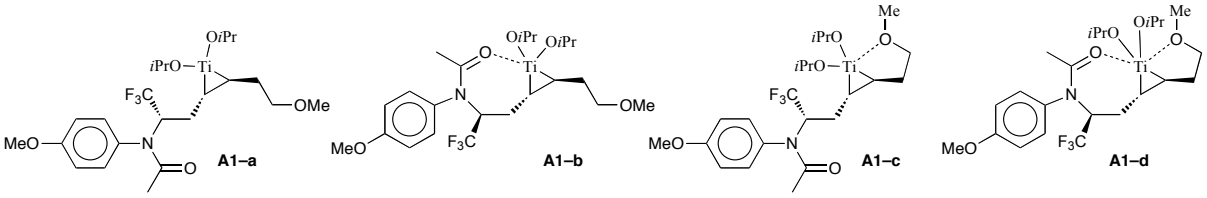


9– N. Ouhamou and Y. Six, *Org. Biomol. Chem.*, 2003, **1**, 3007–3009.

A1 and A2:

First of all, we wanted to get insight into the possibility of an equilibrium between the two titanacyclopropane diastereoisomers **A1** and **A2**. We also needed to determine how favourable, in these complexes, an internal coordination of the titanium atom with the amide or the methoxy groups was.

■ For **A1**, four structures were envisaged: **A1–a**, where the titanium atom is coordinated neither by the amide group, nor by the methoxy group; **A1–b**, where the titanium atom is coordinated by the methoxy group only; **A1–c**, where the titanium atom is coordinated by the methoxy group only; and **A1–d**, where the titanium atom is coordinated by both the amide and the methoxy groups.



The geometry of **A1–a** was optimised after 90 rounds of calculations, with an energy value of 1368.6 kJ.mol^{-1}.

To model **A1–b**, a single bond was drawn between the carbonyl oxygen atom and the titanium centre, with a positive charge (+1) on the oxygen atom and a negative charge (–1) on the titanium atom. The length of this Ti–O bond was constrained at 2.20 Å. This value lies between the length of a fully covalent bond (around 1.98 Å as calculated by us with the Avogadro software) and the distance separating a titanium atom and a ketone oxygen atom coordinated with it (around 2.39 Å as calculated by Wu and Yu).[10] The geometry was optimised after 23 rounds of calculations, with an energy value of 2655.2 kJ.mol^{-1}.

For **A1–c**, a single bond was drawn between the methoxy oxygen atom and the titanium centre, with a positive charge (+1) on the oxygen atom and a negative charge (–1) on the titanium atom. The length of this Ti–O bond was constrained at 2.20 Å. The geometry was optimised after 18 rounds of calculations, with an energy value of 2570.2 kJ.mol^{-1}.

For **A1–d**, single bonds were drawn between the amide oxygen atom and the titanium centre, and between the methoxy oxygen atom and the titanium atom, with a positive charge (+1) on each oxygen atom, and a negative charge (–2) on the titanium atom. The lengths of both Ti–O bonds were constrained at 2.20 Å. The geometry was optimised after 14 rounds of calculations, with an energy value of 2332.4 kJ.mol^{-1}.

These results suggest that the least coordinated **A1–a** is by far the most stable structure, possibly because extra coordination of the metal centre induces steric repulsion between the ligands. Interestingly, however, the double–coordinated structure **A1–d** is found to be more favourable than the mono-coordinated structures **A1–b** and **A1–c**.

■ In Kulinkovich-de Meijere reactions with ligand exchange, such as our intramolecular reactions, the ligand exchange step is considered to be reversible. In most of the examples that can be found in the literature and that involve the use of cyclic Grignard reagents (a *cyclo*-pentylmagnesium or a *cyclo*-hexylmagnesium halide), the substrate is a monosubstituted olefin, and it is usually assumed that the equilibrium is driven in the desired sense because the reverse process would be an unfavourable ligand exchange with a disubstituted olefin (cyclopentene or cyclohexene). In the present case, the substrate is the disubstituted olefin (*E*)–**3c**. To get insight into the formation of **A1**, calculations were carried out on the starting alkenyl amide (*E*)–**3c**, di*iso*propyloxy(η^2-cyclopentene)titanium, and cyclopentene.

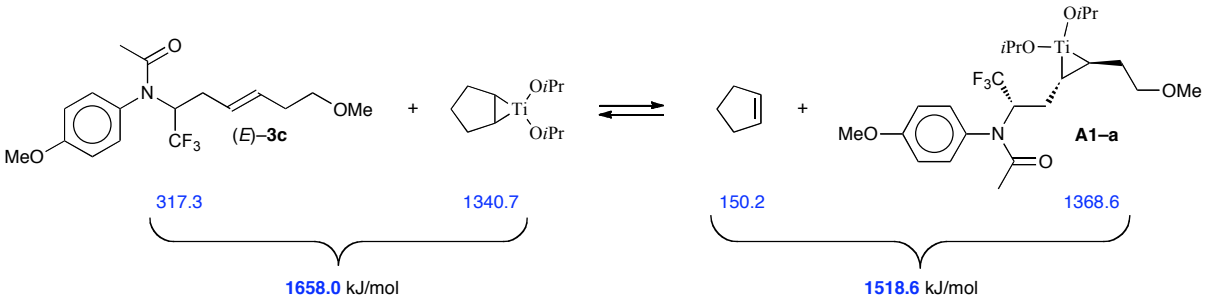
The geometry of (*E*)–**3c** was optimised after 9 rounds of calculations, with an energy value of 317.3 kJ.mol^{-1}.

The geometry of di*iso*propyloxy(η^2-cyclopentene)titanium was optimised after 7 rounds of calculations, with an energy value of 1340.7 kJ.mol^{-1}.

10– Y.-D. Wu and Z.-X. Yu, *J. Am. Chem. Soc.*, 2001, **123**, 5777–5786.

The geometry of cyclopentene was optimised after 6 rounds of calculations, with an energy value of 150.2 kJ.mol^{-1}.

The ligand exchange reaction is displayed below.



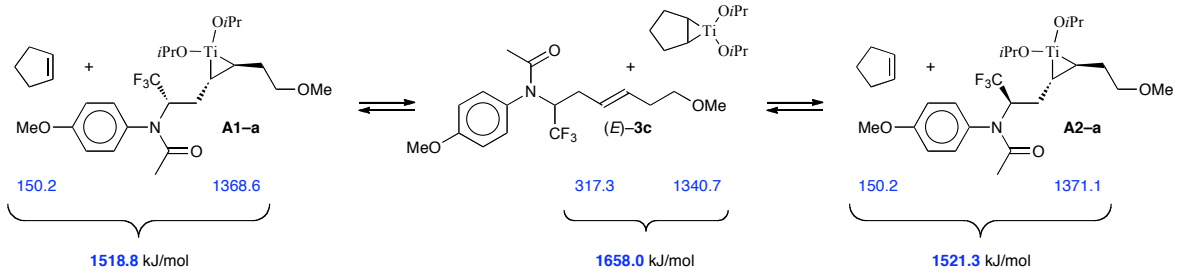
The calculation results suggest that the formation of **A1** is favourable, but the energy difference between the reactants and the products is relatively low. Although a more relevant information would be the energy of the transition state of this transformation,[11] the equilibrium can thus be considered as reversible on the time-scale of the reaction. Indeed, our calculations suggest that the regeneration of (*E*)–**3c** and di*iso*propyloxy(η^2-cyclopentene)titanium from **A1** and cyclopentene is less energetically costly than the internal coordination of the titanium atom in **A1** by the methoxy or the amide groups.

■ For **A2**, similar calculations were performed as in the case of **A1**. We directly assumed, by analogy, that the most stable structure would be **A2–a**, with no internal coordination of the titanium atom with the amide or the methoxy functions.

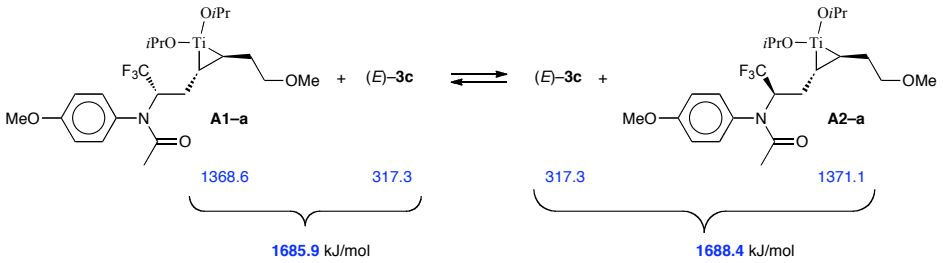
The geometry of **A2–a** was optimised after 60 rounds of calculations, with an energy value of 1371.1 kJ.mol^{-1}.

As a verification, the geometries of **A2–b** and **A2–d** were optimised after 86 and 72 rounds of calculations, with higher energy values of 2730.5 and 2433.7 kJ.mol^{-1}, respectively.

■ The energy difference between **A1** and **A2** is thus found to be insignificant, which supports the hypothesis that these species are in equilibrium under the reaction conditions.



Moreover, the two diastereoisomers **A1** and **A2** could also interconvert directly by ligand exchange with residual substrate (*E*)–**3c** present in the solution.



11– To our knowledge, the mechanism of ligand exchange processes has not been elucidated so far.

B1 and B2:

For the complexes **B1** and **B2**, four structures were considered: **B1–a** and **B2–a**, without internal coordination of the titanium atom by the methoxy group; and **B1–b** and **B2–b**, with coordination of the titanium atom by the methoxy group.

■ For **B1–a** and **B2–a**, the starting geometries were constructed by modifying the optimised structures of **A1–b** and **A2–b**, and no constraints were applied during the calculations.

The geometry of **B1–a** was optimised after 31 rounds of calculations, with an energy value of 722.2 kJ.mol^{-1}.

The geometry of **B2–a** was optimised after 27 rounds of calculations, with an energy value of 534.4 kJ.mol^{-1}.

■ For **B1–b**, the starting geometry was constructed by modifying the optimised structures of **B1–a**. A single bond was drawn between the methoxy oxygen atom and the titanium centre, with a positive charge (+1) on the oxygen atom and a negative charge (–1) on the titanium atom. The length of this Ti–O bond was constrained at 2.20 Å.

The geometry of **B1–b** was optimised after 53 rounds of calculations, with an energy value of 999.1 kJ.mol^{-1}.

The geometry of **B2–b** was not optimised. By analogy with the results obtained with **B1–a** and **B1–b**, its energy value was assumed to be much higher than that of **B2–a**.

A1B1–TS and A2B2–TS:

Finally, calculations were performed to model the transitions states **A1B1–TS** and **A2B2–TS** of the transformations converting **A1** into **B1** and **A2** into **B2** respectively. Again, structures without internal coordination of the titanium atom by the methoxy group (**A1B1–TS–a** and **A2B2–TS–a**), and with this internal coordination (**A1B1–TS–b** and **A2B2–TS–b**) were considered.

■ For **A1B1–TS–a** and **A2B2–TS–a**, the starting geometries were constructed by modifying the optimised structures of **A1–b** and **A2–b**. A single bond was drawn between the carbonyl oxygen atom and the titanium centre, with a positive charge (+1) on the oxygen atom and a negative charge (–1) on the titanium atom. The length of the developing C–C bond was constrained at 2.10 Å, and the distance between the carbon and the titanium atoms in the breaking C–Ti bond was constrained at 2.40 Å.[10]

The geometry of **A1B1–TS–a** was optimised after 4 rounds of calculations, with an energy value of 3580.8 kJ.mol^{-1}.

The geometry of **A2B2–TS–a** was optimised after 2 rounds of calculations, with an energy value of 3792.9 kJ.mol^{-1}.

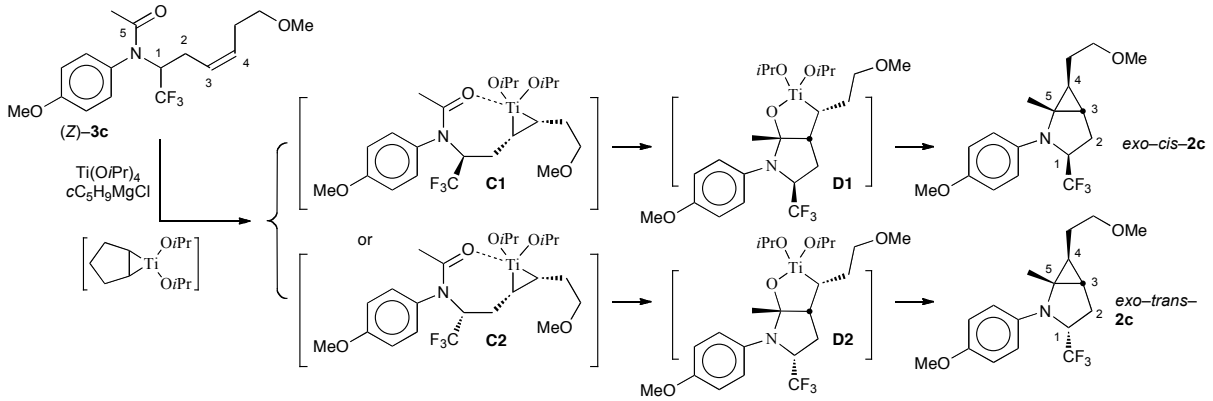
■ For **A1B1–TS–b** and **A2B2–TS–b**, the starting geometries were constructed by modifying the optimised structures of **A1–d** and **A2–d**. Single bonds were drawn between the amide oxygen atom and the titanium centre, and between the methoxy oxygen atom and the titanium atom, with a positive charge (+1) on each oxygen atom, and a negative charge (–2) on the titanium atom. The length of the Ti–O(Me) bond was constrained at 2.20 Å. The length of the developing C–C bond was constrained at 2.10 Å, and the distance between the carbon and the titanium atoms in the breaking C–Ti bond was constrained at 2.40 Å.[10]

The geometry of **A1B1–TS–b** was optimised after 57 rounds of calculations, with an energy value of 3228.6 kJ.mol^{-1}.

The geometry of **A2B2–TS–a** was optimised after 8 rounds of calculations, with an energy value of 3307.8 kJ.mol^{-1}.

• *Intramolecular cyclopropanation of (Z)–**3c***

Similarly to the case of (*E*)–**3c**, the coordination of (*Z*)–**3c** to the titanium atom, by a ligand exchange mechanism, can give two possible titanacyclopropane diastereoisomers **C1** and **C2**, and these are expected to lead diastereospecifically to the corresponding aminocyclopropanes *exo–cis*–**2c** and *exo–trans*–**2c** respectively, *via* the intermediates **D1** and **D2**.



The geometries and energy values of **C1**, **D1**, **C2**, **D2**, and of the transition states **C1D1–TS** and **C2D2–TS** were calculated using the same methods as for **A1**, **B1**, **A2**, **B2**, **A1B1–TS** and **A2B2–TS**.

C1 and C2:

For **C1** and **C2**, we expected that the structures **C1–a** and **C2–a**, where the titanium centre is not coordinated by the amide and methoxy groups, would be the most stable, as for **A1** and **A2**.

The geometry of **C1–a** was optimised after a total of 19 rounds of calculations, with an energy value of 1374.6 kJ.mol^{-1}.

The geometry of **C2–a** was optimised after a total of 83 rounds of calculations, with an energy value of 1381.2 kJ.mol^{-1}.

Nevertheless, some alternative structures were calculated, all giving higher energy values indeed. The geometry of **C1–b** (internal coordination by the amide group) was optimised after a total of 30 rounds of calculations, with an energy value of 2638.3 kJ.mol^{-1}. The geometry of **C2–b** was optimised after a total of 19 rounds of calculations, with an energy value of 2785.9 kJ.mol^{-1}. The geometry of **C1–d** (internal coordination by both the amide and methoxy groups) was optimised after a total of 40 rounds of calculations, with an energy value of 2316.2 kJ.mol^{-1}. The geometry of **C2–d** was optimised after a total of 69 rounds of calculations, with an energy value of 2374.9 kJ.mol^{-1}.

D1 and D2:

The geometry of **D1–a** (without internal coordination of the titanium atom by the methoxy group) was optimised after a total of 14 rounds of calculations, with an energy value of 715.5 kJ.mol^{-1}.

The geometry of **D2–a** was optimised after a total of 17 rounds of calculations, with an energy value of 539.1 kJ.mol^{-1}.

As a verification, the geometry of **D2–b** (with internal coordination of the titanium atom by the methoxy group) was optimised after a total of 3 rounds of calculations, with an energy value of 894.2 kJ.mol^{-1}, much higher than that of **D2–a**.

C1D1–TS and C2D2–TS:

The geometry of the transition state **C1D1–TS–a** (without internal coordination of the titanium atom by the methoxy group) was optimised after 6 rounds of calculations, with an energy value of 3599.1 kJ.mol^{-1}.

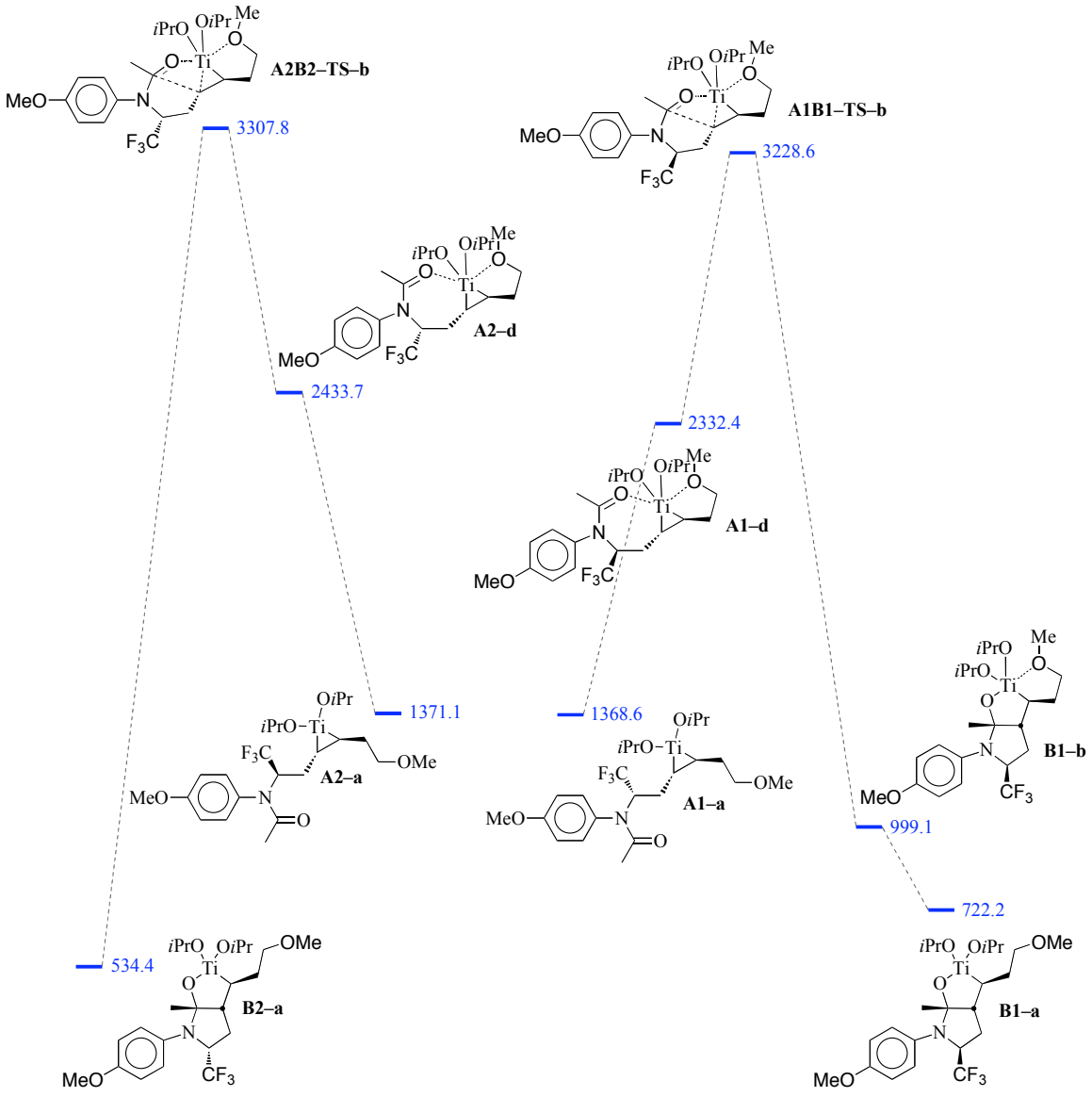
The geometry of **C2D2–TS–a** was optimised after 7 rounds of calculations, with an energy value of 3791.1 kJ.mol^{-1}.

The geometry of **C1D1–TS–b** (with internal coordination of the titanium atom by the methoxy group) was optimised after 40 rounds of calculations, with an energy value of 3154.8 kJ.mol^{-1}.

The geometry of **C2D2–TS–b** was optimised after 6 rounds of calculations, with an energy value of 3435.5 kJ.mol^{-1}.

• *Discussion*

For the transformation of (*E*)–**3c**, the energy profile is displayed below.



• The energy of the transition state **A1B1–TS** is lower than that of **A2B2–TS**. This seems to result from a destabilisation of **A2B2–TS**, caused by the steric repulsion between the CF_3 group and the O*i*Pr ligands of the titanium centre.

• The activation energy of the transformation of **A1** into **B1** [*E*(**A1B1–TS**) – *E*(**A1**)] is lower than that of the transformation of **A2** into **B2** [*E*(**A2B2–TS**) – *E*(**A2**)] (1860 vs 1937 $kJ.mol^{-1}$).

• The formations of the intermediates **B1** and **B2** can be considered to be irreversible, since the energies of **B1** and **B2** are considerably lower than those of **A1** and **A2**.

• It is noteworthy that the intermediate **B2**, leading to the *minor* aminocyclopropane diastereoisomer *endo–trans–***2c** is more stable than **B1**, that leads to the *major* aminocyclopropane diastereoisomer *endo–cis–***2c**. The main reason for this appears to be a better conjugation of the aromatic ring with the lone pair of the nitrogen atom in **B2**. In **B1**, the conformation of the aromatic ring is almost orthogonal to the lone pair of the nitrogen atom because of the steric repulsion of the CF_3 group.

In the light of these features, we have considered two hypotheses.

■ Either (hypothesis 1), once formed, **A1** and **A2** cannot convert into one another (or very slowly).

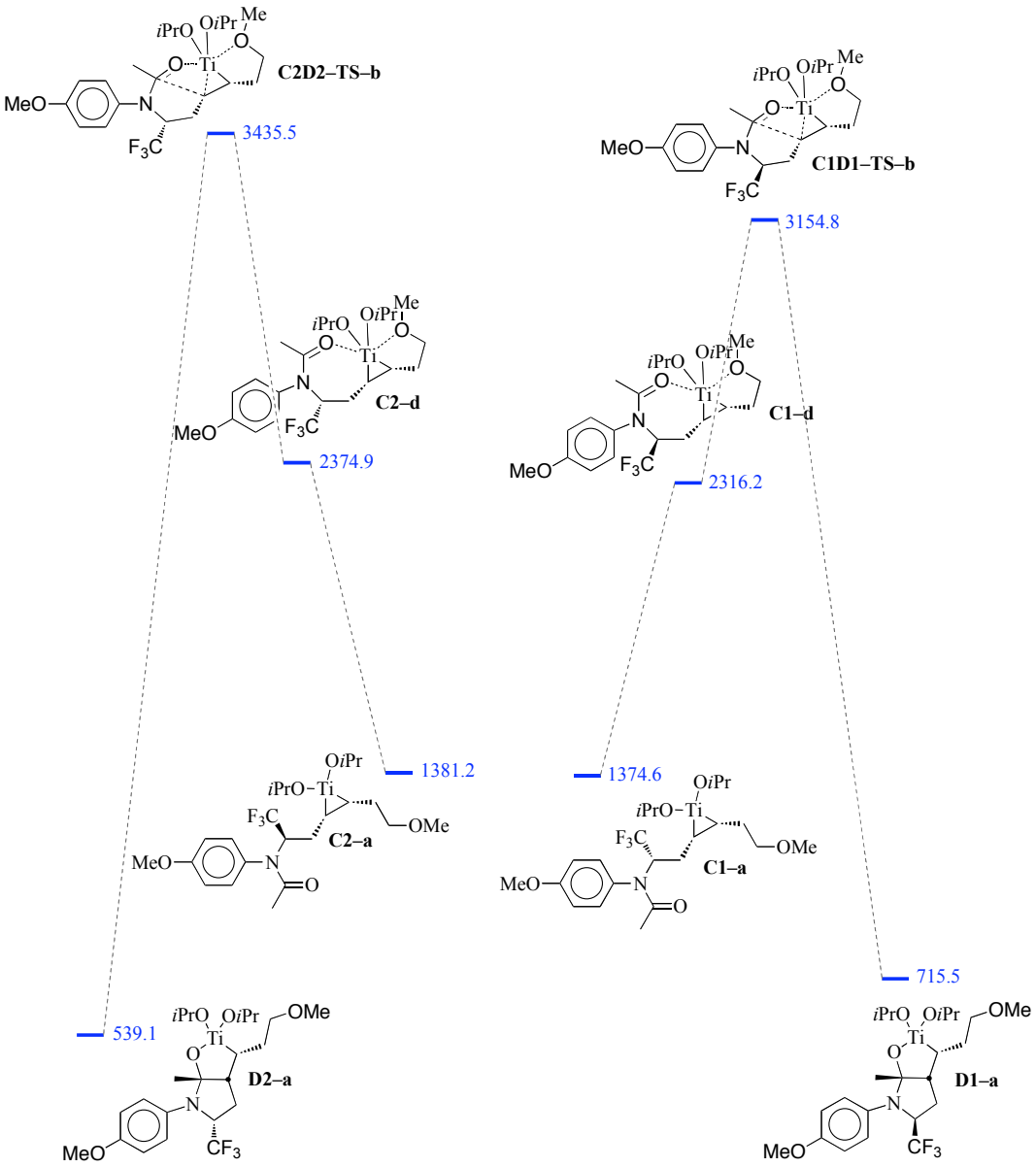
In this situation, the diastereoselectivity would be readily explained by a preferential formation of **A1** over **A2**, and the experimental ratio between the diastereoisomers of the products *endo–cis–***2c** and *endo–trans–***2c** would directly reflect this preference. This hypothesis is perhaps less likely, because the calculated energies of the optimised geometries of **A1** and **A2** are similar, and alkene-ligand exchange processes are considered to be essentially reversible in Kulinkovich-type reactions. It could nonetheless be valid if the activation energy of the transformation of (*E*)–**3c** into **A2** is significantly higher than the activation energy of the transformation of (*E*)–**3c** into **A1**, and in the same range or higher than the activation energies of the transformations leading to **B1** and **B2**. Further work would be needed to clarify this point. Indeed, the elementary steps of the mechanisms of the reactions converting (*E*)–**3c** into **A1** or **A2** are not known, and the mechanism of the possible equilibrium of **A1** and **A2** has not been investigated.

■ Or (hypothesis 2), an equilibrium between the two species **A1** and **A2** takes place.

This situation is supported by our calculations (see further above). The two titanacyclopropanes **A1** and **A2** have close energy values. The diastereoselectivity can then be rationalised by a faster reaction of **A1**. This is consistent with the energy profile, since the activation energy for the transformation leading to the intermediate **B1** is the lowest. We feel that this explanation is the most likely, and it is worth noting that it parallels the proposition formulated by Cha et al. to account for the diastereoselectivity observed in the case of the related Kulinokovich reaction of homoallyl alcohol substrates.[12]

For the transformation of (*Z*)–**3c**, the calculated energy profile is shown hereafter. It is analogous to that obtained for the reaction of (*E*)–**3c** except, interestingly, for the difference between the energy values of the transitions states **C1D1–TS** and **C2D2–TS** (3435.5 – 3154.8 = 280.7 $kJ.mol^{-1}$), which is clearly higher than the difference obtained in the case of (*E*)–**3c** (3307.8 – 3228.6 = 79.2 $kJ.mol^{-1}$). In the context of the most likely hypothesis 2, this is highly consistent with the experimental results: the diastereoisomer ratio of the aminocyclopropane products is 76 : 24 starting from (*E*)–**3c**, and 93 : 7 starting from (*Z*)–**3c**.

12– L. G. Quan, S.-H. Kim, J. C. Lee and J. K. Cha, *Angew. Chem.*, 2002, **114**, 2264–2266 ; *Angew. Chem., Int. Ed.*, 2002, **41**, 2160–2162.



*III.2. The lack of reactivity of the diamide **3g** under the cyclopropanation reaction conditions*

Calculations were carried out in the case of the reaction of the (*R**,*R**) diastereoisomer of **3g** with di*iso*propyloxy(η^2-cyclopentene)titanium, the titanacyclopropane initially formed from Ti(O*i*Pr)$_4$ and *c*C$_5$H$_9$MgCl.

Two types of reactions were considered: the simple coordination of the titanacyclopropane by the diamide **3g**, acting as a ligand; and ligand exchange processes, with the departure of the cyclopentene ligand.

• *The reactants*

The geometry of (*R**,*R**)–**3g** was optimised after a total of 22 rounds of calculations, with an energy value of 531.30 kJ.mol^{-1}.

The geometry of di*iso*propyloxy(η^2-cyclopentene)titanium was optimised after a total of 7 rounds of calculations, with an energy value of 1340.69 kJ.mol^{-1}.

• *Coordination of the complex diisopropyloxy(η^2-cyclopentene)titanium by (R*,R*)–**3g***

Coordination by one of the two amide groups of (*R**,*R**)–**3g**:

The geometry of the resulting complex was optimised after a total of 34 rounds of calculations, with an energy value of 2707.47 kJ.mol^{-1}.

Coordination by both amide groups of (*R**,*R**)–**3g**:

The geometry of the resulting complex was optimised after a total of 19 rounds of calculations, with an energy value of 2345.60 kJ.mol^{-1}.

• *Ligand exchange of the cyclopentene ligand with the diamide (R*,R*)–**3g***

Formation of a complex where the Ti(O*i*Pr)$_2$ moiety is coordinated by the two amide groups only:

The geometry of this complex was optimised after a total of 46 rounds of calculations, with an energy value of 910.35 kJ.mol^{-1}.

Formation of a complex where the Ti(O*i*Pr)$_2$ moiety is coordinated by the alkene group only:

The geometry of this titanacyclopropane complex was optimised after a total of 127 rounds of calculations, with an energy value of 1799. 87 kJ.mol^{-1}.

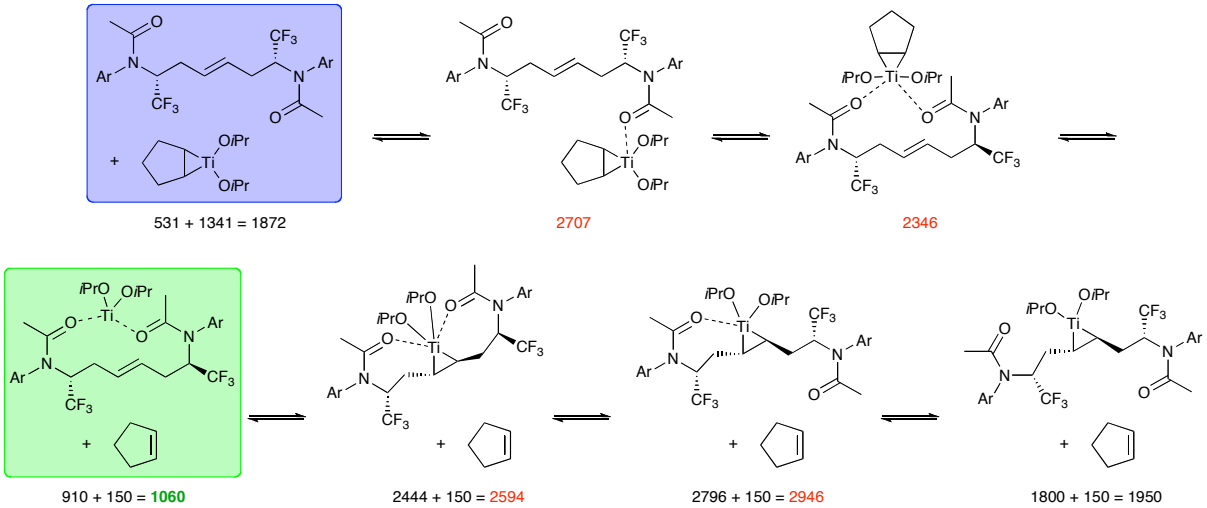
Formation of a complex where the Ti(O*i*Pr)$_2$ moiety is coordinated by the alkene and one of the amide groups:

The geometry of this titanacyclopropane complex was optimised after a total of 72 rounds of calculations, with an energy value of 2796.34 kJ.mol^{-1}.

Formation of a complex where the Ti(O*i*Pr)$_2$ moiety is coordinated to the alkene and both amide groups:

The geometry of this titanacyclopropane complex was optimised after a total of 75 rounds of calculations, with an energy value of 2443.55 kJ.mol^{-1}.

All the possibilities envisaged, with the corresponding energy values, are displayed in the following scheme.



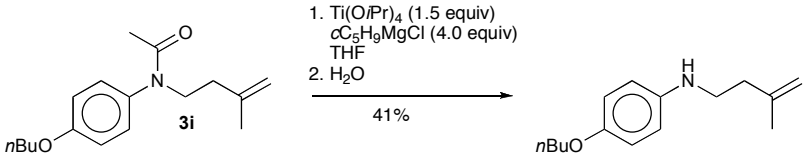
Calculated energy values, in kJ.mol^{-1}, of the optimised geometries of various species that may result from the reaction (displayed in blue) of (*R**,*R**)–**3g** with di*iso*propyloxy(η^2-cyclopentene)titanium. Ar = 4-(OMe)C$_6$H$_4$.

In principle, the various species considered are in equilibrium. Our molecular modelling results suggest that the formation, by a ligand exchange process, of a complex between $Ti(OiPr)_2$ and (*R**,*R**)–**3g**, where the carbon–carbon double bond does not coordinate to the titanium centre, is overwhelmingly favoured (displayed in green in the scheme shown above). This is consistent with the experimental findings: no reaction is observed when (*R**,*R**)–**3g** is subjected to our standard Kulinkovich-de Meijere reaction conditions. Indeed, upon hydrolysis, the stable complex shown in green is expected to restore the starting (*R**,*R**)–**3g**.

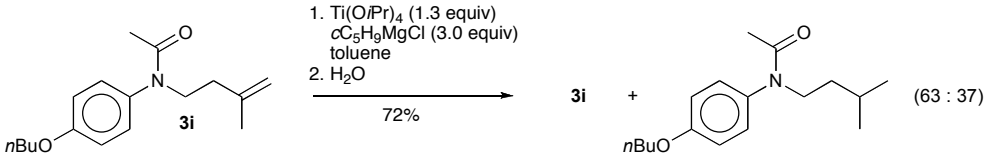
IV. Additional results

• *Attempted intramolecular aminocyclopropanation reactions of* **3i**

a) Under standard conditions, a complex mixture of products was observed from **3i**. Purification by flash column chromatography allowed the isolation of a de-acetylated product in 41% yield, the formation of which may be explained by a direct attack of the Grignard reagent onto the carbonyl group of **3i**.

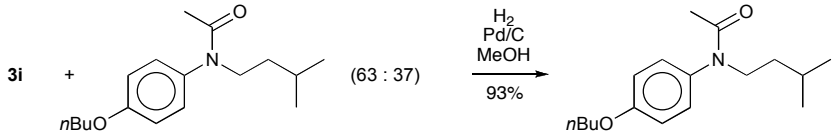


b) Using modified conditions, involving a smaller amount of Grignard reagent, a 63 : 37 mixture of **3i** and a formally dihydrogenated compound was isolated in 72% yield.[13]



c) A similar result was obtained using *cyclo*-hexane as the solvent, and no deuterium incorporation was observed when the reaction was quenched with D_2O.

d) The structure of the "reduced" product was confirmed by submitting the mixture to a catalysed hydrogenation reaction:



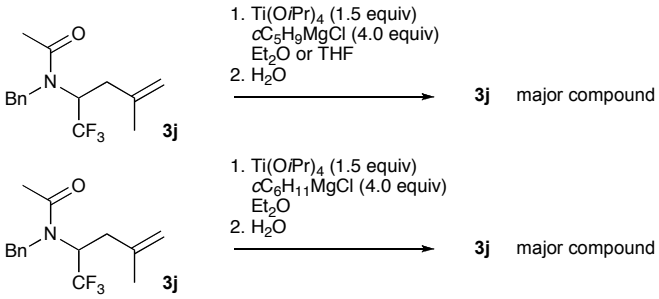
10% palladium on carbon (10 mg) was added to a 63 : 37 mixture of **3i** and *N*-(4-butoxyphenyl)-*N*-*iso*-pentylacetamide (36.2 mg) in methanol (4.0 mL). The mixture was then stirred under hydrogen for 2.7 h. After filtration through celite (rinsing with Et_2O), the solvent was concentrated and *N*-(4-butoxyphenyl)-*N*-*iso*-pentylacetamide was obtained as colourless crystals (33.8 mg, 93%).

***N*-(4-Butoxyphenyl)-*N*-*iso*-pentylacetamide.** Colourless crystals; ν_{max}/cm^{-1} 2955, 2931, 2870, 1657, 1509, 1468, 1396, 1366, 1296, 1284, 1243, 1216, 1169, 973, 836; δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.87 (6 H, d, *J* 6.5), 0.99 (3 H, t, *J* 7.5), 1.37 (2 H, m), 1.51 (2 H, sext *J* 7.5), 1.54 (1 H, thept, *J* 7.0, 6.5), 1.78 (2 H, tt, *J* 7.5, 6.5), 1.80 (3 H, s), 3.65 (2 H, m), 3.97 (2 H, t, *J* 6.5), 6.97 (4 H, AA'BB' system,[4] δ_A 6.90, δ_B 7.04, *N* 9.0, *L* 8.5, *K* 5.5 (*M* could not be measured accurately)); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 13.8, 19.2, 22.5, 22.8, 26.0, 31.3, 36.5, 47.5, 67.9, 115.2, 129.1, 135.8, 158.4, 170.5; *m/z* (ES^+) 286, 300 (MNa^+), 563, 577 (M_2Na^+); *m/z* (ES^+) 300.1946 (MNa^+ $C_{17}H_{27}NNaO_2$ requires 300.1939).

13– Other cases of olefin dihydrogenation under Kulinkovich-type reaction conditions are documented, for instance in the following article, and in the discussion included in the corresponding supporting information: C. Madelaine, Y. Six and O. Buriez, *Angew. Chem.*, 2007, **119**, 8192–8195; *Angew. Chem. Int. Ed.*, 2007, **46**, 8046–8049.

• *Attempted intramolecular aminocyclopropanation reactions of* **3j**

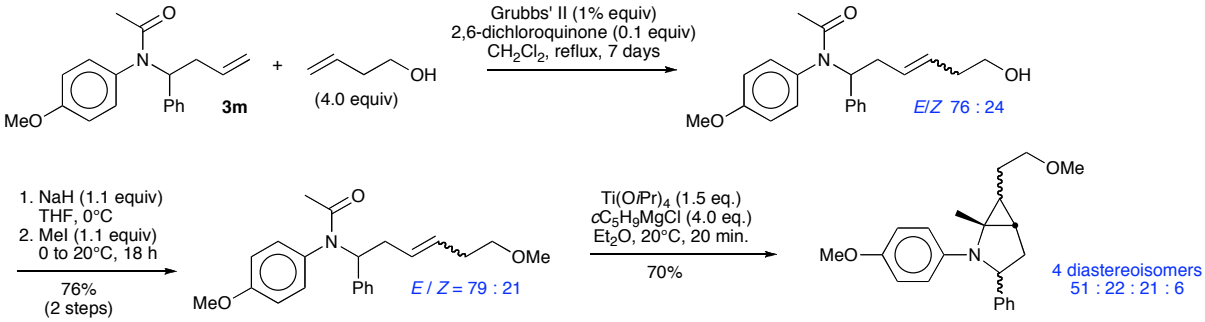
The intramolecular Kulinkovich-reaction of **3j** was attempted under several conditions, leaving it essentially unaffected in every case.



• *Additional example of intramolecular Kulinkovich-de Meijere reaction*

For the sake of clarity in the analysis of the results, the following example was not included in the main text of the article, but may be of interest to the readers. The last step is an intramolecular Kulinkovich-de Meijere reaction, starting from an alkenyl amide with both a disubstituted double bond and a chiral carbon centre α to the nitrogen atom. The reaction was run on a mixture of the two *E* and *Z* diastereoisomers, and the bicyclic aminocyclopropane product was thus produced as a mixture of four diastereoisomers.

• (1*R,5*R**)-6-(2-Methoxyethyl)-2-(4-methoxyphenyl)-1-methyl-3-phenyl-2-azabicyclo[3.1.0]hexane**



a) 2,6-Dichloro-1,4-benzoquinone (10.0% equiv, 636 µmol, 113 mg) and Grubbs II catalyst (1.00% equiv, 63.6 µmol, 54.0 mg) were added to a solution of alkenyl amide **3m** (1.00 equiv, 6.36 mmol, 1.88 g) and but-3-en-1-ol (4.00 equiv, 25.4 mmol, 2.18 mL) in freshly distilled CH_2Cl_2 (32 mL). The mixture was heated at reflux for 7 days. After cooling, the reaction medium was concentrated under reduced pressure to afford a green oil (3.54 g). Analysis of the crude product by ^{13}C NMR spectroscopy gave a 76 : 24 estimation for the *E*/*Z* ratio of the diastereoisomeric cross-metathesis products. Purification by flash column chromatography (silica gel, AcOEt/heptane, gradient from 10% to 50%) led to the isolation of a 83 : 17 mixture of *N*-(6-hydroxy-1-phenylhex-3-enyl)-*N*-(4-methoxyphenyl)acetamide and hex-3-ene-1,6-diol (1.98 g, 5.45 (86% yield) and 1.12 mmol respectively).

(*E*)–*N*-(6-Hydroxy-1-phenylhex-3-enyl)-*N*-(4-methoxyphenyl)acetamide. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.74 (3 H, s), 2.25 (1 H, m), 2.36 (1 H, m), 2.41–2.72 (2 H, m), 2.78 (1 H, br s, O*H*), 3.62 (2 H, t, *J* 6.0), 3.77 (3 H, s), 5.45–5.68 (2 H, m), 6.19 (1 H, dd, *J* 8.5 and 7.0), 6.74 (4 H, br s), 7.04–7.15 (2 H, m), 7.15–7.28 (3 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 23.1, 33.8, 35.9, 55.2, 56.7, 61.6, 113.8, 127.4, 127.9, 128.7, 129.3, 129.5, 131.1 (br s), 131.3, 139.4, 159.0, 171.1.

(*Z*)–*N*-(6-Hydroxy-1-phenylhex-3-enyl)-*N*-(4-methoxyphenyl)acetamide. δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signal 1.75 (3 H, s); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) characteristic signals 28.7, 31.2, 56.9, 128.1, 128.3, 139.3, 171.0.

b) Sodium hydride (60% in oil, 1.08 equiv, 8.31 mmol, 332 mg) was carefully added to a solution of the 83 : 17 mixture of *N*-(6-hydroxy-1-phenylhex-3-enyl)-*N*-(4-methoxyphenyl)acetamide and hex-3-ene-1,6-diol prepared above (1.00 equiv, 5.45 + 2 × 1.12 = 7.69 mmol of hydroxyl groups, 675 mg) in THF (8.0 mL), at 0°C. Methyl

iodide (1.08 equiv, 8.31 mmol, 517 µL) was then added at 0°C, and the mixture was allowed to warm to 20°C and stirred for 19 h. The reaction medium was diluted with Et_2O (30 mL), and 0.3 N HCl aq. soln (30 mL) was added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford a brown oil (2.10 g). Purification by flash column chromatography (silica gel, AcOEt/heptane, gradient from 10% to 100%) allowed the isolation of pure *N*-(6-methoxy-1-phenylhex-3-enyl)-*N*-(4-methoxyphenyl)acetamide (*E*/*Z* 79 : 21 as estimated by GC/MS, 1.65 g, 4.78 mmol, 75% over two steps from **3m**), pure (*E*)–*N*-(6-methoxy-1-phenylhex-3-enyl)-*N*-(4-methoxyphenyl)acetamide (27.3 mg, 77.2 µmol, 1% over two steps from **3m**), and pure *N*-(6-hydroxy-1-phenylhex-3-enyl)-*N*-(4-methoxyphenyl)acetamide (*E*/*Z* 80 : 20 as estimated by ^{13}C NMR spectroscopy, 104 mg, 306 µmol, 5% over two steps from **3m**).

***N*-(6-Methoxy-1-phenylhex-3-enyl)-*N*-(4-methoxyphenyl)acetamide (*E*/*Z* 79 : 21).** Brown oil; ν_{max}/cm^{-1} 2924, 1650, 1385, 1315, 1292, 1246, 1107, 1029, 966, 836, 734, 700; *m/z* (ES^+) 354 (MH^+), 373, 376 (MNa^+), 377, 729 (M_2Na^+); *m/z* (ES^+) 376.1892 (MNa^+ $C_{22}H_{27}NNaO_3$ requires 376.1889).

(*E*)–*N*-(6-Methoxy-1-phenylhex-3-enyl)-*N*-(4-methoxyphenyl)acetamide. Pale yellow oil; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.74 (3 H, s), 2.25 (2 H, td, *J* 7.0 and 5.5), 2.43–2.64 (2 H, m), 3.31 (3 H, s), 3.37 (2 H, t, *J* 7.0), 3.78 (3 H, s), 5.54 (2 H, AB part of an ABX_2Y_2 system, δ_A 5.51, δ_B 5.57, J_{AB} 15.5, J_{AX} 5.5, J_{AY} 0, J_{BX} 0, J_{BY} 6.0), 6.20 (1 H, t, *J* 8.0), 6.74 (4 H, br s), 7.08–7.18 (2 H, m), 7.18–7.27 (3 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) 23.3, 32.9, 34.0, 55.3, 56.3, 58.4, 72.4, 113.8, 127.4, 128.0, 128.5, 128.8, 129.6, 131.3 (br s), 131.6, 139.8, 159.1, 170.9.

(*Z*)–*N*-(6-Methoxy-1-phenylhex-3-enyl)-*N*-(4-methoxyphenyl)acetamide. δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 1.75 (3 H, s), 2.34 (2 H, m), 6.22 (1 H, dd, *J* 8.5 and 7.5); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) characteristic signals 28.3, 28.8, 56.4, 58.5, 72.0, 113.8, 127.4, 139.7.

c) Titanium(IV) *iso*-propoxide (1.50 equiv, 4.50 mmol, 1.33 mL) was added to a solution of *N*-(6-methoxy-1-phenylhex-3-enyl)-*N*-(4-methoxyphenyl)acetamide (*E*/*Z* 79 : 21, 1.00 equiv, 3.00 mmol, 1.06 g) in freshly distilled Et_2O (60 mL), followed by *cyclo*-pentylmagnesium chloride (1.64 M *in* Et_2O, 4.00 equiv, 12.0 mmol, 7.32 mL), dropwise at 20°C. After 20 minutes of stirring, water (30 mL) was added to the dark solution, which was exposed to air, and stirring is continued until decolouration. Et_2O (60 mL) and water (60 mL) were then added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (60 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a brown-yellow oil (1.15 g). Analysis of the crude product by ^1H NMR spectroscopy revealed the presence of four diastereoisomeric aminocyclopropane products *endo-cis* (32.4%), *endo-trans* (14.0%), *exo-cis* (13.6%) and *exo-trans* (4.0%), i.e. an overall yield of 64%, an *endo*/*exo* ratio of 73 : 27, and *cis*/*trans* ratios of 70 : 30 and 77 : 23 for the *endo* and *exo* diastereoisomers respectively. Flash chromatography (neutral alumina, activity II, AcOEt/heptane, gradient from 0% to 20%) led to the isolation of pure (1*R**,5*R**)-6-(2-Methoxyethyl)-2-(4-methoxyphenyl)-1-methyl-3-phenyl-2-azabicyclo[3.1.0]hexane as a mixture of the four diastereoisomers (*endo-cis*/*endo-trans*/*exo-cis*/*exo-trans* ratio of 55 : 21 : 17 : 7, 705 mg, 2.09 mmol, 70%).

(1*R,3*R**,5*R**,6*S**)-6-(2-Methoxyethyl)-2-(4-methoxyphenyl)-1-methyl-3-phenyl-2-azabicyclo[3.1.0]hexane (*endo-cis*).** δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 1.42 (1 H, td, *J* 7.5 and 1.0), 1.70 (3 H, s), 2.14 (1 H, ddd, *J* 14.0, 8.0 and 4.0), 2.53 (1 H, ddd, *J* 14.0 and 10.0), 3.31 (3 H, s), 3.34-3.61 (2 H, m), 3.68 (3 H, s), 4.47 (1 H, dd, *J* 10.0 and 4.0, C*H*Ph), 6.61 (4 H, AA'BB' system,[4] δ_A 6.52, δ_B 6.69, *N* 9.0, *L* 8.5, *K* 5.5 (*M* could not be measured accurately)), 7.02–7.40 (5 H, m); δ_C(75.5 MHz; $CDCl_3$; Me_4Si) characteristic signals 21.1, 22.7, 24.9, 26.4, 34.5, 48.2, 55.6, 58.6, 72.7, 73.2, 114.4, 125.2, 126.5, 128.7, 142.0, 146.7, 151.3.

(1*R,3*S**,5*R**,6*S**)-6-(2-Methoxyethyl)-2-(4-methoxyphenyl)-1-methyl-3-phenyl-2-azabicyclo[3.1.0]hexane (*endo-trans*).** δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 3.38 (3 H, s), 3.65 (3 H, s), 5.21 (1 H, dd, *J* 10.0 and 7.0, C*H*Ph).

(1*R,3*R**,5*R**,6*R**)-6-(2-Methoxyethyl)-2-(4-methoxyphenyl)-1-methyl-3-phenyl-2-azabicyclo[3.1.0]hexane (*exo-cis*).** δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 3.39 (3 H, s), 3.69 (3 H, s), 4.26 (1 H, dd, *J* 9.0 and 6.0, C*H*Ph).

(1*R,3*S**,5*R**,6*R**)-6-(2-Methoxyethyl)-2-(4-methoxyphenyl)-1-methyl-3-phenyl-2-azabicyclo[3.1.0]hexane (*exo-trans*).** δ_H(300 MHz; $CDCl_3$; Me_4Si) characteristic signals 3.41 (3 H, s), 3.64 (3 H, s), 5.20 (1 H, dd, *J* 8.5 and 7.5, C*H*Ph).