Asymmetric Induction in 8π Electrocyclizations. Design of a Removable Chiral Auxiliary

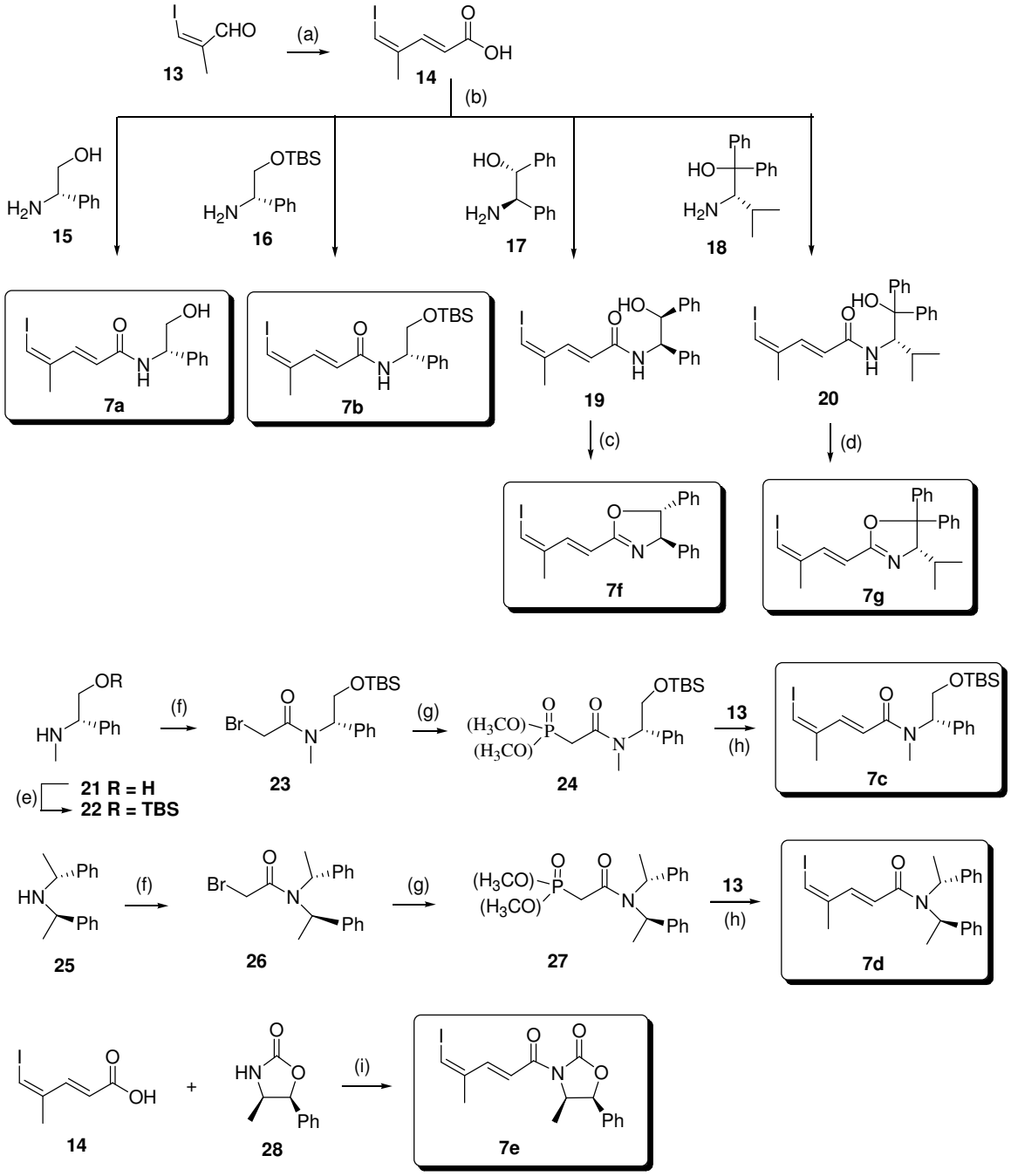
Keunsoo Kim, Joseph W. Lauher, and Kathlyn A. Parker*

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794-3400

kparker@notes.cc.sunysb.edu

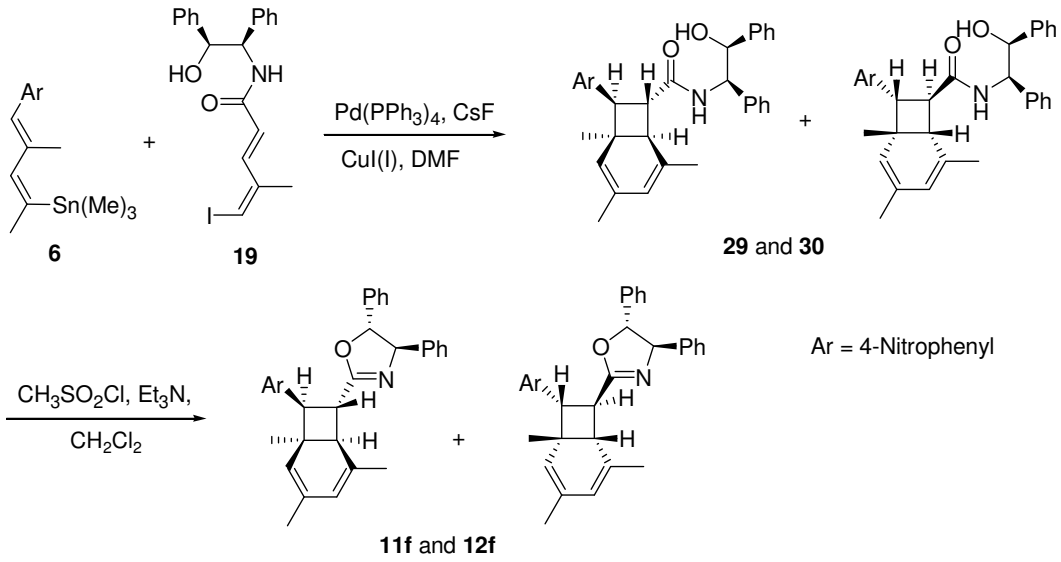
Supporting Information: Experimental Procedures

Scheme 4. Summary of synthetic routes for preparing iododienes **7a-g.**

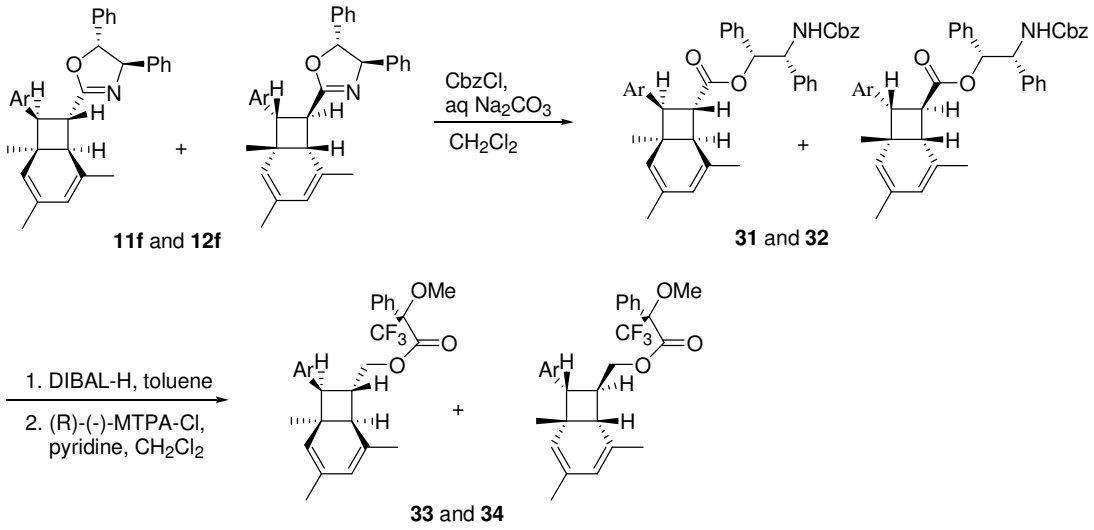


(a) 1. $Ph_3P{=}CHCO_2Me$, CH_2Cl_2 2. KOH, MeOH/H_2O (b) R_1-NH_2, DCC, DMAP, CH_2Cl_2 (c) 1. MsCl, Et_3N, CH_2Cl_2 2. NaOH, CH_3OH, H_2O (d) CH_3SO_3H, CH_2Cl_2 (e) TBS-Cl, Et_3N, DMAP, CH_2Cl_2 (f) Bromoacetyl bromide, CH_2Cl_2:H_2O, K_2CO_3 (g) $(CH_3O)_3P$ (h) DBU, LiCl, THF (i) Pivaloyl chloride, Et_3N, n-BuLi, THF.

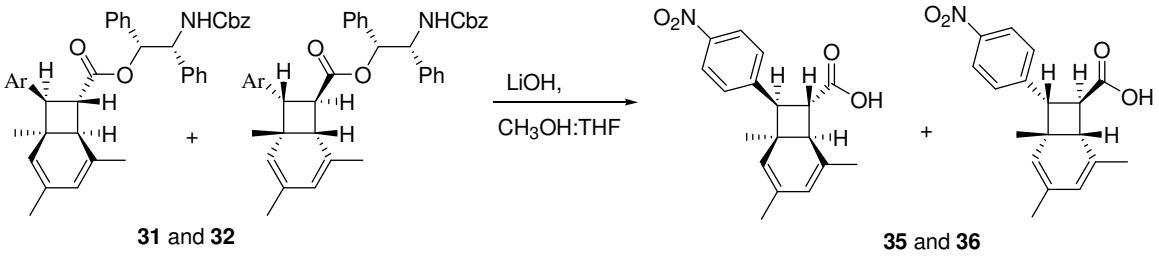
Scheme 5. Preparation of 1:1 mixture of **11f** and **12f.**



Scheme 6. Preparation of (S)-Mosher esters **33** and **34** from **11f** and **12f.**



Scheme 7. Preparation of acids **35** and **36** from **31** and **32.**

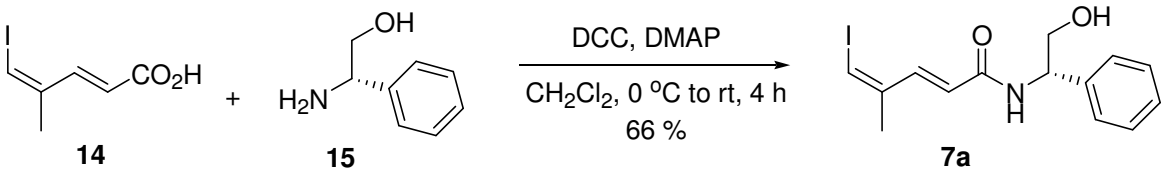


General experimental methods

All air- and moisture-sensitive reactions were carried out under Argon (Ar) atmosphere with freshly distilled solvents and oven-dried or flame-dried glassware. Handling of solvents and solutions for air- and moisture-sensitive reactions was performed by carefully dried glass syringe or cannula on a positive pressure of Ar atmosphere. Unless indicated otherwise, commercially available reagents were used as supplied without further purification. Tetrahedrofuran (THF) and diethyl ether (Et_2O) for reactions were distilled from sodium-benzophenone ketyl and dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Dimethylforamide (DMF), which has extra dry with molecular sieve, was purchased from ACROS and carefully maintained in a positive pressure. For Stille coupling/8π, 6π electrocyclizations, the reaction mixture was thoroughly degassed with a stream of Ar both before and after adding tetrakistriphenylphosphine palladium. Then it was immediately wrapped with aluminum foil.

Chromatography was carried out with HPLC grade ethyl acetate (EtOAc), *n*-hexane, and methanol. All experiments were monitored by thin layer chromatography (TLC). Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or staining with a 10% solution of phosphomolybdenic acid (PMA) in ethanol and then heating. Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh). For compounds **11a-g** and **12a-g**, preparative TLC was performed on Whatman® TLC plates (1000 μm). All ^{1}H NMR spectra for bicyclo[4.2.0]octadiene compounds were recorded with a Varian Inova-600 (600 MHz) instrument. Multiplicities are abbreviated as follows: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet, bs = broad singlet. All ^{13}C NMR spectra were recorded with a Varian Inova-400 (100 MHz) spectrometer. Infrared spectra were collected with a Perkin-Elmer 1600 Series FT-IR instrument. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer. X-ray crystallography was performed on an Oxford Gemini X-Ray Diffractometer.

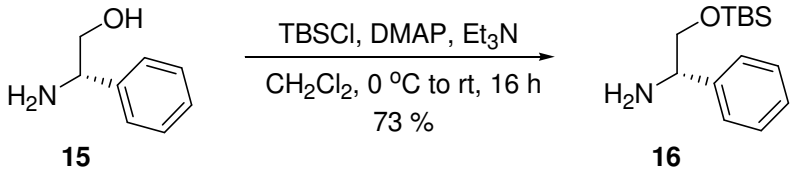
Diastereomeric excesses (%de) for **11a-g** and **12a-g** and **33** and **34** were calculated on the basis of the ^{1}H NMR spectra.



Amide 7a. The procedure of Ordonez et al[1] was followed to prepare iododienes **7a**-**d**.

To a solution of (*S*)-(+)-2-phenylglycinol **15** (132.1 mg, 0.96 mmol), which was purchased from ACROS, and (Z)-5-iodo-4-methyl-penta-2,4-dienoic acid[2] **14** (210.4 mg, 0.89 mmol) in dry CH_2Cl_2 (30 mL) was slowly added dicyclohexylcarbodiimide (DCC) (197.2 mg, 0.96 mmol) and 4-(*N*,*N*-dimethylamino) pyridine (DMAP) (13.1 mg, 0.11 mmol) in dry CH_2Cl_2 (12 mL) at 0 °C under Ar atmosphere. The reaction mixture was allowed to warm to rt. After stirring for further 4 h, the reaction mixture was filtered through Celite® and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:1) to provide 210.3 mg (66 %) of **7a** as white solid.

R_f: 0.30 (EtOAc/*n*-hexane, 1/1); IR: 3390, 1646, 1600, 1417 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.53 (d, J = 15.2 Hz, 1H), 7.22-7.32 (m, 5H), 6.60 (s, 1H), 6.36 (d, J = 15.2 Hz, 1H), 5.06 (t, J = 4.0 Hz, 1H), 3.75 (m, 2H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 166.7, 141.2, 139.9, 128.4, 127.3, 126.9, 125.2, 86.2, 65.0, 56.1, 19.7; HRMS(ESI-MS) Calcd. for $C_{14}H_{17}INO_2$ $[(M + H)]^+$ 358.0226, found 358.0297.



Amine 16.[3] Ziegler's silylation procedure was used. To a stirring solution of **15** (98.1 mg, 0.71 mmol) in dry CH_2Cl_2 (2.5 mL) was added triethylamine (180 µL, 1.29 mmol) followed by DMAP (9.0 mg, 0.07 mmol). After 5 min, *tert*-butyldiphenylchlorosilane (TBS-Cl) (214.5 mg, 0.78 mmol) was added in one portion. The reaction mixture was stirred for 16 h at rt, quenched with H_2O (5 mL), and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:3 to 1:2) to provide 129.2 mg (73 %) of **16** as colorless oil.

R_f: 0.66 (EtOAc/*n*-hexane, 1/2); IR: 3388, 1603, 1257, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.47 (m, 5H), 4.14 (dd, J = 8.4 Hz, 3.9 Hz, 1H), 3.80 (dd, J = 9.8 Hz, 3.9 Hz, 1H), 3.59 (dd, J = 9.6 Hz, 8.4 Hz, 1H), 1.90 (bs, 2H), 0.97 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.6, 127.6, 127.2, 57.9, 26.2, 18.6, -5.1

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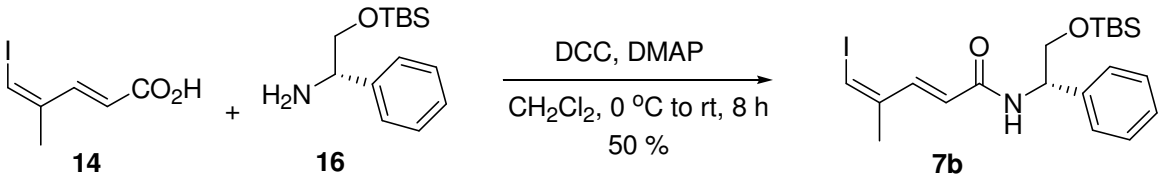
[1] Ordoñez, M.; Hernández-Fernández, E.; Montiel-Pérez, M.; Bautista, R.; Bustos, P.; Rojas-Cabrera, H.; Fernández-Zertuche, M.; García-Barradas, O. *Tetrahedron: Asymmetry,* **2007**, *18*, 2427-2436.

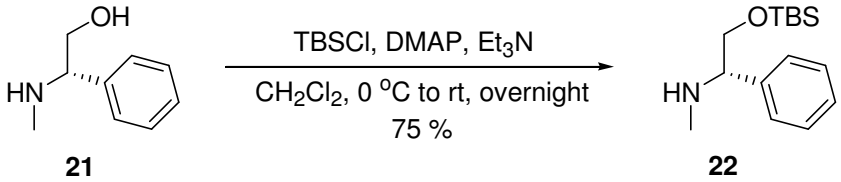
[2] (a) Beaudry, C. M.; Trauner, D. *Oranic Lett*. **2002**, *4*, 2221-2224. (b) Parker, K. A.; Wang, Z. *Organic Lett*. **2006**, *8*, 3553-3556.

[3] Ziegler, F.E.; Lim, H. *J. Org. Chem*. **1984**, *49*, 3278-3281.



Amide 7b. To a solution of **16** (49.2 mg, 0.20 mmol) and **14** (45.6 mg, 0.19 mmol) in dry CH_2Cl_2 (2.0 mL) was slowly added DCC (47.6 mg, 0.23 mmol) and DMAP (5.6 mg, 0.05 mmol) in dry CH_2Cl_2 (1.0 mL) at 0 °C under Ar atmosphere. The reaction mixture was allowed to warm to rt. After stirring for further 8 h, the reaction mixture was filtered on a Celite® and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:5) to provide 45.0 mg (50 %) of **7b** as viscous oil.

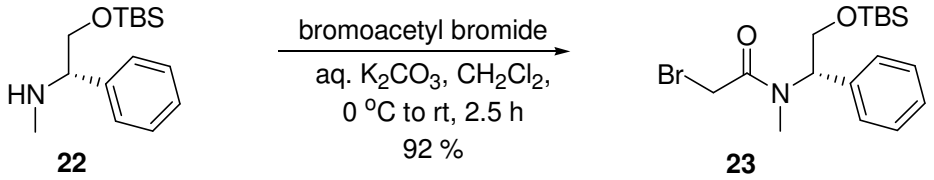
R_f: 0.40 (EtOAc/*n*-hexane, 1/5); IR: 3284, 3060, 1651, 1614, 1539 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 15.6 Hz, 2H), 7.23-7.30 (m, 5H), 6.53 (s, 1H), 6.40 (d, J = 7.6 Hz, 1H), 6.06 (d, J = 15.2 Hz, 1H), 5.10 (tt, J = 4.0 Hz, 4.0 Hz, 1H), 3.93 (dd, J = 10.4 Hz, 4.4 Hz, 1H), 3.84 (dd, J = 10.4 Hz, 4.4 Hz, 1H), 1.98 (s, 3H), 0.83 (s, 9H), -0.08 (d, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 141.6, 140.8, 140.2, 128.6, 127.6, 127.1, 125.3, 87.0, 66.3, 54.9, 26.1, 21.3, 18.5, -5.4; HRMS(ESI-MS) Calcd. for $C_{20}H_{31}INO_2Si$ $[(M + H)]^+$ 472.1091, found 472.1173.



Amine 22. To a stirring solution of (*S*)-(+)-2-(*N*-methylamino)-2-phenylethanol (**21**)[4] (66.4 mg, 0.44 mmol) in CH_2Cl_2 (1.5 mL) was added triethylamine (95 µL, 0.68 mmol) followed by DMAP (5.4 mg, 0.04 mmol). After 5 min, TBS-Cl (131.3 mg, 0.48 mmol) was added in one portion. The reaction mixture was stirred for 14 h at rt, quenched with H_2O (5 mL), and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:6) to provide 87.0 mg (75 %) of **22** as pale yellow oil.

R_f: 0.27 (EtOAc/*n*-hexane, 1/6); IR: 3304, 2871, 2799 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.34 (m, 5H), 3.52-3.68 (m, 3H), 2.31 (s, 3H), 0.89 (s, 9H), 0.03 (s, 6H).

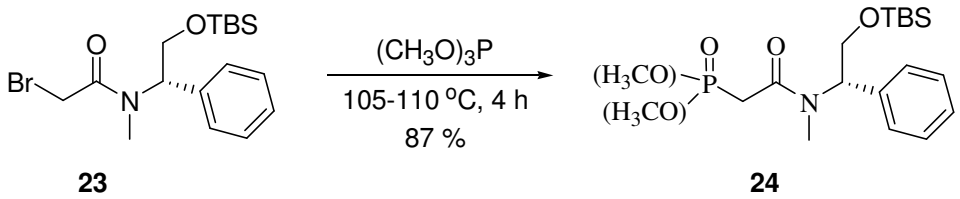
[4] Huszthy, P.; Oue, M.; Bradshaw, J. S.; Zhu, C. Y.; Wang,T. M.; Dalley, N. K.; Curtis, J. C.; Izatt, R. M. *J. Org. Chem.*, **1992**, *57*, 5383-5394.



22 **23**

Bromoacetamide 23. To a mixture of K_2CO_3 (108.0 mg, 0.79 mmol) and **22** (151.0 mg, 0.56 mmol) in a 3:2 mixture of CH_2Cl_2/H_2O (7.5 mL) at 0 °C was added dropwise bromoacetyl bromide (120 μL, 1.38 mmol). The reaction mixture was allowed to warm to rt, stirred for further 4 h, and quenched with H_2O (5 mL). After extracting with CH_2Cl_2 (3 x 10 mL), the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:1) to provide 280.0 mg (92 %) of **23** as colorless viscous oil.

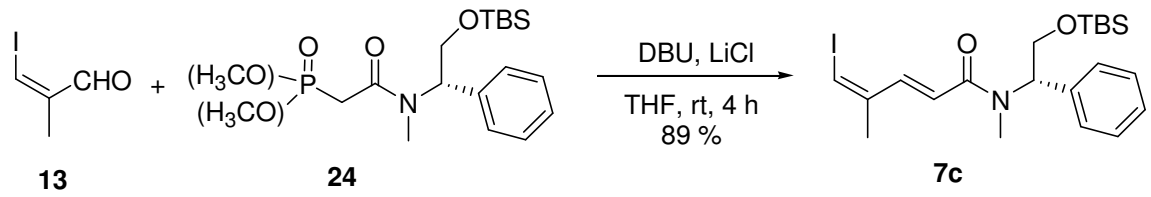
R_f: 0.42 (EtOAc/*n*-hexane, 1/3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-7.37 (m, 5H), 5.77 (t, J = 6.0 Hz, 0.5H), 5.16 (dd, J = 9.8 Hz, 4.2 Hz, 0.5H), 4.35 (d, J = 10.5 Hz, 0.5H), 3.90-4.20 (m, 3.5H), 2.92 (s, 1.5H), 2.67 (s, 1.5H), 0.90 (s, 4.5H), 0.88 (s, 4.5H), 0.08 - 0.11 (m, 6H).



23 **24**

Phosphonoacetamide 24. A mixture of **23** (251.2 mg, 0.65 mmol) and trimethyl phosphate (0.7 mL, 5.99 mmol) was heated for 3 h at 105-110 °C. The reaction mixture was allowed to cool to rt, and then evaporated to remove volatile compounds under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane:CH_3OH, 5:3:2) to provide 233.4 mg (87 %) of **24** as colorless viscous oil.

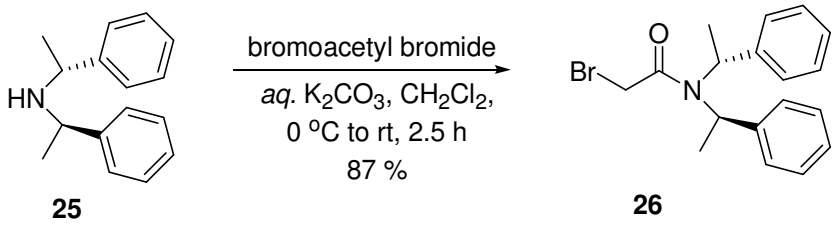
R_f: 0.53 (EtOAc/*n*-hexane/CH_3OH, 5/3/2); IR: 2850, 1640, 1253, 1033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.36 (m, 5H), 5.82 (t, J = 6.0 Hz, 0.5H), 5.25 (dd, J = 9.5 Hz, 3.6 Hz, 0.5H), 4.00-4.17 (m, 2H), 3.72-3.83 (m, 8H), 2.94 (s, 1.5H), 2.69 (s, 1.5H), 0.89 (s, 4.5H), 0.88 (s, 4.5H), 0.07-0.09 (m, 6H).



13 **24** **7c**

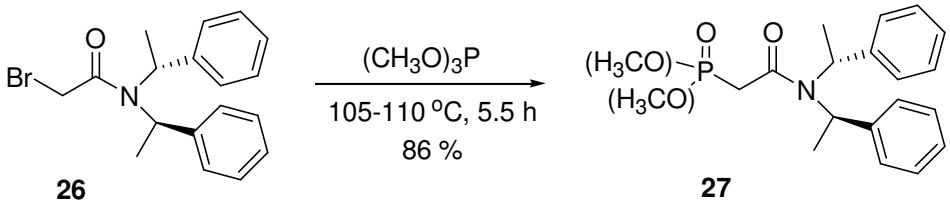
Amide 7c. A sample of (Z)-3-iodo-2-methyl-propenal[2] (**13**) was prepared from (Z)-3-iodo-2-methylprop-2-en-1-ol (104.9 mg, 0.53 mmol) by the literature procedure and dissolved in 6.0 mL of dry THF. This was added by syringe over 10 min at 0 °C under

Ar atmosphere to a stirred suspension solution of **24** (232.8 mg, 0.56 mmol), 1,8-diazabicyclo- [5.4.0]undec-7-ene (DBU) (260.3 mg, 1.71 mmol), and LiCl (72.1 mg, 1.70 mmol) in dry THF (24 mL). The resulting solution was allowed to warm to rt and completed by checking with TLC. The reaction mixture was quenched with saturated NH_4Cl (60 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:5) to provide 227.4 mg (89 %) of **7c** as colorless viscous oil.
R_f: 0.55 (EtOAc/*n*-hexane, 1/6); IR: 2928, 2856, 1641, 1601, 1118 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.64 (d, J = 15.0 Hz, 0.5H), 7.54 (d, J = 15.0 Hz, 0.5H), 7.21-7.35 (m, 5H), 6.65 (d, J = 15.6 Hz, 0.5H), 6.53 (d, J = 15.6 Hz, 0.5H) 6.49 (s, 1H), 5.90 (s, 0.5H), 5.17 (s, 0.5H), 4.16 (t, J = 5.4 Hz, 0.5H), 4.14 (d, J = 4.8 Hz, 1H), 4.06 (t, J = 9.6 Hz, 0.5H), 2.92 (s, 1.5H), 2.80 (s, 1.5H), 2.02 (s, 1.5H), 1.97 (s, 1.5H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 143.0, 142.0, 141.2, 138.2, 129.0, 128.7, 128.3, 127.6, 127.2, 124.0, 122.8, 86.6, 85.8, 62.1, 57.6, 26.0, 21.4, 18.3, -5.3; HRMS(ESI-MS) Calcd. for $C_{21}H_{33}INO_2Si$ $[(M + H)]^+$ 486.1247, found 486.1320.



25 **26**

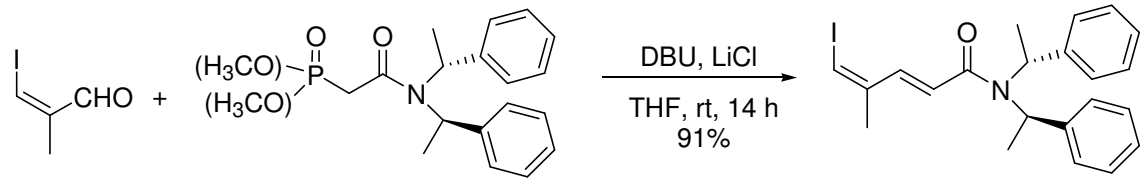
Bromoacetamide 26. To a mixture of K_2CO_3 (395.4 mg, 2.90 mmol) and **(+)**-bis[(*R*)-1-phenylethyl]amine **25** (445.0 mg, 1.98 mmol), which was purchased from SIGMA-ALDRICH, in a 3:2 mixture of CH_2Cl_2/ H_2O (25 mL) was added dropwise bromoacetyl bromide (0.30 mL, 3.45 mmol) at 0 °C. The reaction mixture was stirred for 2.5 h at rt, and then quenched with H_2O (15 mL). After extracting with CH_2Cl_2 (3 x 30 mL), the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:3) to provide 593.2 mg (87 %) of **26** as pale yellow sticky oil,
R_f: 0.27 (EtOAc/*n*-hexane, 3/7); IR: 2979, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.98-7.21 (m, 10H), 5.17 (bs, 1H), 5.01 (bs, 1H), 3.94 (dd, J = 16.4 Hz, 11.6 Hz, 2H), 1.78 (bs, 3H), 1.71 (bs, 3H).



26 **27**

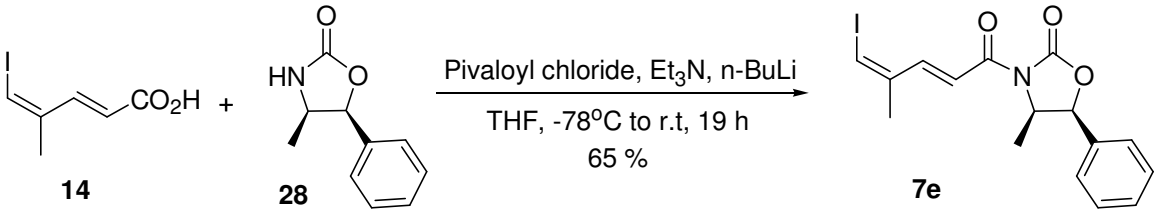
Phosphonoacetamide 27. A mixture of **26** (314.8 mg, 0.91 mmol) and trimethyl phosphate (1.0 mL, 8.48 mmol) was heated for 5.5 h at 105-110 °C. The reaction mixture

was allowed to cool to rt, and then evaporated to remove volatile compounds under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane:CH_3OH, 5:4:1) to provide 295.2 mg of **27** (86 %) as white solid.
R_f: 0.53 (EtOAc/*n*-hexane/CH_3OH, 5/4/1); IR: 1654, 1052 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.10-7.21 (m, 10H), 5.40 (bs, 1H), 5.05 (d, J = 6.0 Hz, 1H), 3.75 (t, J = 10.8 Hz, 6H), 2.80-2.95 (m, 2H), 1.79 (d, J = 7.2 Hz, 3H), 1.72 (d, J = 6.6 Hz, 3H).



13 **27** **7d**

Amide 7d. A solution of **27** (72.8 mg, 0.19 mmol) in dry THF (8.0 mL) was treated with DBU (90.6 mg, 0.59 mmol) and LiCl (25.2 mg, 0.59 mmol) at rt under Ar atmosphere. After stirring for 5 min, a solution of **13** (43.2 mg, 0.22 mmol) in dry THF (1.5 mL) was added by syringe over 5 min. The reaction mixture stirred for 14 h at rt, quenched by addition of saturated NH_4Cl solution (15 mL), and extracted with EtOAc (3 x 15 mL). The combined extracts were washed with H_2O (15 mL) followed by brine (15 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:5) to provide 77.1 mg (91 %) of **7d** as colorless viscous oil.
R_f: 0.53 (EtOAc/*n*-hexane, 1/5); IR: 2977, 1637, 1596 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.20 (d, 1H, J = 15.6 Hz), 7.09-7.39 (m, 10H), 6.66 (s, 1H), 6.20 (bs, 1H), 5.84 (d, J = 15.0 Hz, 1H), 4.82 (bs, 1H), 1.75 (bs, 6H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 141.5, 141.3, 128.6, 125.7, 86.0, 21.1; HRMS(ESI-MS) Calcd. for $C_{22}H_{25}INO$ $[(M + H)]^+$ 446.0903, found 446.0983.

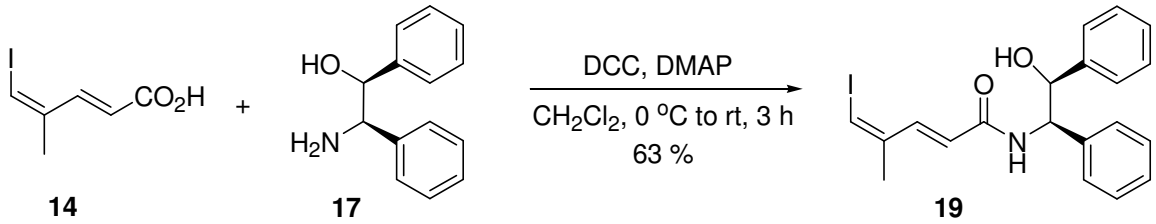


14 **28** **7e**

Oxazolidinone 7e. The procedure of Takacs[5] was adapted. To a stirred solution of **14** (200.5 mg, 0.84 mmol) and triethylamine (160 µL, 1.15 mmol) in dry THF (12 mL) was added pivaloyl chloride (112.4 mg, 0.93 mmol) at -78 °C. The resulting slurry solution was stirred for 15 min at -78 °C, continued for further 45 min at 0 °C, and then the solution was again cooled to -78 °C. In a separate flask, a stirred solution of (4*R*, 5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone **28** (158.0 mg, 0.89 mmol), which was purchased

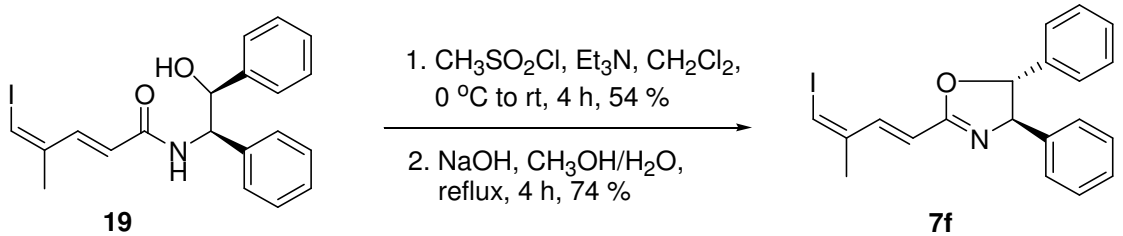
[5] Takacs, J. M.; Jaber, M. R.; Swanson, B. J.; Mehrman, S. J. *Tetrahedron: Asymmetry,* **1998**, 9, 4313-4324.

from ACROS, in dry THF (12 mL) was treated with *n*-butyllithium (2.0M in *n*-hexane) (0.6 mL, 0.89 mmol) at -78 ^{o}C, and the resulting solution was added to the dienoate slurry by syringe over 10 min. The resulting viscous slurry was stirred for 20 min at -78 ^{o}C, and then allowed to warm to rt and stirred for further 16 h. The reaction mixture was quenched by the addition of H_2O (25 mL) and the organic phase was concentrated under vacuum. The residue was taken up in CH_2Cl_2 (3 x 30 mL) and washed successively with portions of 0.5N HCl (25 mL), saturated *aq*. $NaHCO_3$, (25 mL), brine (25 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:6) to provide 220.0 mg (65 %) of **7e** as white solid.
R_f: 0.33 (EtOAc/*n*-hexane, 1/6); IR: 1779, 1678, 1605, 1351 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 15.6 Hz, 1H), 7.49 (d, J = 15.2 Hz, 1H), 7.29-7.41 (m, 5H), 6.70 (s, 1H), 5.68 (d, J = 7.2 Hz, 1H), 4.83 (m, 1H), 2.06 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 153.3, 146.3, 141.7, 133.5, 129.0, 128.9, 125.9, 121.8, 89.8, 79.3, 55.3, 21.4, 14.8; HRMS(ESI-MS) Calcd. for $C_{16}H_{17}INO_3$ $[(M + H)]^+$ 398.0175, found 398.0260.



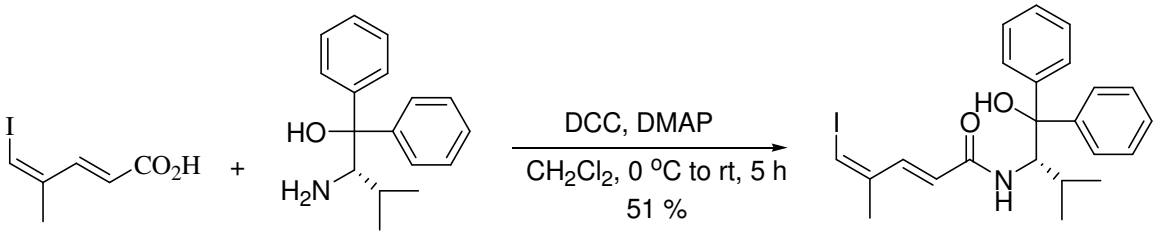
14 **17** **19**

Amide 19. To a solution of (1*S*, 2*R*)-2-amino-1,2-diphenylethanol **17** (154.3 mg, 0.72 mmol), which was purchased from ACROS, and **14** (189.7 mg, 0.79 mmol) in dry CH_2Cl_2 (20 mL) was slowly added DCC (159.0 mg, 0.77 mmol) and DMAP (10.6 mg, 0.09 mmol) in dry CH_2Cl_2 (8.0 mL) at 0 ^{o}C under Ar atmosphere. The reaction mixture was stirred for 3 h at rt, filtered through Celite®, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 2:3) to provide 196.8 mg (63 %) of **19** as white solid.
R_f: 0.57 (EtOAc/*n*-hexane, 1/2); IR: 3364, 1646, 1610, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 15.6 Hz, 1H), 7.22 (m, 6H), 7.02 (m, 4H), 6.56 (s, 1H), 6.40 (d, J = 7.2 Hz, 1H), 6.05 (d, J = 15.6 Hz, 1H), 5.39 (dd, J = 4.2 Hz, 3.6 Hz, 1H), 5.13 (d, J = 4.2 Hz, 1H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 142.2, 140.8, 139.9, 137.0, 128.1, 126.7, 124.8, 87.5, 59.9, 21.2.



19 **7f**

Oxazoline 7f. The procedure of Du *et al*. was adapted. [6] To an ice-cooled solution of **19** (79.0 mg, 0.18 mmol) and triethylamine (90 μL, 0.64 mmol) in dry CH_2Cl_2 (3.2 mL) was added methanesulfonyl chloride (30 μL, 0.39 mmol) via syringe in one portion. The reaction mixture was allowed to warm to rt and stirred for further 4 h. Then saturated NH_4Cl solution was poured into the reaction mixture and the organic layer was separated. The water layer was extracted by CH_2Cl_2 (3 x 10 ml). Then, the organic extracts were combined and the resulting solution was dried over $MgSO_4$ and concentrated under vacuum The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:2.5) to provide 50.0 mg (54 %) of mesylate as viscous oil.
R_f: 0.64 (EtOAc/*n*-hexane, 1:2.5); IR: 3285, 3056, 1715, 1625, 1326, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 15.6 Hz, 1H), 7.17-7.24 (m, 10H), 6.55 (s, 1H), 6.06 (d, J = 7.2 Hz, 1H), 5.98 (d, J = 15.6 Hz, 1H), 5.62 (d, J = 8.0 Hz, 1H), 4.86 (t, J = 7.6 Hz, 1H), 2.42 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 145.9, 137.8, 136.8, 136.0, 128.9, 128.7, 127.3, 117.4, 77.9, 62.8, 42.0, 12.7.
The mesylate (50.0 mg, 0.10 mmol) was dissolved in methanol (1.0 mL) and a solution of NaOH (15.1 mg, 0.38 mmol) in H_2O (1.0 mL) was added in one portion. After refluxing for 4 h, the reaction mixture was allowed to cool to rt and the solvent was concentrated under vacuum. After adding H_2O (10 mL), the *aq*. layers were extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:2.5) to provide 30.6 mg (74 %) of **7f** as viscous oil.
R_f: 0.57 (EtOAc/*n*-hexane, 1/2.5); IR: 3062, 3032, 2916, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 15.6 Hz, 1H), 7.24-7.41 (m, 10H), 6.57 (s, 1H), 6.50 (d, J = 15.6 Hz, 1H), 5.35 (d, J = 7.6 Hz, 1H), 5.13 (d, J = 7.6 Hz, 1H), 2.06 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 142.0, 141.5, 140.3, 129.0, 128.1, 126.0, 119.3, 89.1, 86.9, 78.7, 21.1; HRMS(ESI-MS) Calcd. for $C_{20}H_{19}INO$ $[(M + H)]^+$ 416.0433, found 416.0504.

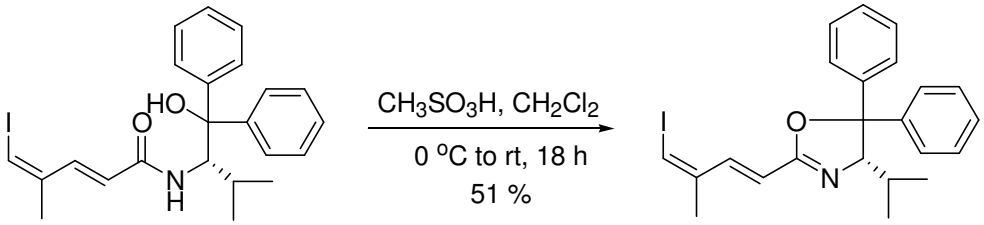


14 **18** **20**

Amide 20. To a solution of (*S*)-(-)-2-amino-3-methyl-1,1-diphenyl-1-butanol **18** (114.7 mg, 0.45 mmol), which was purchased from ALDRICH, and **14** (104.0 mg, 0.44 mmol) in dry CH_2Cl_2 (10 mL) was slowly added DCC (87 mg, 0.42 mmol) and DMAP (7.0 mg, 0.06 mmol) in dry CH_2Cl_2 (8.0 mL) at 0 °C under Ar atmosphere. The reaction mixture was allowed to warm to rt. After stirring for further 5 h, the reaction mixture was filtered on a Celite® and the filtrate was concentrated under vacuum. The residue was

[6] Han, L.; Jiaxi, S.; Du, D.-M. *Organic Lett*. **2007**, *9*, 4725-4728; see the Supporting Information for the procedure.

purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:3) to provide 106.2 mg (51 %) of **20** as white solid.
R_f: 0.42 (EtOAc/*n*-hexane, 1/3); IR: 3416, 3291, 1641, 1609, 1127 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.17–7.49 (m, 11H), 6.52 (s, 1H), 6.27 (d, J = 9.0 Hz, 1H), 5.94 (d, J = 15.6 Hz, 1H), 5.08 (dd, J = 9.9 Hz, 2.4 Hz, 1H), 1.92 (d, J = 1.2 Hz, 3H), 0.92 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 146.6, 145.7, 141.3, 140.8, 128.7, 128.6, 127.1, 127.0, 125.6, 119.6, 87.0, 82.4, 58.3, 29.5, 23.2, 21.3, 18.1.

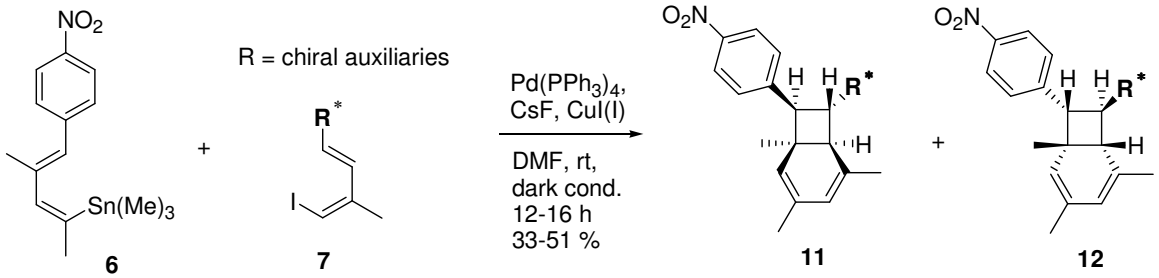


20 **7g**

Oxazoline 7g. The procedure of Ginotra and Singh[7] was adapted. Methanesulfonic acid (22 μL, 0.34 mmol) was added dropwise to a solution of **20** (47 mg, 0.10 mmol) in dry CH_2Cl_2 (4.7 mL) at 0 °C under Ar atmosphere. The reaction mixture was allowed to warm to rt and stirred for further 18 h. The resulting solution was diluted with CH_2Cl_2 (20 mL), washed with *aq*. $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL). The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:3) to provide 23.0 mg (51 %) of **7g** as white solid.
R_f: 0.65 (EtOAc/*n*-hexane, 1/3); IR: 3059, 2959, 1651, 970, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, J = 16.2 Hz, 1H), 7.25-7.57 (m, 10H), 6.54 (s, 1H), 6.43 (d, J = 15.9 Hz, 1H), 4.71 (d, J = 4.5 Hz, 1H), 2.04 (d, J = 1.5 Hz, 3H), 1.85 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H), 0.59 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 145.3, 141.6, 140.6, 128.6, 128.1, 128.0, 127.6, 127.1, 126.3, 119.6, 93.0, 86.3, 79.7, 30.4, 22.2, 21.1, 17.1; HRMS(ESI-MS) Calcd. for $C_{23}H_{25}INO$ $[(M + H)]^+$ 458.0903, found 458.0977.

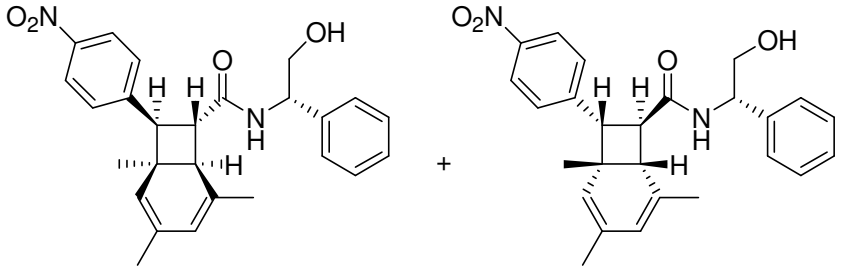
General procedure to prepare 11a-g and 12a-g via Stille coupling/8π, 6π electro-cyclization[8]

[7] Ginotra, S. K.; Singh, V. K. *Tetrahedron,* **2006**, *62*, 3573-3581.
[8] Beaudry, C. M.; Trauner, D. *Organic Lett*. **2005**, *7*, 4475-4477.



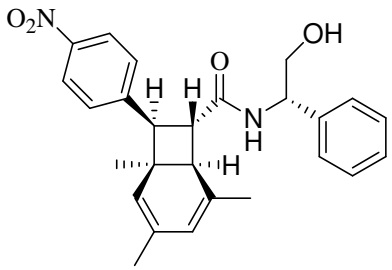
Bicyclooctadienes 11 and 12. To a solution of stannane **6** (0.1 mmol) and iododiene **7** (0.1 mmol) in anhydrous DMF (2.5 mL) were added cesium fluoride, CsF (0.2 mmol) and copper iodide, CuI(I) (0.02 mmol) at rt under degassing with a stream of Ar. After adding tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$ (0.01 mmol), the reaction flask was immediately wrapped with aluminum foil and continued degassing for further 5 min. The reaction mixture stirred for 12-16 h, and then diluted with EtOAc (25 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 25 mL). The combined *aq*. layers were extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by chromatography on silica gel (EtOAc/*n*-hexane) to provide a mixture of bicyclo[4.2.0]octadiene compounds **11** and **12**.

Analytical data for **11a** and **12a**



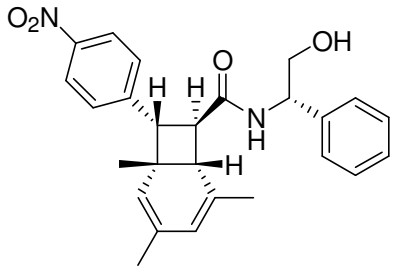
The general procedure was applied to the coupling of **6** (32.4 mg, 0.088 mmol) and **7a** (30.9 mg, 0.087 mmol) with CsF (30.0 mg, 0.197 mmol), CuI(I) (3.8 mg, 0.020 mmol), $Pd(PPh_3)_4$ (10.2 mg, 0.009 mmol), and DMF (3.6 mL). Preparative chromatography (EtOAc:*n*-hexane, 1:1) afforded 5.1 mg (14 %) of **11a** and 9.5 mg (25 %) of **12a** in a ratio of 2 : 3.

11a (slower moving isomer)



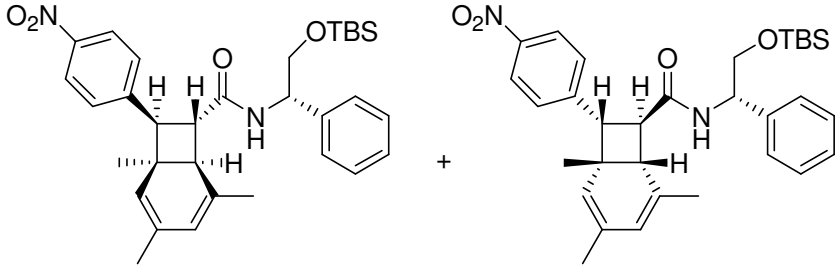
R_f: 0.30 (EtOAc/*n*-hexane, 1/1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.17 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.14-7.30 (m, 5H), 6.04 (d, J = 5.4 Hz, 1H), 5.49 (s, 1H), 5.06 (dd, J = 11.4 Hz, 4.8 Hz, 1H), 4.48 (s, 1H), 3.88 (d, J = 5.4 Hz, 2H), 3.79 (d, J = 10.2 Hz, 1H), 3.31 (dd, J = 9.6 Hz, 9.0 Hz, 1H), 2.80 (d, J = 9.0 Hz, 1H), 1.84 (s, 3H), 1.65 (s, 3H), 1.25 (s, 3H).

12a (faster moving isomer)



R_f: 0.40 (EtOAc/*n*-hexane, 1/1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.24-7.35 (m, 5H), 6.09 (d, J = 6.0 Hz, 1H), 5.46 (s, 1H), 5.04 (dd, J = 11.4 Hz, 4.8 Hz, 1H), 4.48 (s, 1H), 3.84 (d, J = 5.4 Hz, 2H), 3.83 (d, J = 10.8 Hz, 1H), 3.30 (dd, J = 9.3 Hz, 8.4 Hz, 1H), 2.73 (d, J = 9.0 Hz, 1H), 1.71 (s, 3H), 1.64 (s, 3H), 1.24 (s, 3H).

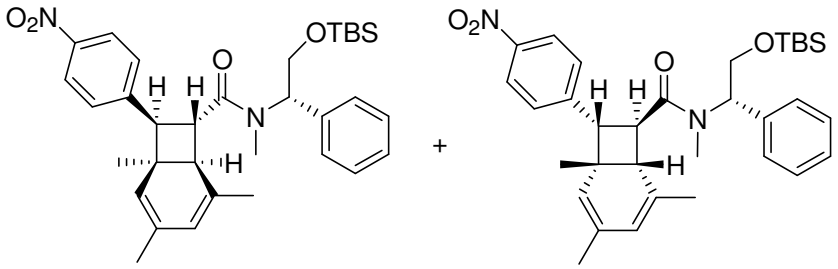
Analytical data for **11b** and **12b**



The general procedure was applied to the coupling of **6** (12.4 mg, 0.034 mmol) and **7b** (16.2 mg, 0.034 mmol) with CsF (10.5 mg, 0.069 mmol), CuI(I) (1.3 mg, 0.007 mmol), $Pd(PPh_3)_4$ (4.0 mg, 0.004 mmol), and DMF (1.2 mL). Preparative chromatography (EtOAc:*n*-hexane, 1/5) afforded 9.7 mg (51 %) of an inseparable mixture in a ratio of 2 : 3 or 3 : 2.

R_f: 0.47 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.09-7.29 (m, 5H), 6.15 (d, J = 7.8 Hz, 0.5H), 6.13 (d, J = 10.8 Hz, 0.5H), 5.48 (s, 0.4H), 5.46 (s, 0.6H), 4.97 (m, 1H), 4.47 (s, 0.4H), 4.45 (s, 0.6H), 3.79-3.86 (m, 2H), 3.71 (dd, J = 10.8 Hz, 9.6 Hz, 1H), 3.33 (t, J = 9.0 Hz, 0.4H), 3.29 (t, J = 9.0 Hz, 0.6H), 2.80 (d, J = 8.4 Hz, 0.4H), 2.75 (d, J = 9.0 Hz, 0.6H), 1.83 (s, 1.25H), 1.74 (s, 1.75H), 1.66 (s, 1.25H), 1.64 (s, 1.75H), 1.23 (s, 1.75H), 1.23 (s, 1.25H), 0.75 (s, 3.6H), 0.74 (s, 5.4H), 0.14-0.20 (m, 6H).

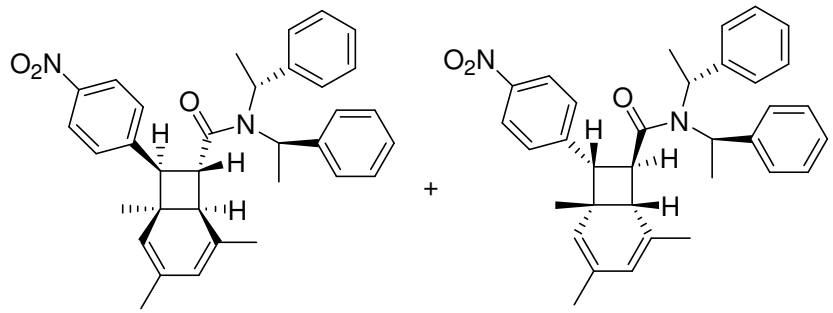
Analytical data for **11c** and **12c**



The general procedure was applied to the coupling of **6** (12.9 mg, 0.035 mmol) and **7c** (14.5 mg, 0.030 mmol) with CsF (9.7 mg, 0.064 mmol), CuI(I) (1.2 mg, 0.006 mmol), $Pd(PPh_3)_4$ (4.7 mg, 0.004 mmol), and DMF (1.2 mL). Preparative chromatography (EtOAc/*n*-hexane, 1/5) afforded 7.3 mg (44 %) of an inseparable mixture in a ratio of 1 : 1.

R_f: 0.52 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.21-7.38 (m, 5H), 6.92 (d, J = 7.2 Hz, 1H), 6.73 (d, J = 9.0 Hz, 1H), 5.86 (t, J = 6.0 Hz, 0.5H), 5.53 (s, 0.5H), 5.45 (s, 0.5H), 4.84 (t, J = 6.6 Hz, 0.5H), 4.52 (s, 0.5H), 4.31 (s, 0.5H), 4.06-4.17 (m, 1H), 4.03 (d, J = 6.0 Hz, 1H), 3.98 (d, J = 9.6 Hz, 0.5H), 3.88 (d, J = 6.6 Hz, 0.5H), 3.78 (t, J = 9.6 Hz, 0.5H), 3.73 (t, J = 9.6 Hz, 0.5H), 3.03 (s, 1.5H), 2.96 (d, J = 11.4 Hz, 0.5H), 2.85 (d, J = 8.4 Hz, 0.5H), 2.76 (s, 1.5H), 1.86 (s, 1.5H), 1.66 (s, 1.5H), 1.65 (s, 3H), 1.26 (s, 3H), 0.90 (s, 4.5H), 0.88 (s, 4.5H), -0.06-0.08 (m, 6H).

Analytical data for **11d** and **12d**



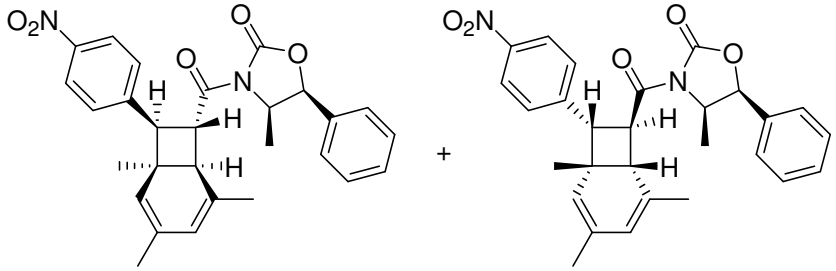
The general procedure was applied to the coupling of **6** (37.5 mg, 0.102 mmol) and **7d** (47.8 mg, 0.107 mmol) with CsF (33.1 mg, 0.218 mmol), CuI(I) (4.2 mg, 0.022 mmol), $Pd(PPh_3)_4$ (12.3 mg, 0.011 mmol), and DMF (4.0 mL). Preparative chromatography (EtOAc:*n*-hexane, 1:5) afforded 9.6 mg (18 %) of the slower moving isomer and 14.5 mg (27 %) of the faster moving isomer in a ratio of 2 : 3.

The slower moving isomer

R_f: 0.50 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (d, J = 7.8 Hz, 2H), 7.13-7.19 (m, 6H), 7.03 (t, J = 6.6 Hz, 2H), 6.74 (bs, 2H), 6.63 (bs, 2H), 5.56-5.59 (bs, 1H), 5.55 (s, 1H), 4.78 (d, J = 5.4 Hz, 1H), 4.30 (s, 1H), 3.80 (d, J = 9.0 Hz, 2H), 3.60 (dd, J = 8.4 Hz, 7.8 Hz, 1H), 2.88 (d, J = 8.4 Hz, 1H), 1.74 (s, 3H), 1.67 (s, 3H), 1.66 (d, J = 7.2 Hz, 3H), 1.63 (bs, 3H), 1.14 (s, 3H).

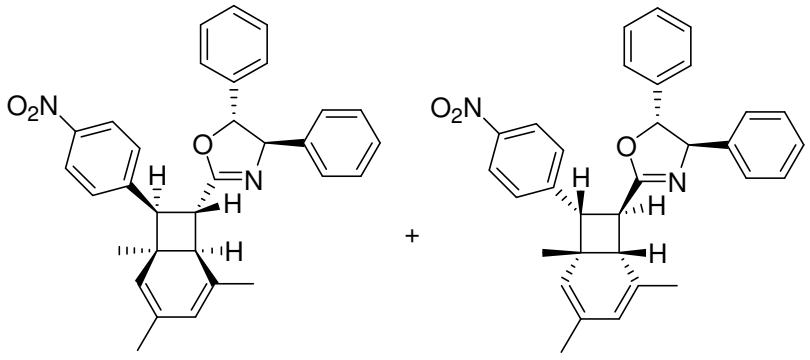
The faster moving isomer
R_f: 0.55 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.11 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.11-7.20 (m, 6H), 7.01 (bs, 2H), 6.79 (d, J = 7.8 Hz, 2H), 5.46 (s, 1H), 5.27 (s, 1H), 5.21 (bs, 1H), 4.96 (d, J = 6.0 Hz, 1H), 4.45 (s, 1H), 3.79 (d, J = 9.6 Hz, 2H), 3.67 (dd, J = 8.7 Hz, 8.4 Hz, 1H), 2.95 (d, J = 8.4 Hz, 1H), 1.68 (d, J = 6.6 Hz, 3H), 1.64 (s, 3H), 1.63 (s, 3H), 1.50 (d, J = 6.6 Hz, 3H), 1.18 (s, 3H).

Analytical data for **11e** and **12e**



The general procedure was applied to the coupling of **6** (34.0 mg, 0.092 mmol) and **7e** (41.7 mg, 0.107 mmol) with CsF (27.4 mg, 0.180 mmol), CuI(I) (5.0 mg, 0.026 mmol), $Pd(PPh_3)_4$ (13.5 mg, 0.011 mmol), and DMF (3.0 mL). Preparative chromatography (EtOAc:*n*-hexane, 1:6) afforded 15.7 mg (36 %) of an inseparable mixture in a ratio of 1 : 1.
R_f: 0.42 (EtOAc/*n*-hexane, 1/6); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, J = 9.0 Hz, 1H), 8.17 (d, J = 9.0 Hz, 1H), 7.24-7.46 (m, 7H), 5.62 (d, J = 7.2 Hz, 0.5H), 5.59 (d, J = 7.2 Hz, 0.5H), 5.51 (s, 0.5H), 5.50 (s, 0.5H), 5.13 (t, J = 9.0 Hz, 0.5H), 5.11 (t, J = 9.0 Hz, 0.5H), 4.76 (q, J = 6.6 Hz, 1H), 4.42 (s, 0.5H), 4.41 (s, 0.5H), 3.90 (d, J = 10.2 Hz, 0.5H), 3.84 (d, J = 10.2 Hz, 0.5H), 2.86 (d, J = 8.4 Hz, 0.5H), 2.80 (d, J = 8.4 Hz, 0.5H), 1.73 (s, 1.5H), 1.69 (s, 1.5H), 1.67 (s, 1.5H), 1.67 (s, 1.5H), 1.28 (s, 3H), 0.91 (d, J = 7.2 Hz, 1.5H), 0.82 (d, J = 6.0 Hz, 1.5H).

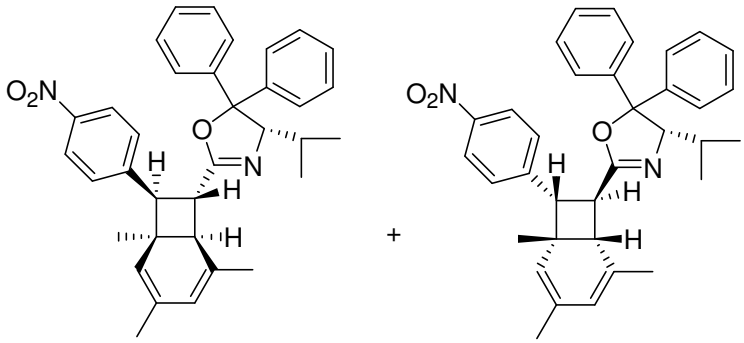
Analytical data for **11f** and **12f**



The general procedure was applied to the coupling of **6** (29.4 mg, 0.080 mmol) and **7f** (32.2 mg, 0.077 mmol) with CsF (27.4 mg, 0.180 mmol), CuI(I) (5.0 mg, 0.026 mmol), $Pd(PPh_3)_4$ (9.5 mg, 0.008 mmol), and DMF (2.2 mL). Preparative chromatography

(EtOAc:*n*-hexane, 1/5) afforded 15.8 mg (42 %) of an inseparable mixture in a ratio of 1 : 6.
R_f: 0.38 (EtOAc/*n*-hexane, 1/5); IR: 3054, 2916, 1660, 1599, 1520, 1348, 1265 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.21 (d, J = 9.0 Hz, 2H), 7.44 (d, J = 9.0 Hz, 2H), 7.24-7.38 (m, 8H), 7.14 (d, J = 7.2 Hz, 2H), 5.50 (s, 1H), 5.24 (d, J = 6.6 Hz, 1H), 5.07 (d, J = 7.2 Hz, 0.85H), 5.03 (d, J = 7.2 Hz, 0.15H), 4.52 (s, 1H), 4.00 + 3.97 (d, J = 10.2 Hz, 1H), 3.72 (t, J = 9.6 Hz, 1H), 2.96 + 2.94 (d, J = 9.6 Hz, 1H), 1.90 (s, 0.49H), 1.85 (s, 2.51H), 1.65 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 145.6, 133.7, 131.5, 129.2, 128.5, 128.4, 127.1, 126.5, 126.0, 123.9, 123.8, 123.1, 121.4, 121.3, 90.3, 57.1, 56.6, 47.2, 46.1, 45.2, 44.6, 40.9, 28.6, 22.3, 22.2, 22.1, 22.0; HRMS(ESI-MS) Calcd. for $C_{32}H_{31}N_2O_3$ $[(M + H)]^+$ 491.2256, found 491.2344.

Analytical data for **11g** and **12g**

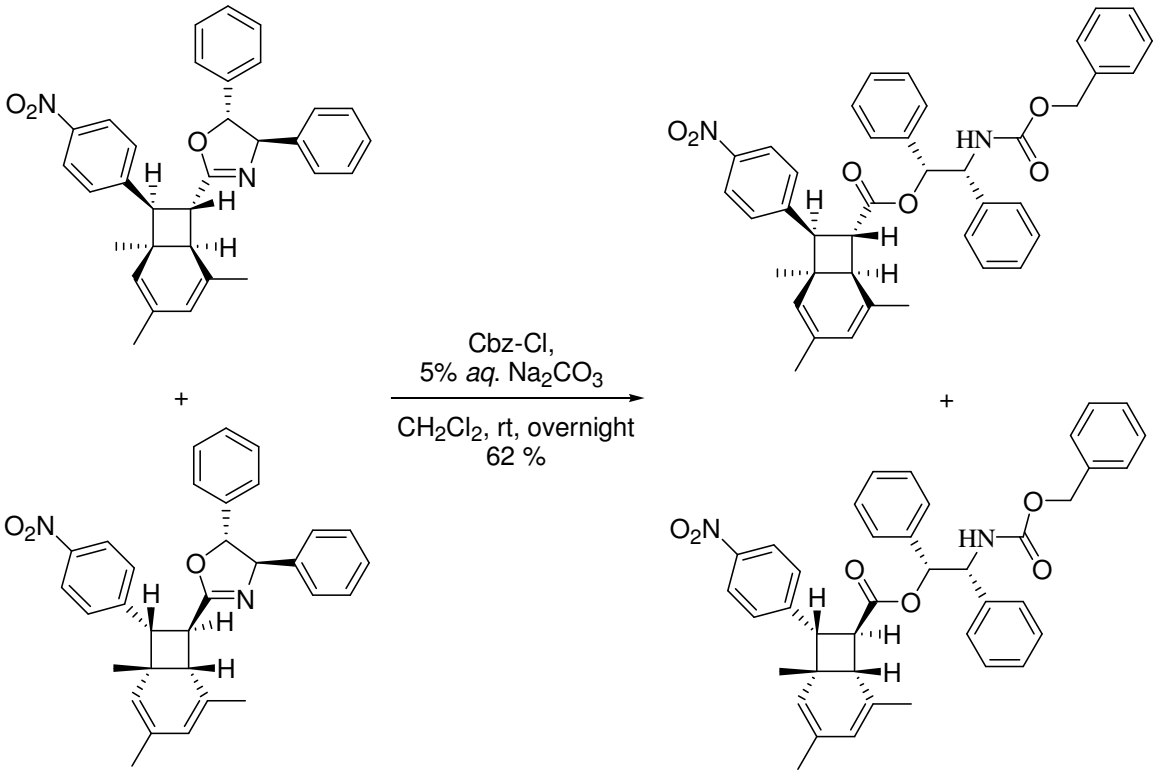


The general procedure was applied to the coupling of **6** (20.8 mg, 0.057 mmol) and **7g** (22.9 mg, 0.050 mmol) with CsF (18.2 mg, 0.120 mmol), CuI(I) (2.5 mg, 0.013 mmol), $Pd(PPh_3)_4$ (6.9 mg, 0.006 mmol), and DMF (1.5 mL). Preparative chromatography (EtOAc:*n*-hexane, 1:5) afforded 8.9 mg (33 %) of an inseparable mixture of in a ratio of 1 : 3 or 3 : 1.
R_f: 0.50 (EtOAc/*n*-hexane, 1/5); ^1H NMR (600 MHz, $CDCl_3$): δ 8.17 (d, J = 7.8 Hz, 0.5H), 8.15 (d, J = 9.0 Hz, 1.5H), 7.22-7.47 (m, 12H), 5.45 (s, 1H), 4.64 (br, 1H), 4.51 (s, 0.75H), 4.49 (s, 0.25H), 3.90 (br, 0.75H), 3.78 (br, 0.25H), 3.63 (bs, 1H), 2.88 (bs, 0.25H), 2.78 (bs, 0.75H), 1.72 (m, 1H), 1.61 (s, 6H), 1.30 (s, 3H), 0.97 (d, J = 6.6 Hz, 0.75H), 0.96 (d, J = 6.0 Hz, 2.25H), 0.48 (d, J = 6.6 Hz, 0.75H), 0.43 (d, J = 6.6 Hz, 2.25H).

Determination of absolute stereochemistry and stereoselectivity for 12f

Confirmation of the absolute stereochemistry. The hydrolysis strategy of Barluenga *et al.* was employed.[9]

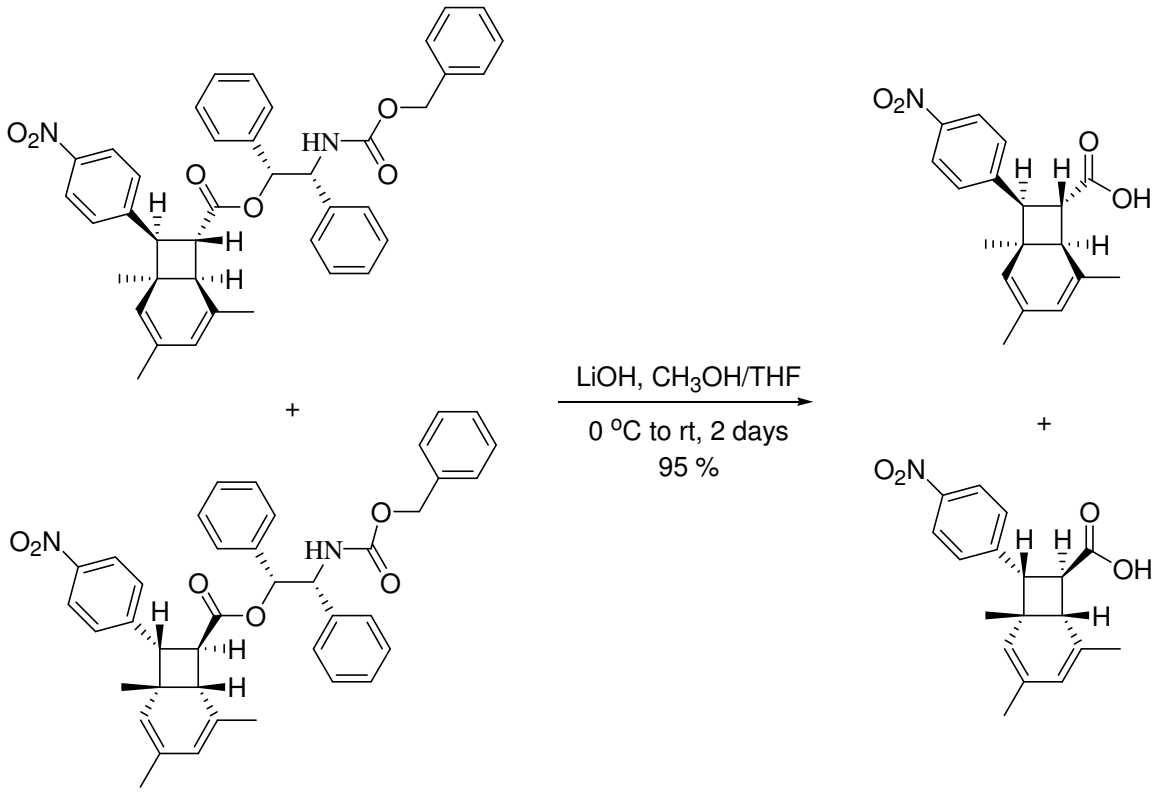
[9] (a) Barluenga, J.; Suarez-Sobrino, A. L.; Tomas, M.; Garcia-Granda, S.; Santiago -Garcia, R. *J. Am. Chem. Soc.* **2001,** *123***,** 10494- 10501. (b) Minhas, G. S.; Pilch, D. S.; Kerrigan, J. E.; LaVoie, E. J.; Rice, J. E. *Bioorganic & Medicinal. Chemistry Letters* **2006**, *16*, 3891-3895. (c) Cho, S. J.; Jensen, N. H.; Kurome, T.; Kadari, S.; Manzano, M. L.; Malberg, J. E.; Caldarone. B.; Roth, B. L.; Kozikowski, A.P. *J. Med. Chem.* **2009**, *52*, 1885-1902.



11f and **12f** **31** and **32**

Bicyclooctadienes 31 and 32. To a solution of **11f** and **12f** (15.3 mg, 0.031 mmol) in dry CH_2Cl_2 (0.5 mL), 5% *aq*. Na_2CO_3 (0.5 mL) and benzyl chloroformate (Cbz-Cl) (9.7 mg, 0.057 mmol) was added at rt and then stirred overnight. After addition of H_2O (1.5 mL), the resulting solution was extracted with CH_2Cl_2. Then the combined organic layers were washed first with 5% *aq*. Na_2CO_3, second with H_2O, and then dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by preparative chromatography (EtOAc/*n*-hexane, 1:5) to provide 12.4 mg (62 %) of an inseparable mixture as sticky oil.

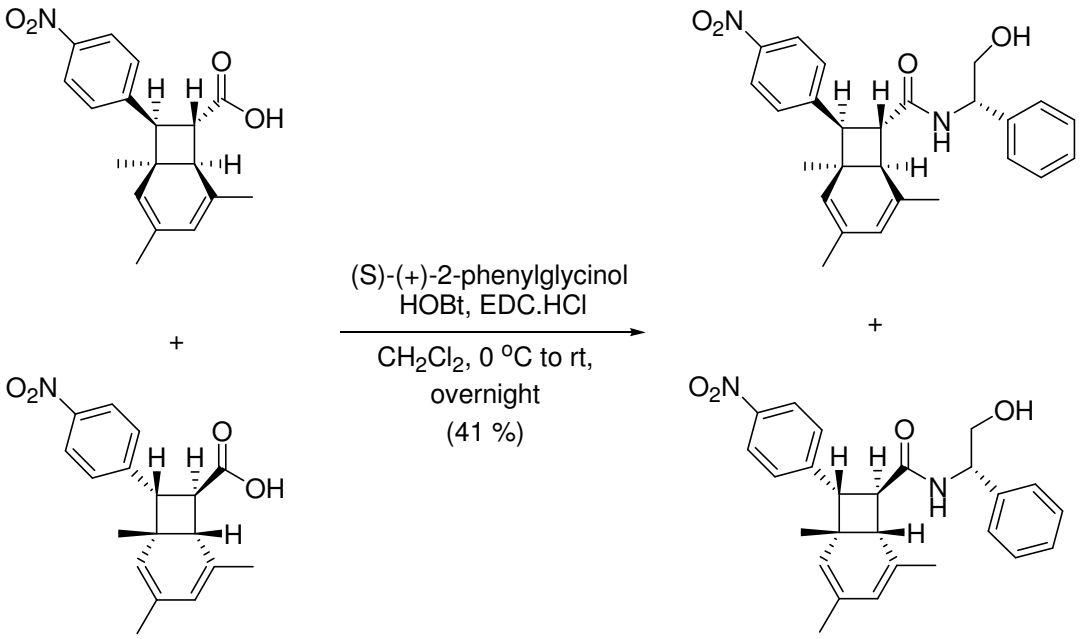
R_f: 0.38 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 + 8.14 (d, J = 7.8 Hz, 2H), 7.37 (d, J = 4.8 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 7.23-7.35 (m, 5H), 7.20 (dd, J = 3.0 Hz, 2.4 Hz, 2H), 7.16 (t, J = 7.2 Hz, 2H), 7.05 (dd, J = 3.0 Hz, 2.4 Hz, 2H), 6.99 (d, J = 7.8 Hz, 2H), 6.07 (d, J = 6.0 Hz, 0.17H), 6.03 (d, J = 6.6 Hz, 0.83H), 5.44 (s, 1H), 5.36 + 5.27 (bs, 1H), 5.10 (s, 1H), 5.01 (t, J = 9.6 Hz, 1H), 4.98 (d, J = 17.4 Hz, 1H), 4.42 (s, 1H), 3.61 (d, J = 10.2 Hz, 1H), 3.46 (t, J = 9.3 Hz, 1H), 2.70 (d, J = 8.4 Hz, 0.83H), 2.64 (d, J = 9.0 Hz, 0.17H), 1.68 + 1.66 (s, 3H), 1.63 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 155.8, 147.1, 145.6, 138.3, 136.7, 136.4, 134.3, 131.4, 128.5, 128.3, 127.2, 123.8, 123.6, 121.3, 121.1, 94.6, 77.9, 67.2, 56.8, 46.1, 45.5, 45.3, 44.5, 28.7, 22.3, 21.6.



31 and **32** **35** and **36**

Bicyclooctadienes 35 and 36. To a solution of **31** and **32** (12.4 mg, 0.019 mmol) in dry THF (1.0 mL) and CH_3OH (0.5 mL), LiOH (4.1 mg, 0.171 mmol) was added at 0 °C. The reaction mixture was stirred 2 days at rt, and washed with H_2O (5 mL). The combined solution was acidified to pH = 2 and then extracted with Et_2O (3 x 5 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by preparative chromatography (EtOAc:*n*-hexane, 1:2) provide 5.6 mg (95 %) of a white solid.

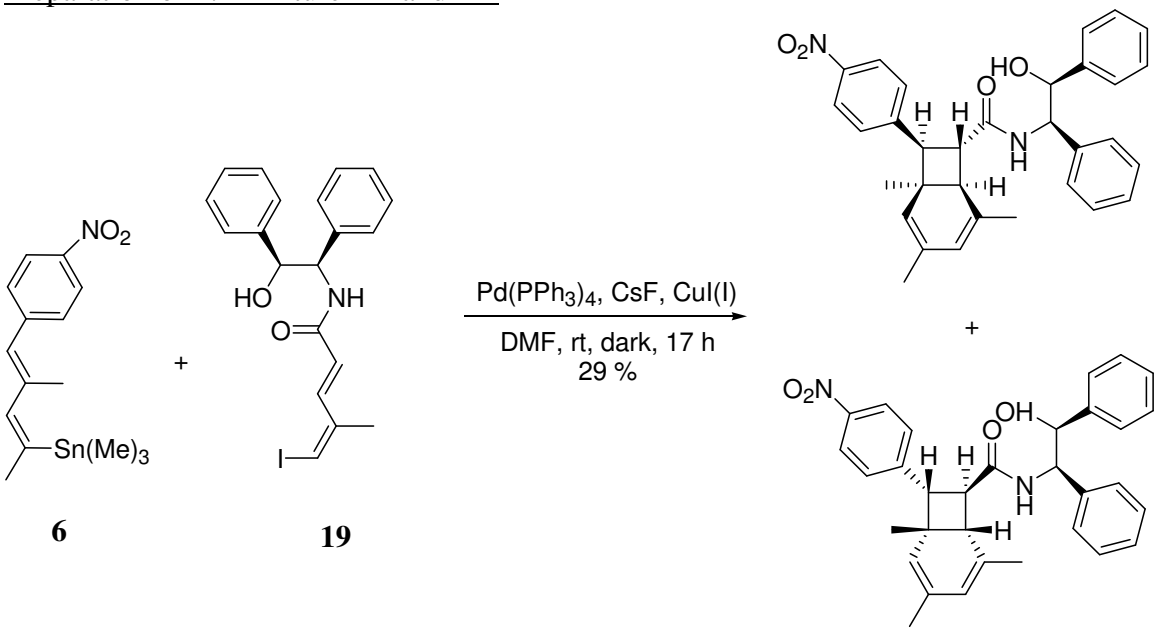
R_f: 0.51 (EtOAc/*n*-hexane, 1/2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 5.47 (s, 1H), 4.42 (s, 1H), 3.74 (d, J = 10.5 Hz, 1H), 3.49 (dd, J = 9.0 Hz, 1H), 2.76 (d, J = 9.0 Hz, 1H), 1.81 (s, 3H), 1.62 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3, 147.1, 145.6, 134.2, 131.4, 128.3, 123.7, 122.8, 122.7, 121.3, 121.2, 56.1, 46.0, 45.8, 44.5, 28.6, 22.2, 21.7.



35 and **36** **11a** and **12a**

Bicyclooctadienes 11a and 12a. To a stirred solution of **35** and **36** (5.6 mg, 0.018 mmol) in dry CH_2Cl_2 (1.0 mL) were added (S)-(+)-2-phenylglycinol (5.1 mg, 0.037 mmol), 1-hydroxybenzotriazole (HOBt) (3.0 mg, 0.023 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl (EDC· HCl) (6.9 mg, 0.036 mmol). The mixture was stirred for 1 h at 0 °C, allowed to warm to rt, and then followed overnight. The reaction mixture was washed with 5% *aq*. citric acid, saturated *aq*. $NaHCO_3$, and saturated NaCl. Then, the organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to provide 3.2 mg (41 %) of crude **11a** and **12a**.
* On TLC, the R_f value of the major component of this mixture of **11a** and **12a** from **35** and **36** was identical with that of authentic**12a**.

Preparation of 1:1 mixture **11f** and **12f**

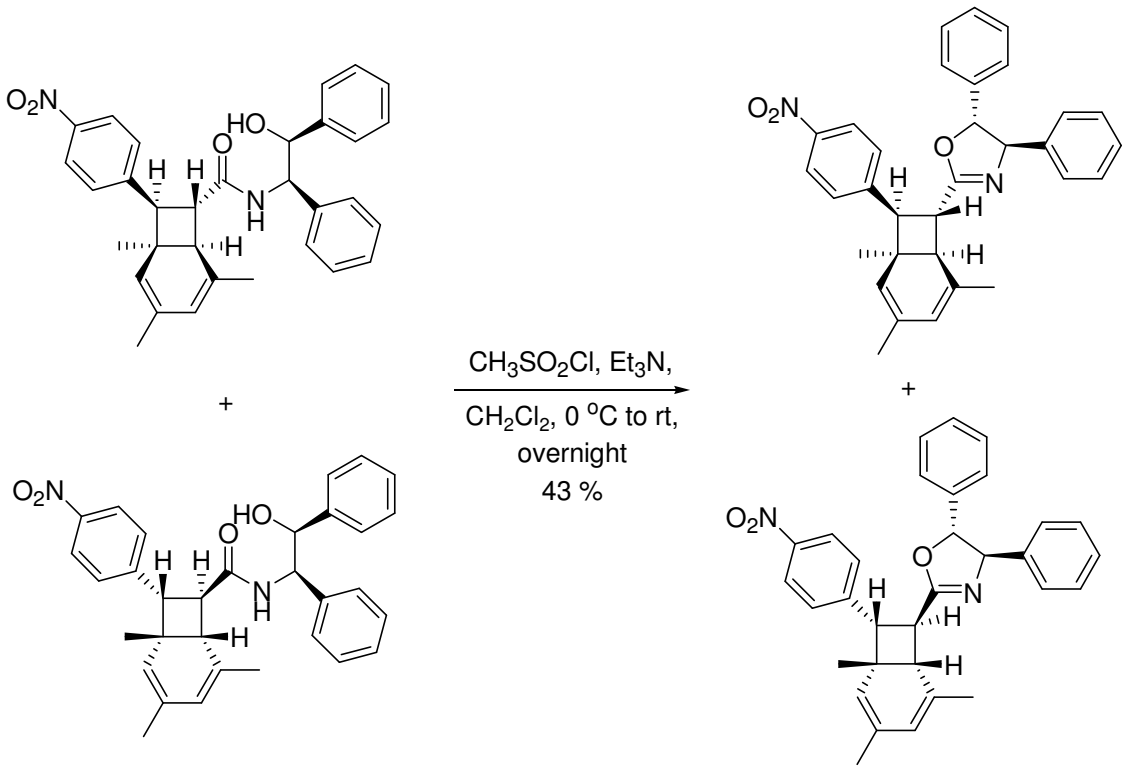


6 **19**

29 and **30**

Bicyclooctadienes 29 and 30. To a solution of **19** (33.4 mg, 0.077 mmol) and **6** (32.5 mg, 0.088 mmol) in anhydrous DMF (2.0 mL) were added CsF (22.6 mg, 0.151 mmol) and CuI(I) (5.6 mg, 0.029 mmol) at rt under degassing with a stream of Ar. After adding $Pd(PPh_3)_4$ (11.3 mg, 0.001 mmol), the reaction flask was immediately wrapped with aluminum foil and continued degassing for 5 min. The reaction mixture stirred for further 17 h, and then diluted with EtOAc (5 mL). The organic layer was washed with saturated NH_4Cl solution (3 x 5 mL). The combined *aq*. layers were extracted with EtOAc (3 x 5 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by preparative chromatography (EtOAc:*n*-hexane, 1:2) to provide 11.8 mg (29 %) of an inseparable mixture as a white solid.

R_f: 0.45 (EtOAc/*n*-hexane, 1/2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19 (d, J = 8.4 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H) 7.29 (d, J = 8.4 Hz, 1H), 7.10-7.24 (m, 6H), 7.01 (d, J = 7.2 Hz, 1H), 6.98 (d, J = 7.2 Hz, 1H), 6.92 (d, J = 7.2 Hz, 1H), 6.88 (d, J = 7.2 Hz, 1H), 6.01 (d, J = 8.4 Hz, 1H), 5.96 (d, J = 8.4 Hz, 1H), 5.48 (s, 0.5H), 5.43 (s, 0.5H), 5.25 (dd, J = 8.4 Hz, 7.8 Hz, 0.5H), 5.21 (dd, J = 8.4 Hz, 7.8 Hz, 0.5H), 3.75 (d, J = 10.2 Hz, 0.5H), 3.74 (d, J = 10.2 Hz, 0.5H), 3.69 (d, J = 10.2 Hz, 0.5H), 3.68 (d, J = 9.6 Hz, 0.5H), 3.30 (dd, J = 9.3 Hz, 8.4 Hz, 0.5H), 3.25 (dd, J = 9.3 Hz, 8.4 Hz, 0.5H), 2.75 (d, J = 8.4 Hz, 0.5H), 2.67 (d, J = 9.0 Hz, 0.5H), 1.78 (s, 1.5H), 1.65 (s, 1.5H), 1.63 (s, 3H), 1.24 (s, 1.5H), 1.22 (s, 1.5H).

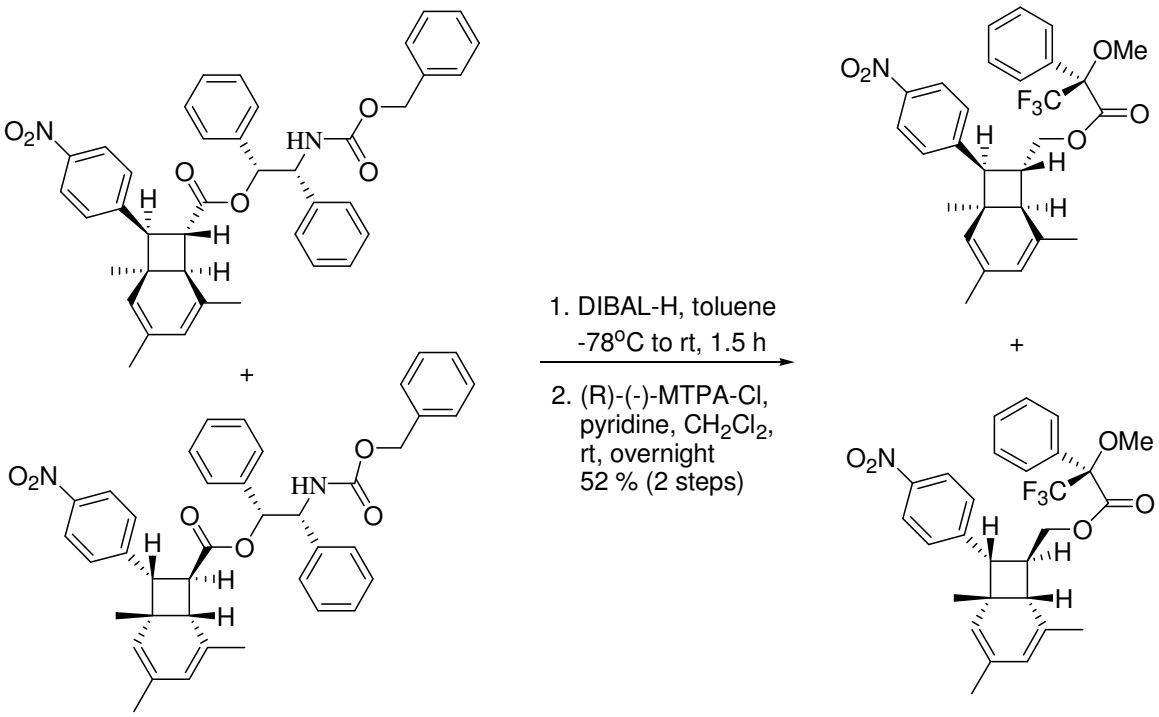


29 and **30** **11f** and **12f**

1:1 Mixture of 11f and 12f. To an ice-cooled solution of **29** and **30** (11.8 mg, 0.023 mmol) and triethylamine (20 μL, 0.143 mmol) in dry CH_2Cl_2 (1.0 mL) was added dropwise methanesulfonyl chloride (5 μL, 0.065 mmol) in dry CH_2Cl_2 (0.5 mL) via syringe. The reaction mixture was allowed to warm to rt and stirred overnight. Then saturated NH_4Cl solution (10 mL) was poured into the reaction mixture and the organic layer was separated. The *aq*. layer was extracted with CH_2Cl_2 (2 x 5 ml) and the combined extracts were dried over $MgSO_4$ and the solvent was removed under vacuum to afford 4.7 mg (43 %) of a pale yellow solid.

* Spectroscopic properties of 1:1 mixture of **11f** and **12f** were in agreement with **11f** and **12f** values above.

Calculation of the stereoselectivity

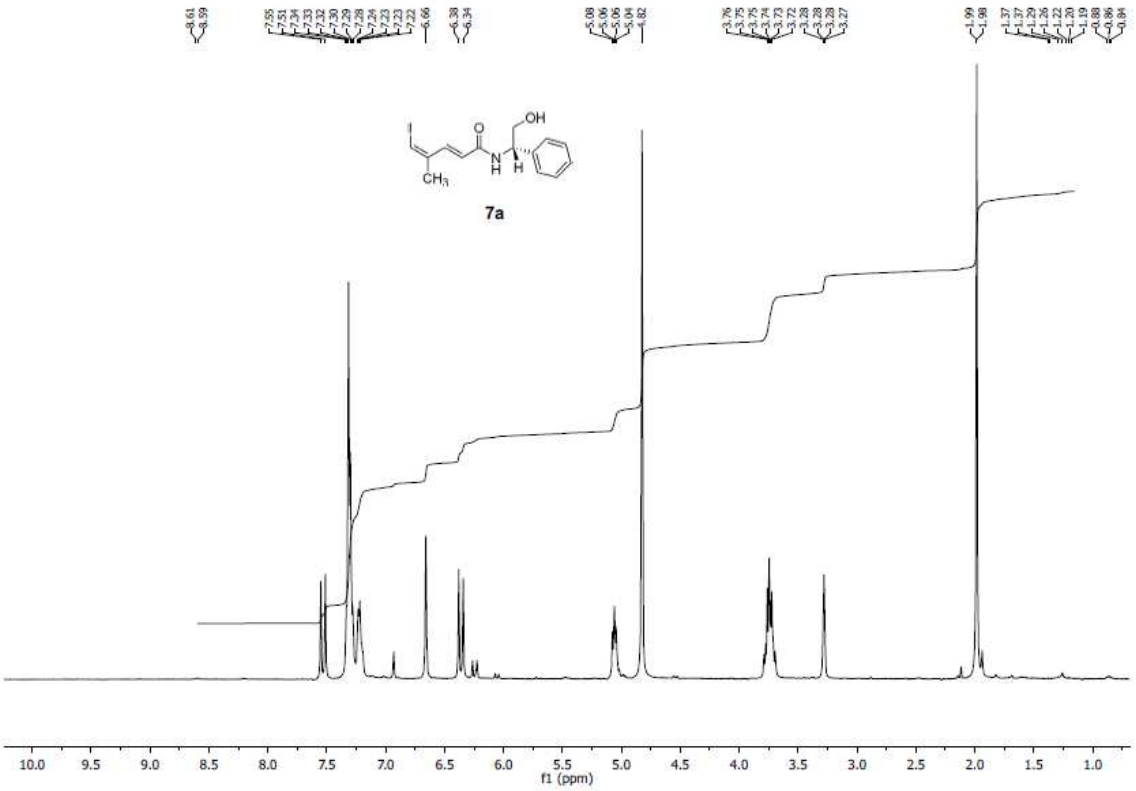


31 and **32** **33** and **34**

(S)-Mosher esters 33 and 34. [10] To a stirred solution of **31** and **32** (7.8 mg, 0.012 mmol) in dry toulene (0.5 mL) was added diisobutylaluminum hydride (DIBAL-H) (1.0 M in CH_2Cl_2 35 μL, 0.024 mmol) via syringe at -78 °C. The reaction mixture was stirred for 30 min at -78 °C, and then allowed to warm to rt. The reaction solution was again cooled to 0 °C, quenched with EtOAc (0.5 mL), and allowed to warm to rt. After pouring H_2O (2 mL) into the reaction solution, the *aq*. layer was extracted by CH_2Cl_2 (2 x 3 ml) and the combined extracts were washed with saturated NH_4Cl solution and brine. The organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to afford 4.2 mg of crude bicyclo[4.2.0]octadiene substrate bearing methyl alcohol as yellow solid. The crude (4.2 mg, 0.014 mmol) of CH_2Cl_2 (1.4 mL) solution was treated with DMAP (3.6 mg, 0.030 mmol). Then (R)-(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride, (R)-(-)-MTPA-Cl, (10 μL, 0.039 mmol) was added via syringe and the reaction solution was stirred overnight. After removing volatile compounds under vacuum, the residue was purified by preparative chromatography (EtOAc/*n*-hexane, 1:5) to provide 3.2 mg (52 % for the two steps) of an inseparable mixture as pale yellow solid.
R_f: 0.59 (EtOAc/*n*-hexane, 1/5); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 (d, J = 8.4 Hz, 2H), 7.23-7.42 (m, 7H), 5.42 (s, 0.16H), 5.40 (s, 0.84H), 4.48 (dd, J = 7.8 Hz, 6.0 Hz, 0.86H), 4.33 (s, 1H), 4.32 (m, 0.28H), 4.22 (dd, J = 11.4 Hz, 6.4 Hz, 0.86H), 3.44 (s, 2.56H), 3.41 (s, 0.44H), 3.28 (d, J = 10.2 Hz, 1H), 3.01 (m, 1H), 2.26 (d, J = 8.4 Hz, 1H), 1.69 (s, 3H), 1.60 (s, 3H), 1.23 (s, 3H).

^{1}H NMR and ^{13}C NMR spectra for new compounds

[10] For an informative review of the Mosher ester technique, see Hoye, T.R.; Jeffrey, C.S.; Shao, F. *Nature Protocols* **2007**, *2*, 2451-2458.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5.04
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O
N
H
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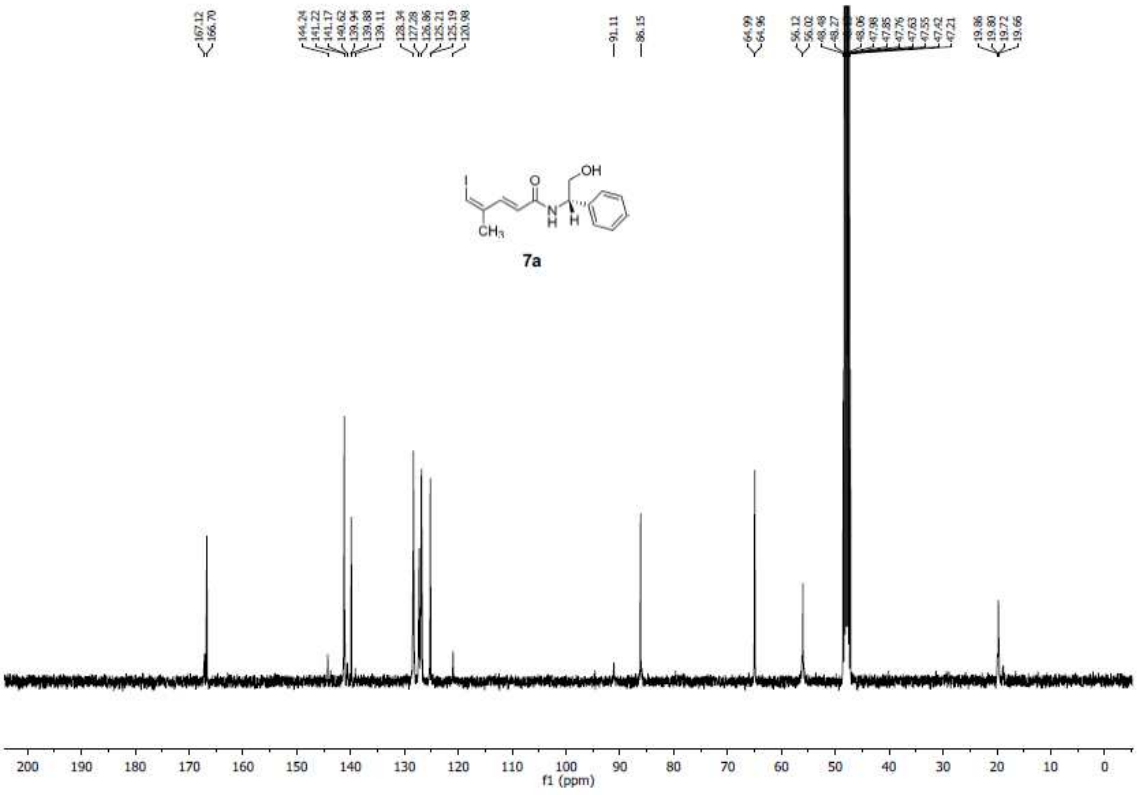
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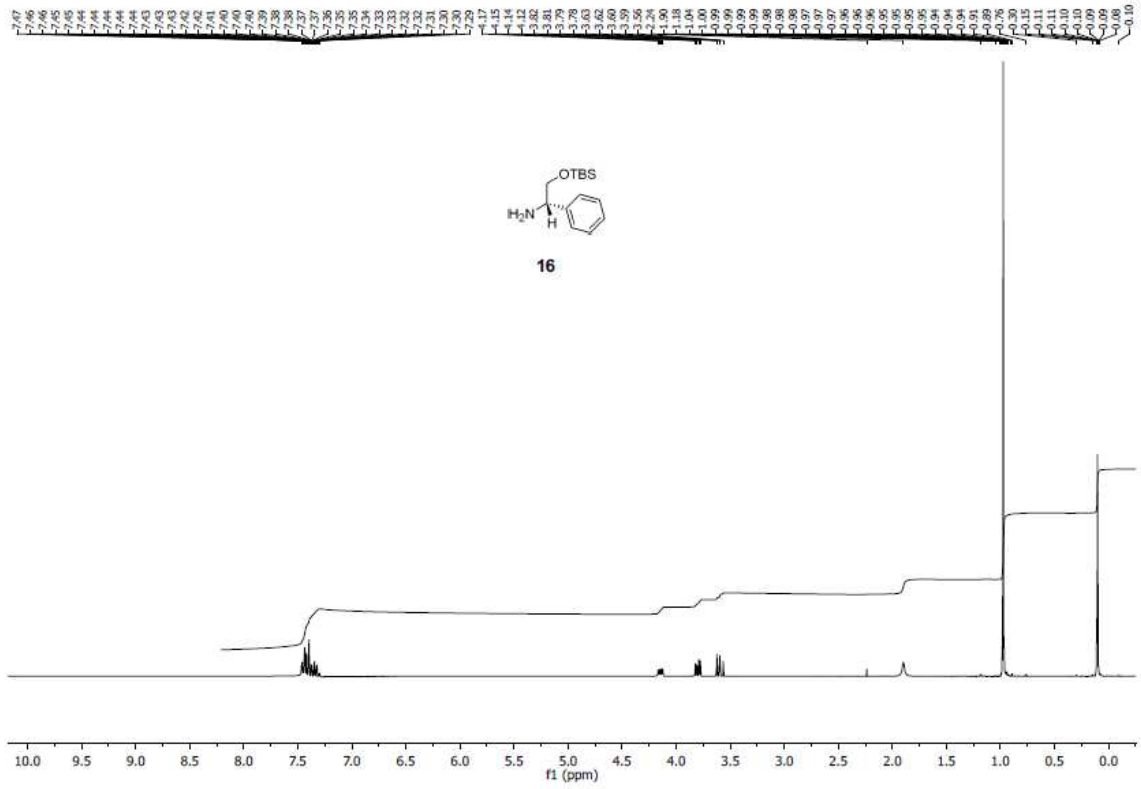
f1 (ppm)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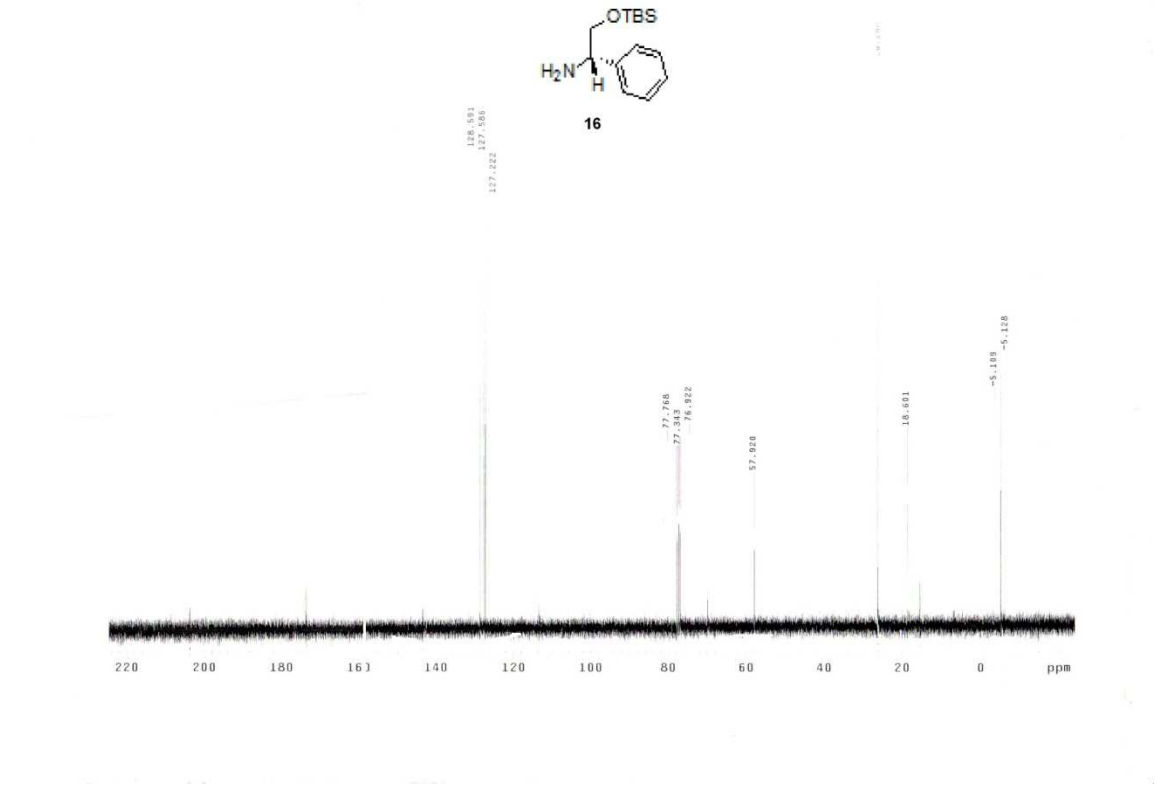
f1 (ppm)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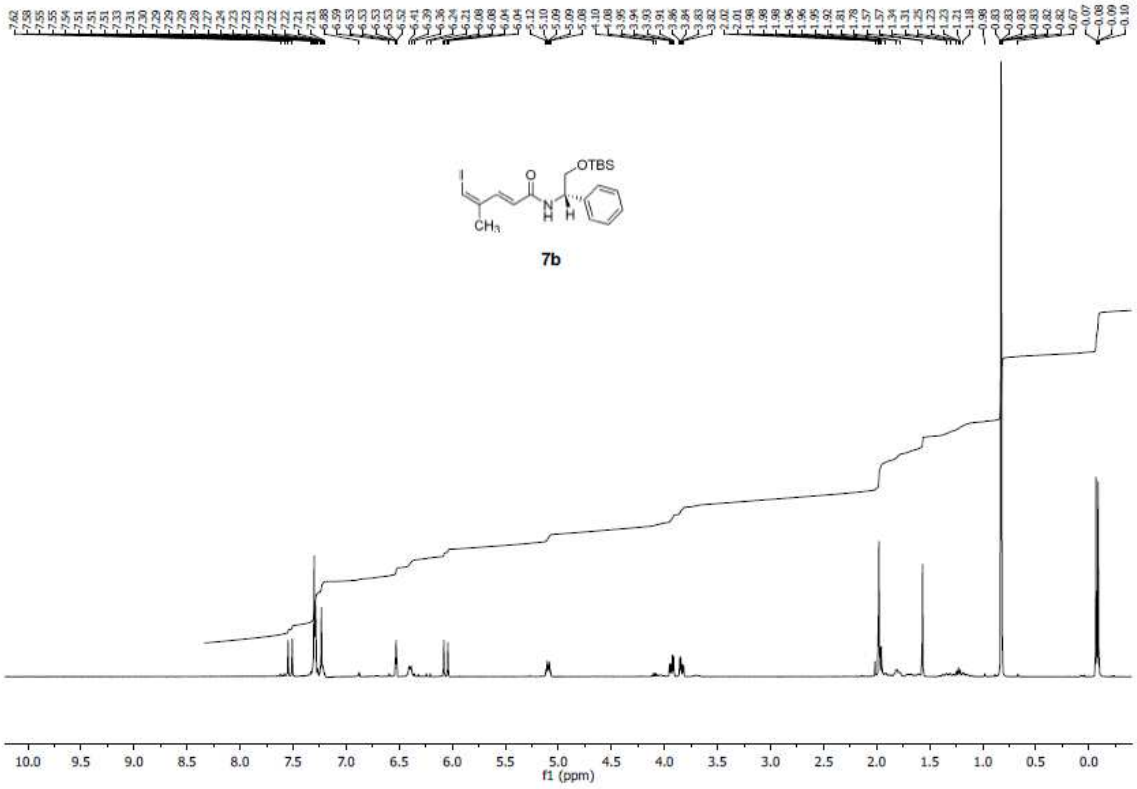
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7b
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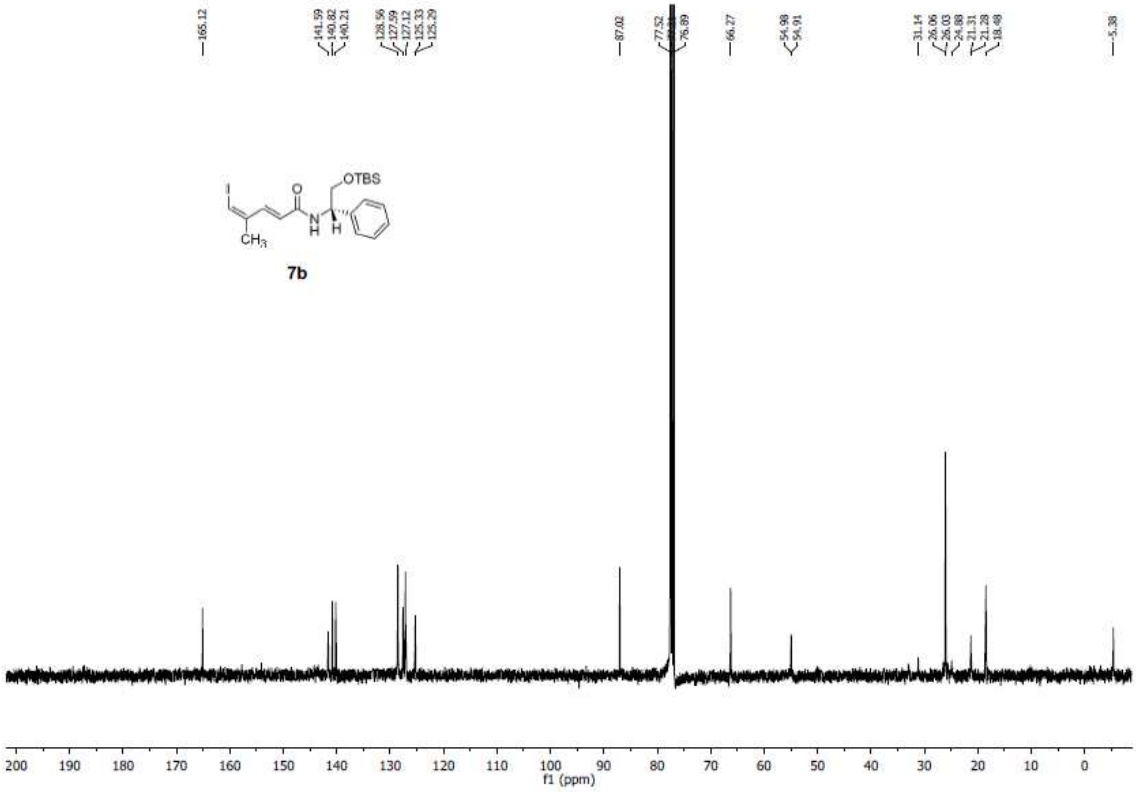
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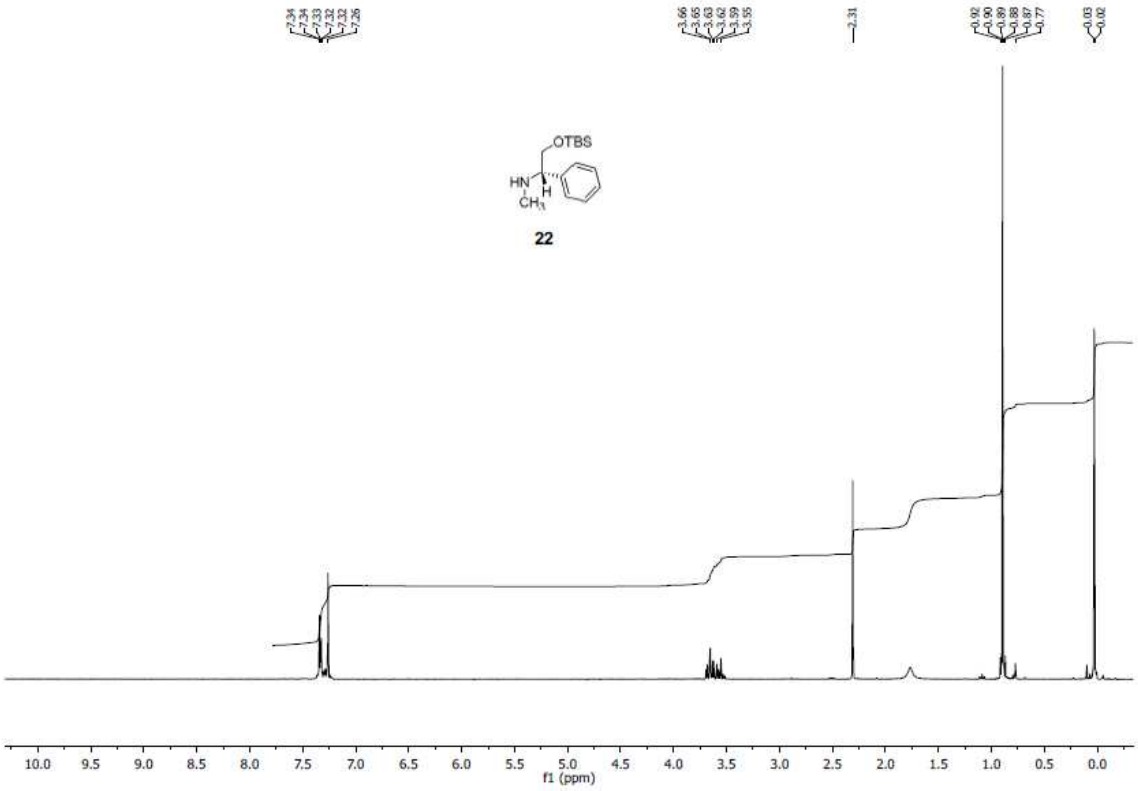
f1 (ppm)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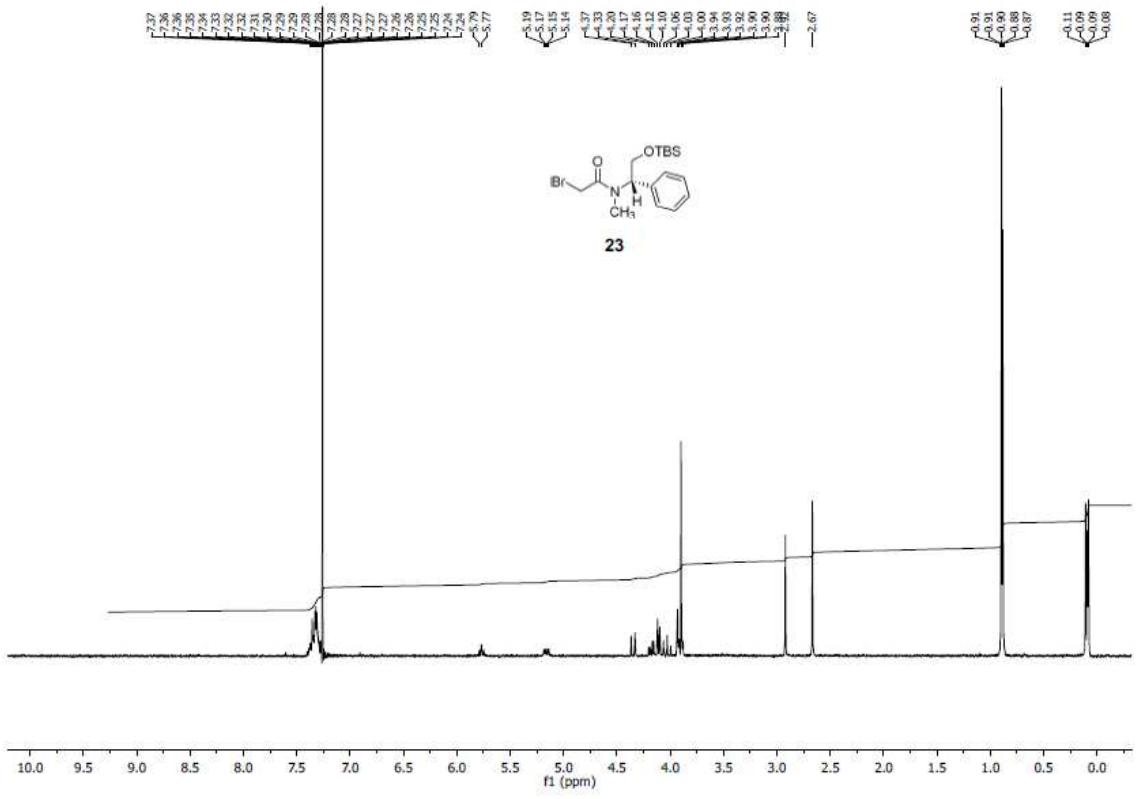
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3.90
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0.91
0.90
0.88
0.87
0.11
0.09
0.09
0.08
OTBS
Br
O
N
CH3
H
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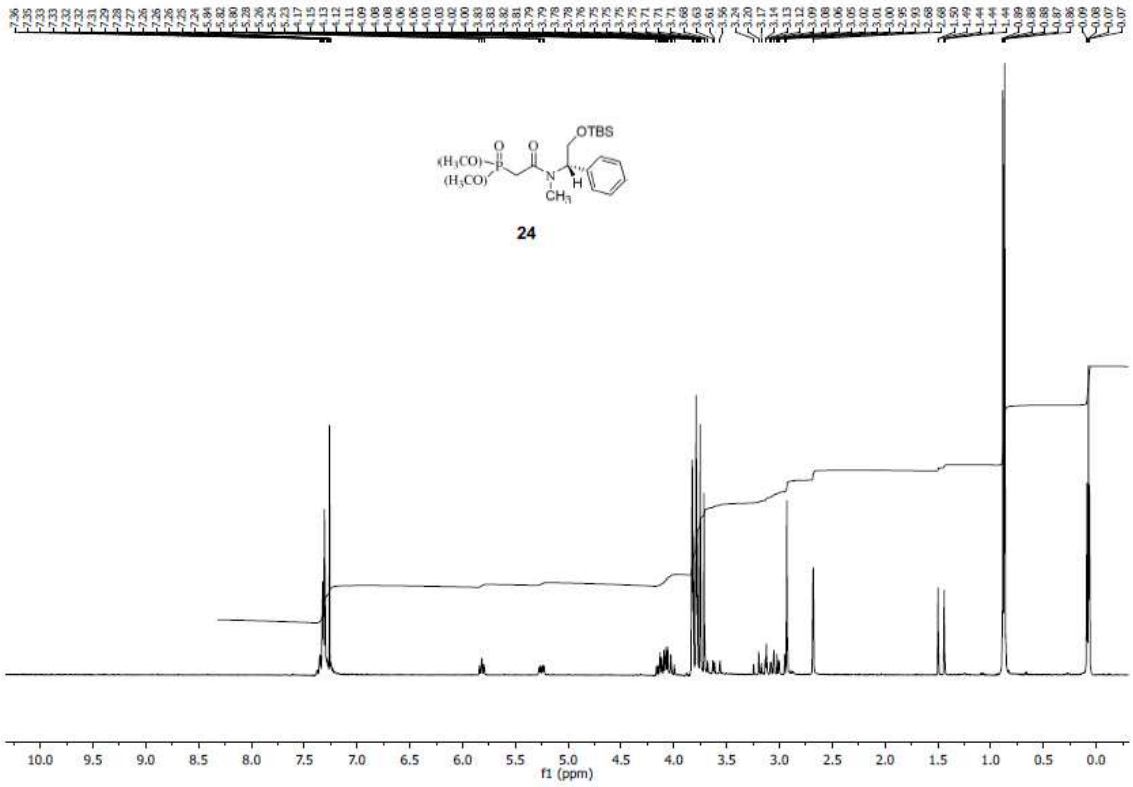
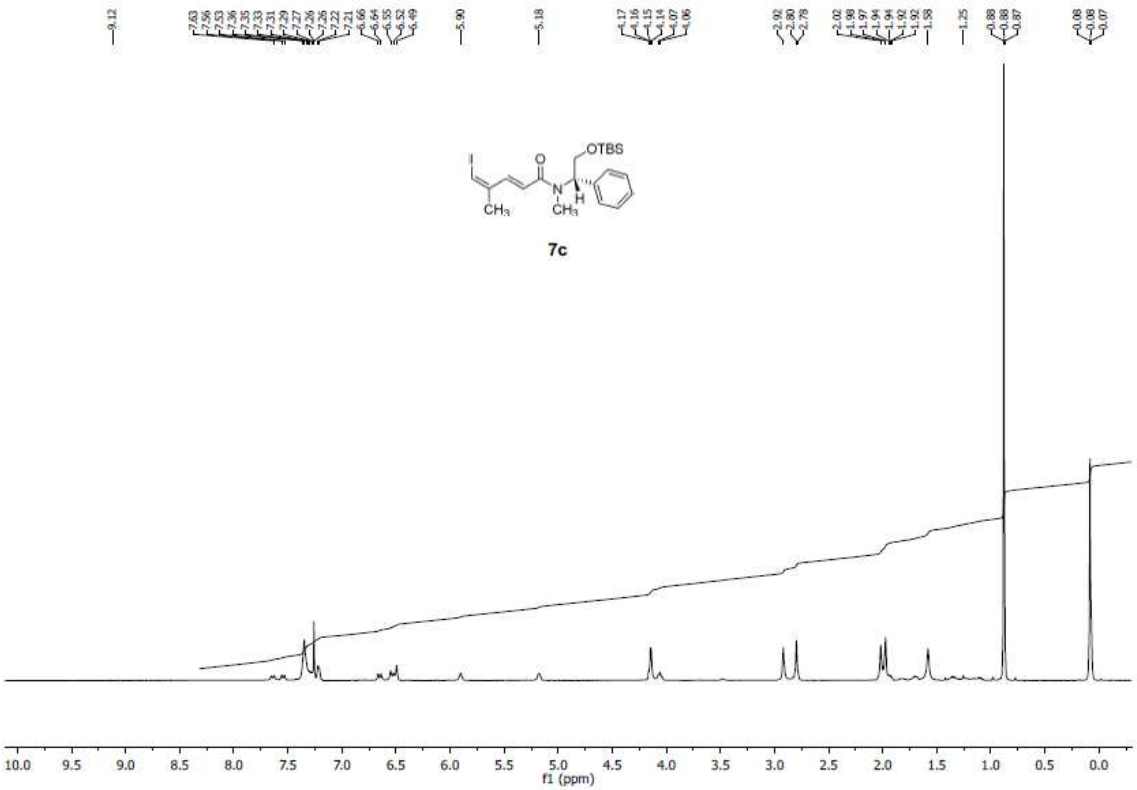
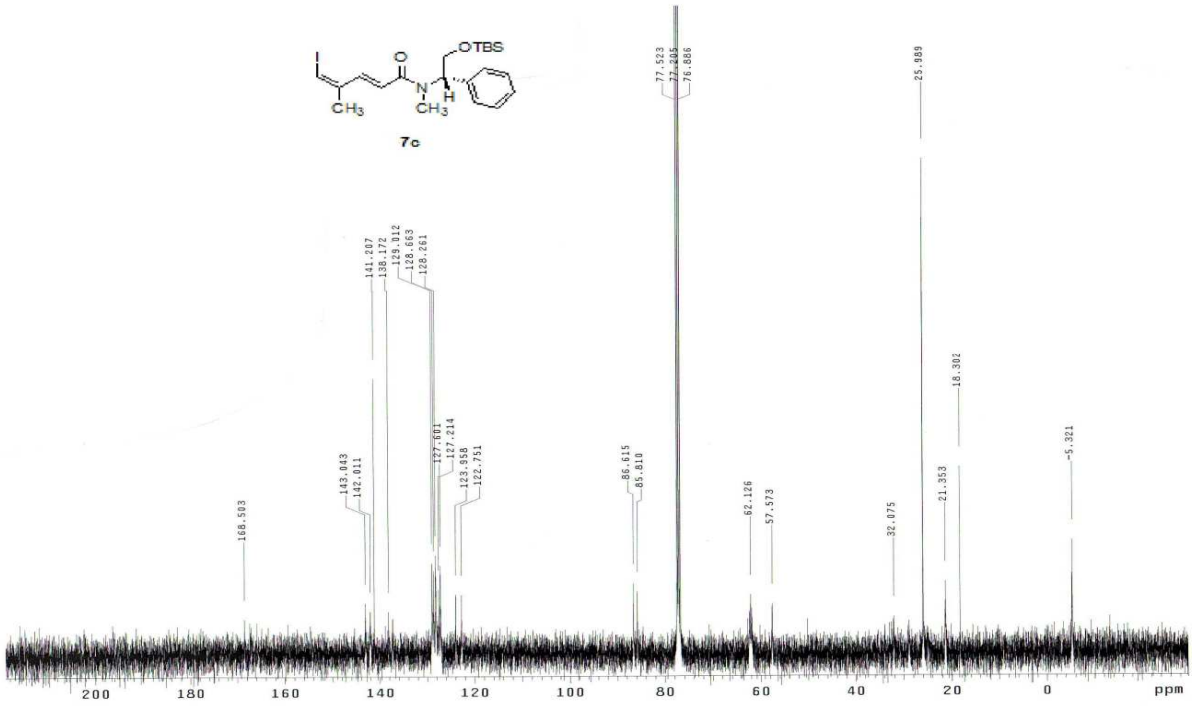
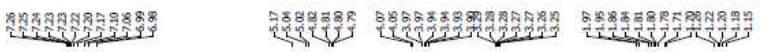
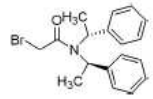
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


OTBS
(H3CO)
(H3CO)
CH3
24
f1 (ppm)

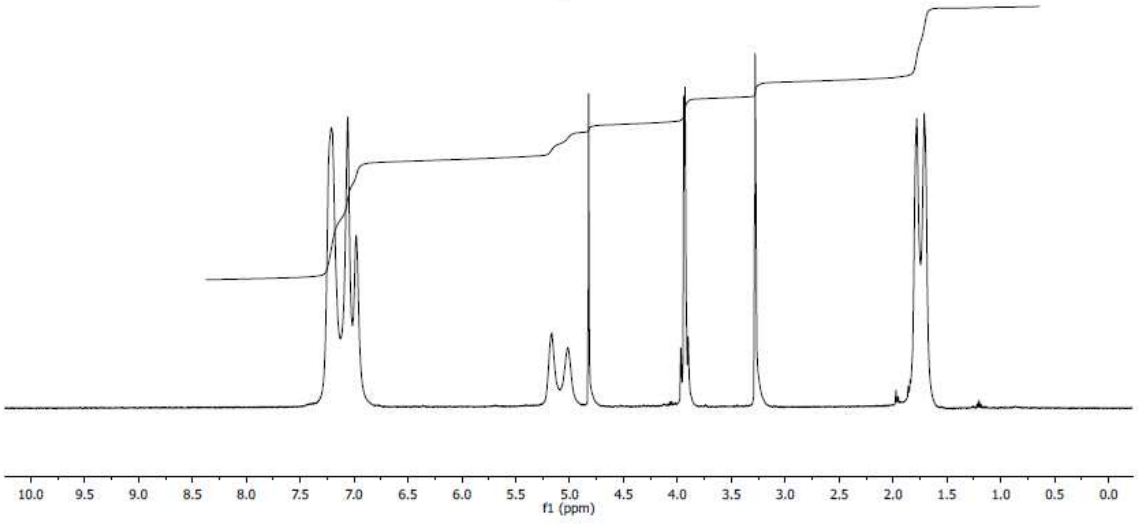

OTBS
CH3
CH3
7c
f1 (ppm)

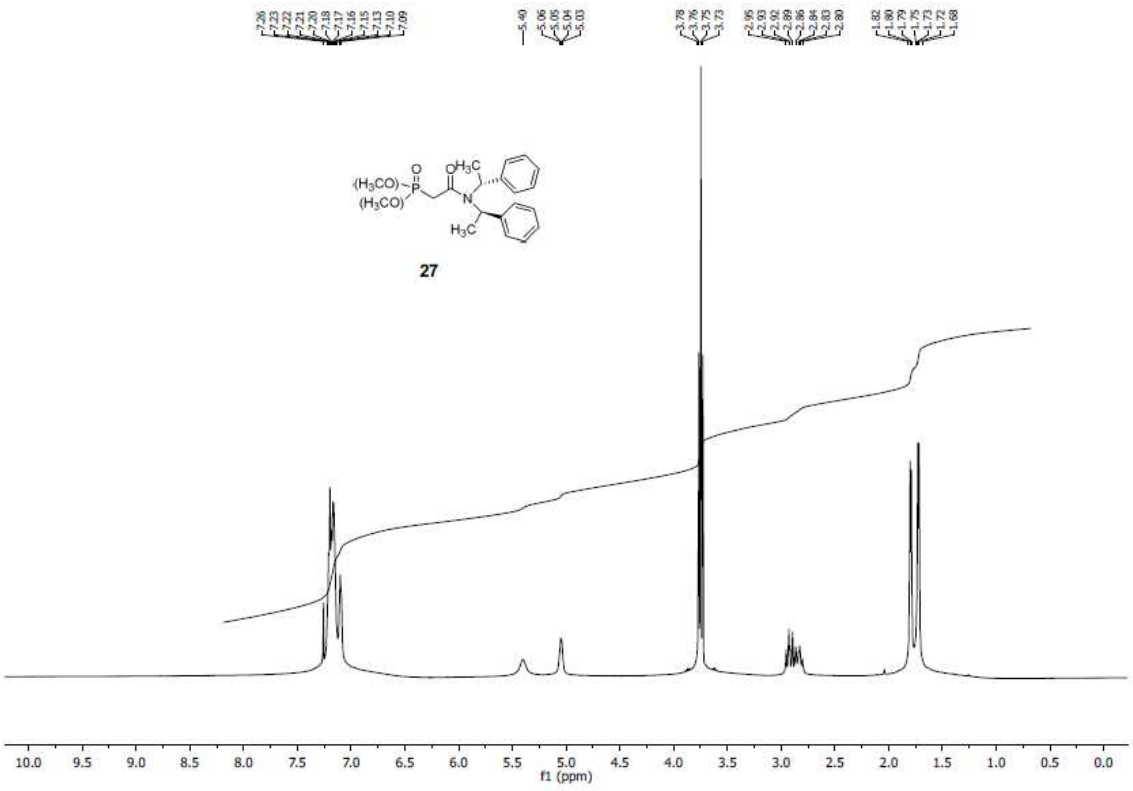

OTBS
O
N
H
CH3
CH3
I
7c
168.593
143.043
142.011
141.207
138.172
129.012
128.663
128.461
127.601
127.214
123.958
122.751
86.615
85.810
77.523
77.205
76.886
62.126
57.573
32.075
25.989
21.353
18.302
-5.321
200
180
160
140
120
100
80
60
40
20
0
ppm

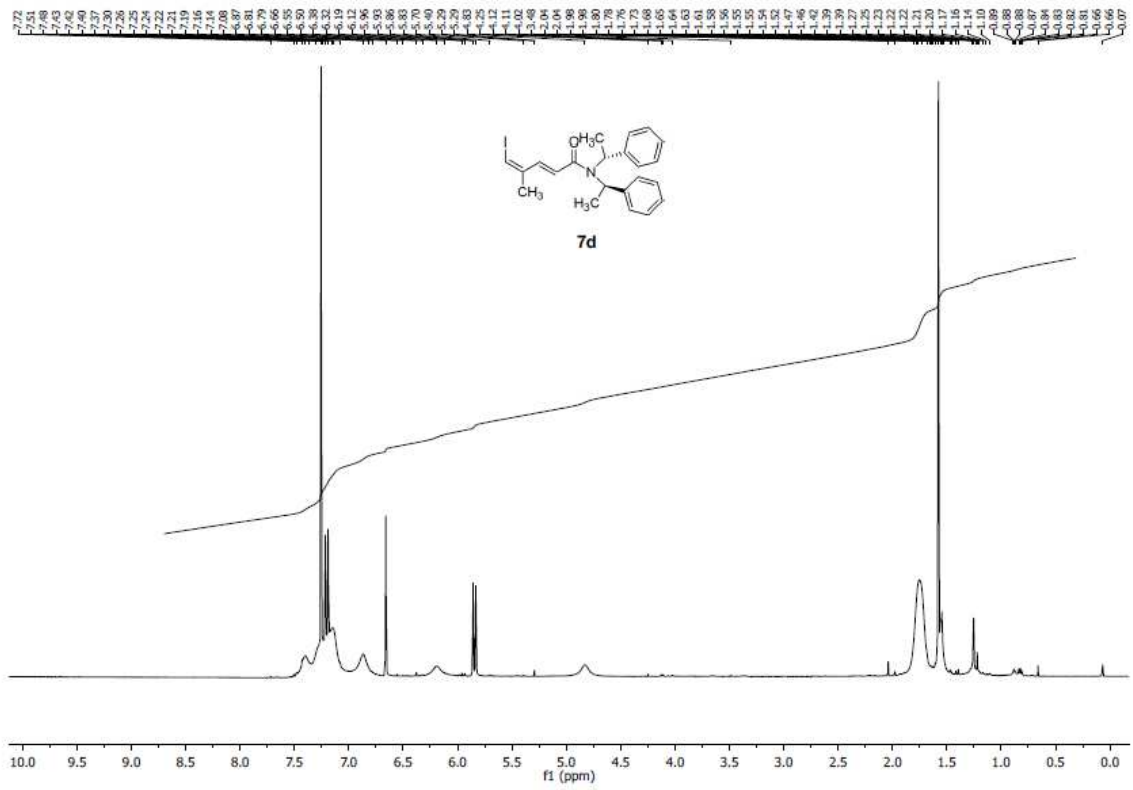


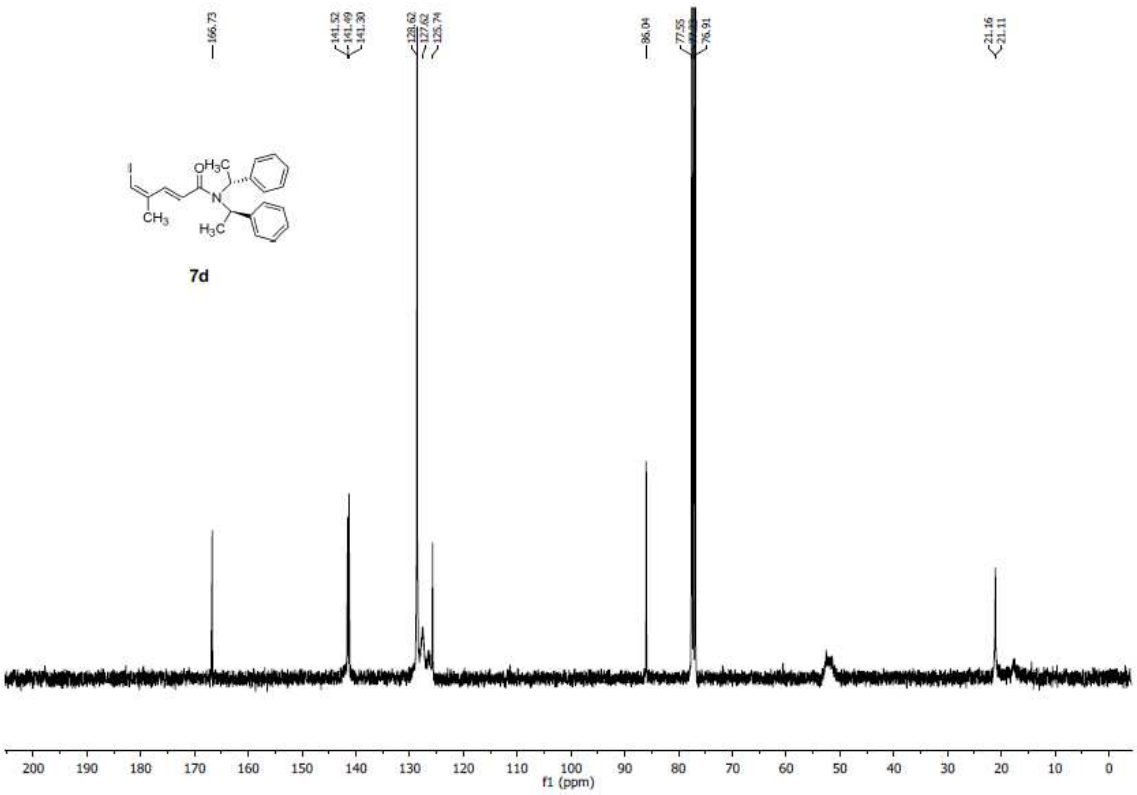

O
H3C
Br
N
H3C

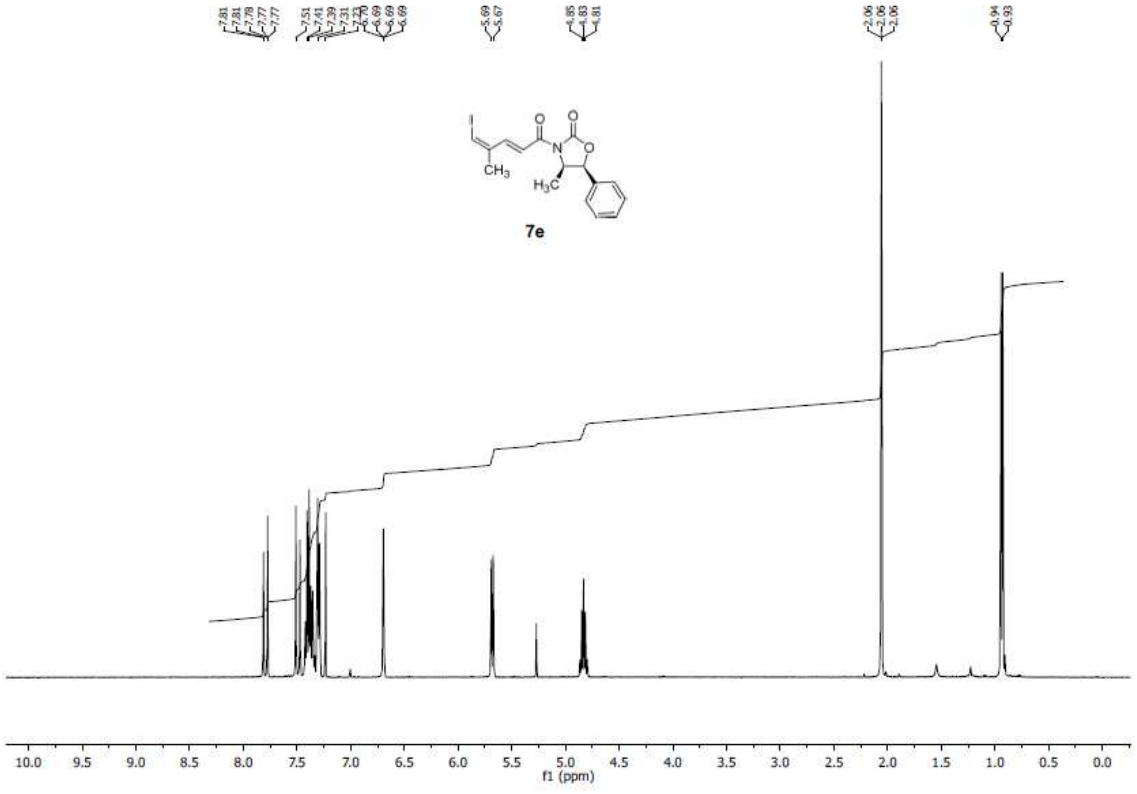
26

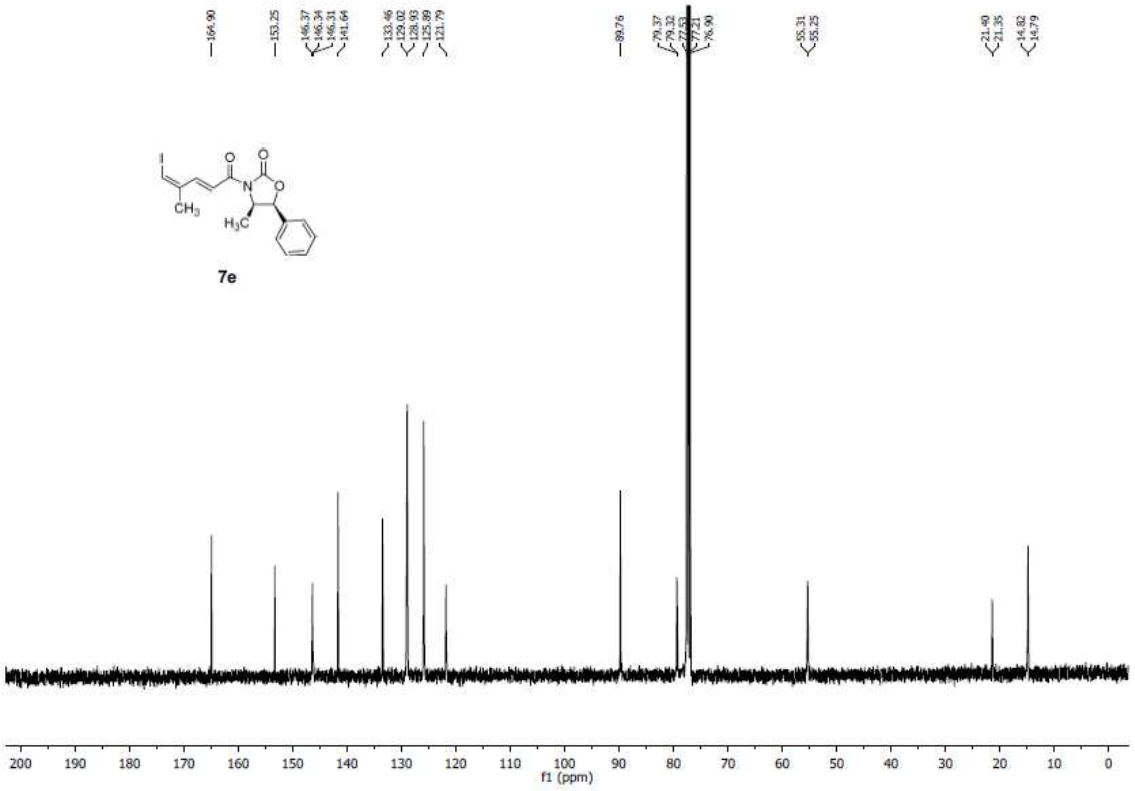

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

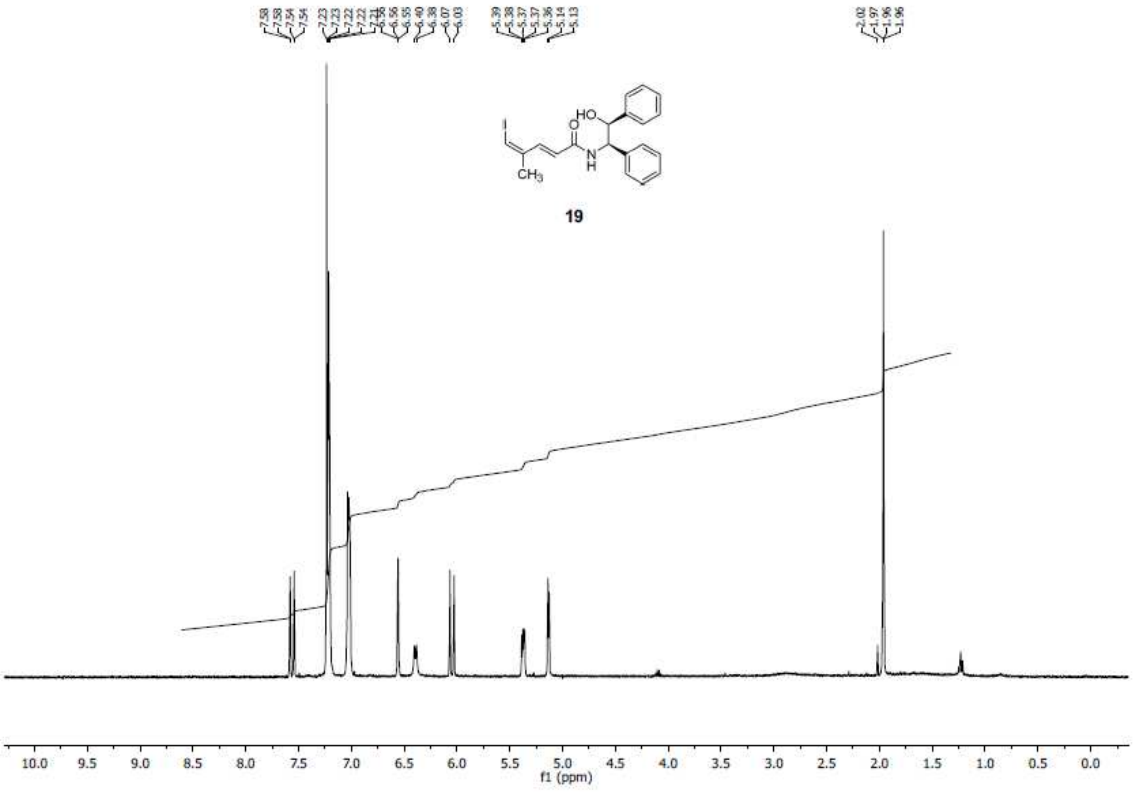

(H3CO)
(H3CO)
O
O
H3C
N
H3C
27
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

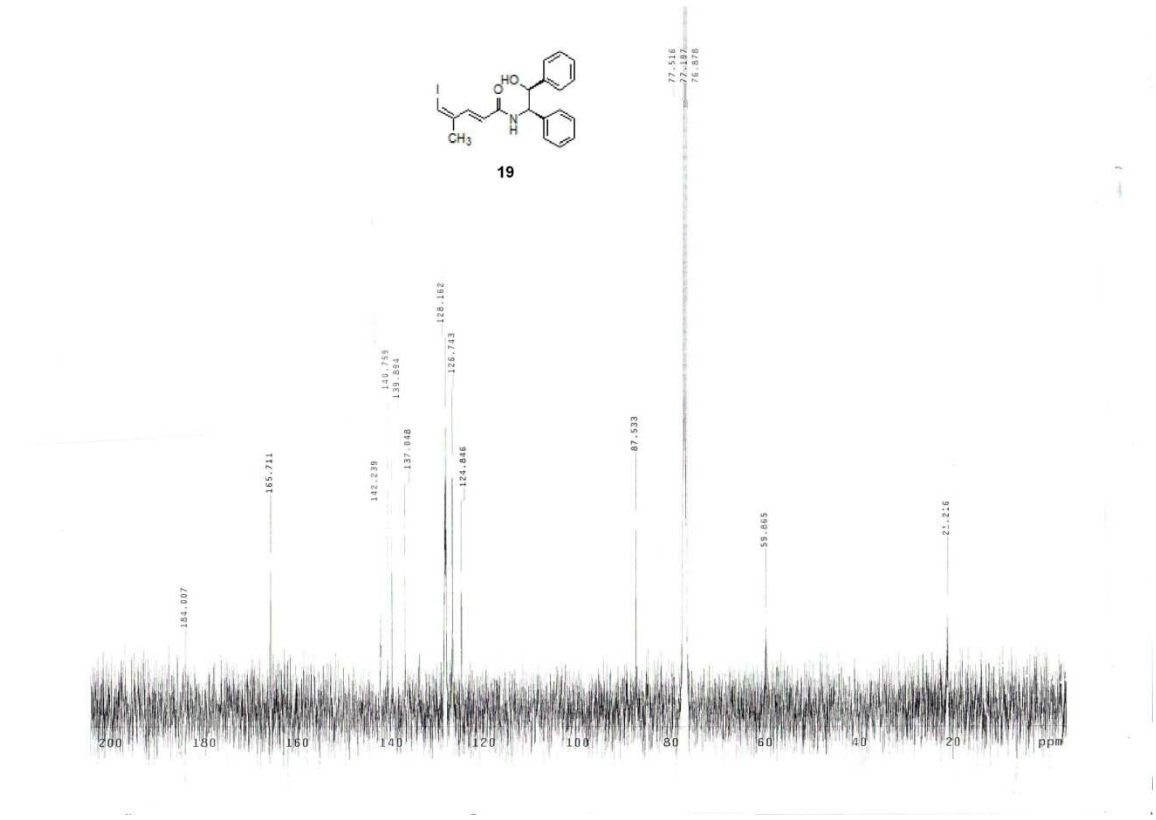

I
CH3
O
H3C
N
H3C
7d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

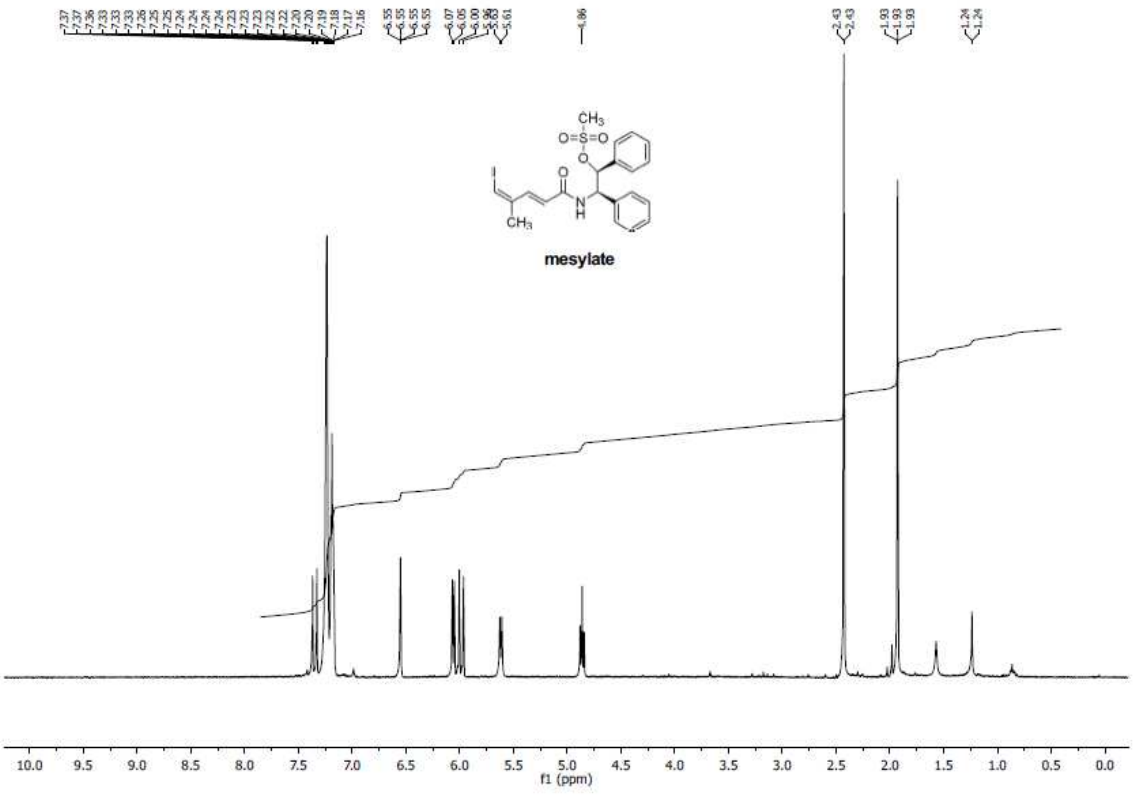

166.73
141.52
141.49
141.30
128.62
127.62
125.74
86.04
77.55
76.91
21.16
21.11
7d
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

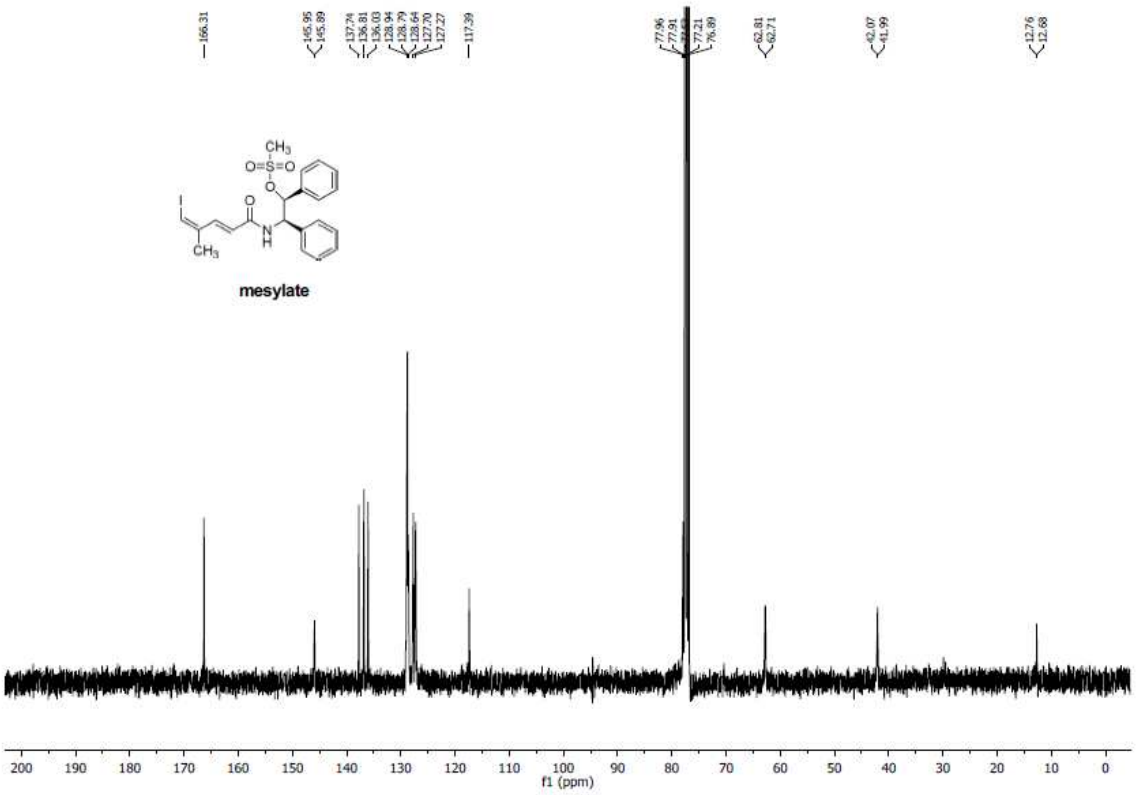

7.81
7.81
7.78
7.77
7.77
7.51
7.41
7.39
7.31
6.69
6.69
6.69
5.69
5.67
4.85
4.83
4.81
2.06
2.06
2.06
0.94
0.93
7e
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

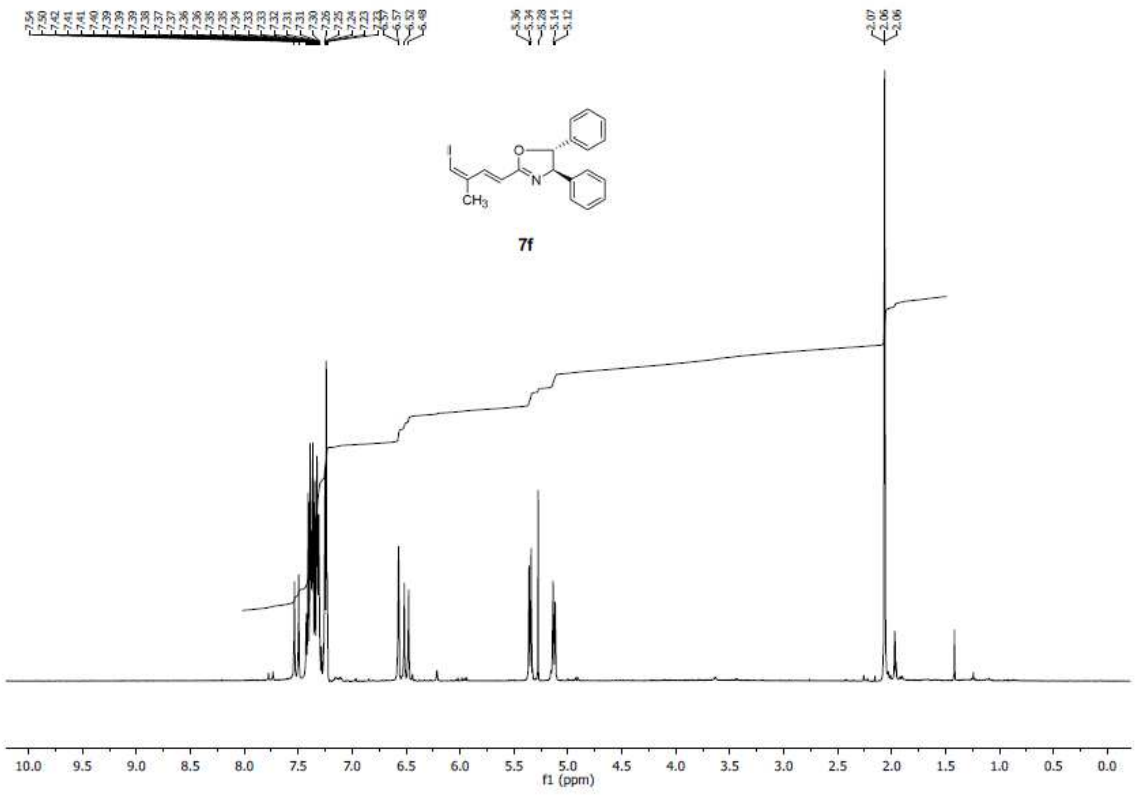

164.90
153.25
146.37
146.34
146.31
141.64
133.46
129.02
128.93
125.89
121.79
89.76
79.37
79.32
77.53
77.21
76.90
55.31
55.25
21.40
21.35
14.82
14.79
7e
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

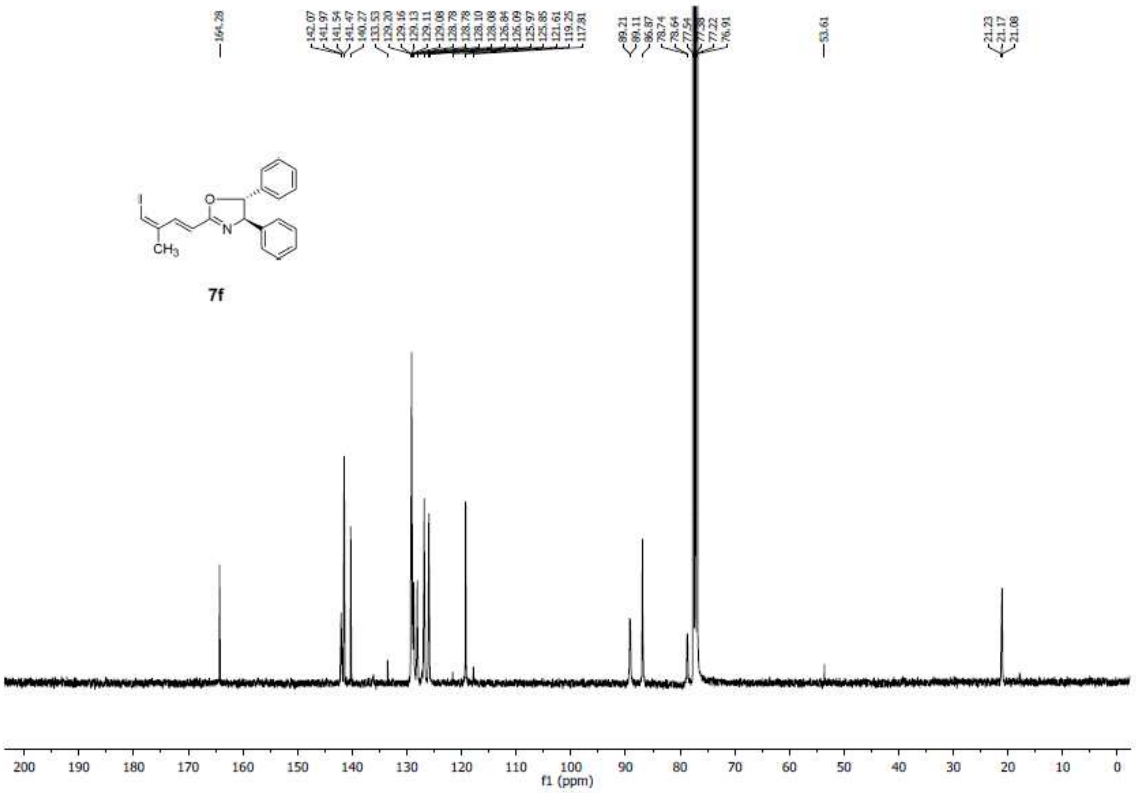

7.58
7.58
7.54
7.54
7.23
7.23
7.22
7.22
7.21
6.56
6.55
6.40
6.38
6.07
6.03
5.39
5.38
5.37
5.37
5.36
5.14
5.13
2.02
1.97
1.96
1.96
19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

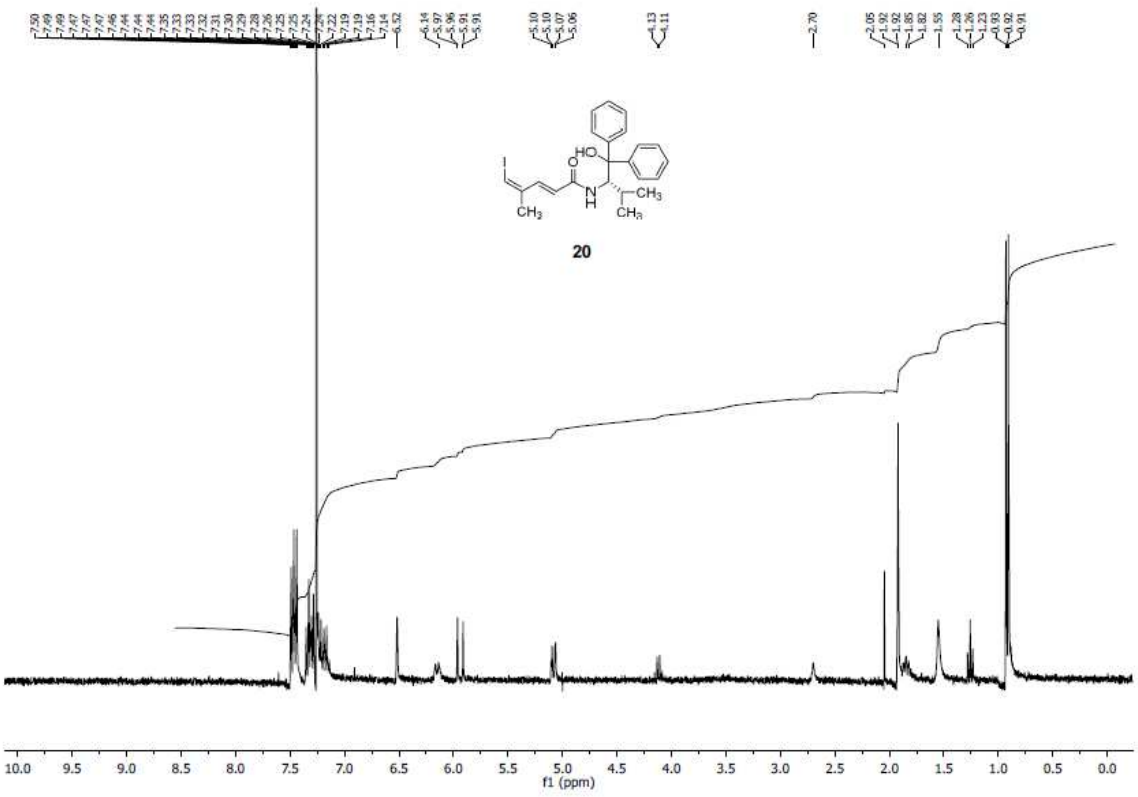

19
184.007
165.711
142.239
140.759
139.884
137.048
128.162
126.743
124.846
87.533
77.516
77.197
76.878
59.865
21.216
200
180
160
140
120
100
80
60
40
20
ppm

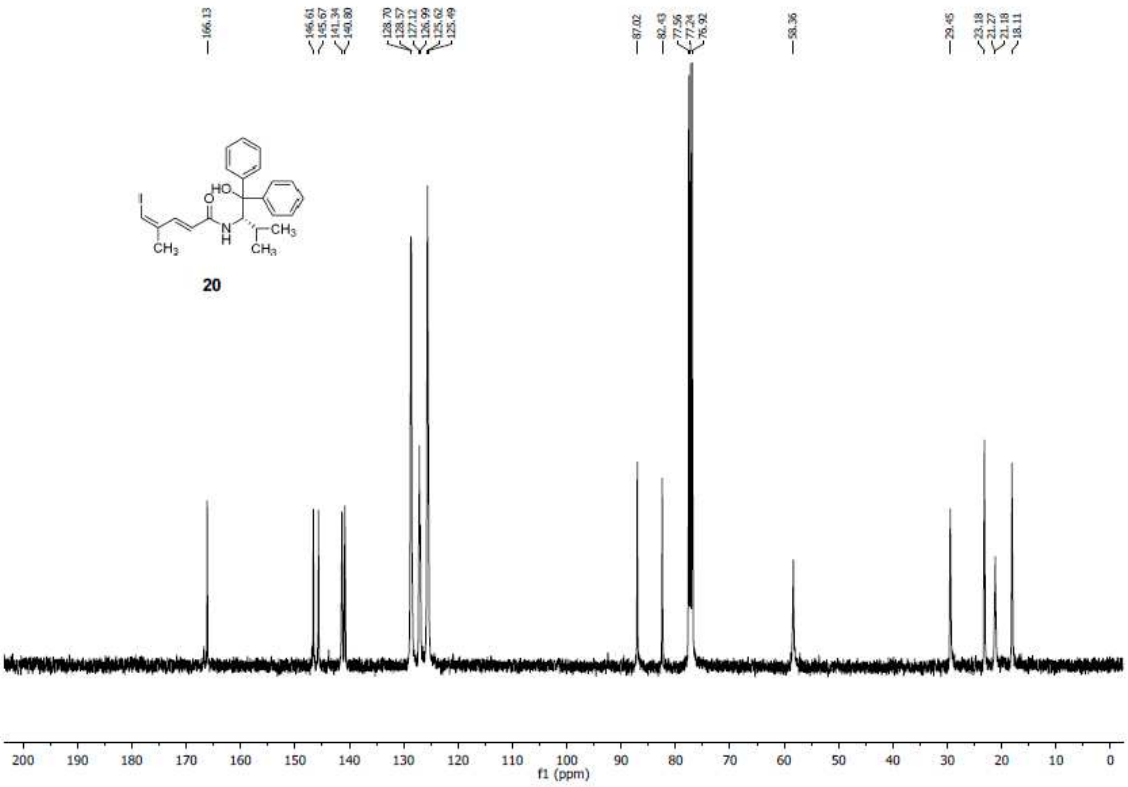

mesylate
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

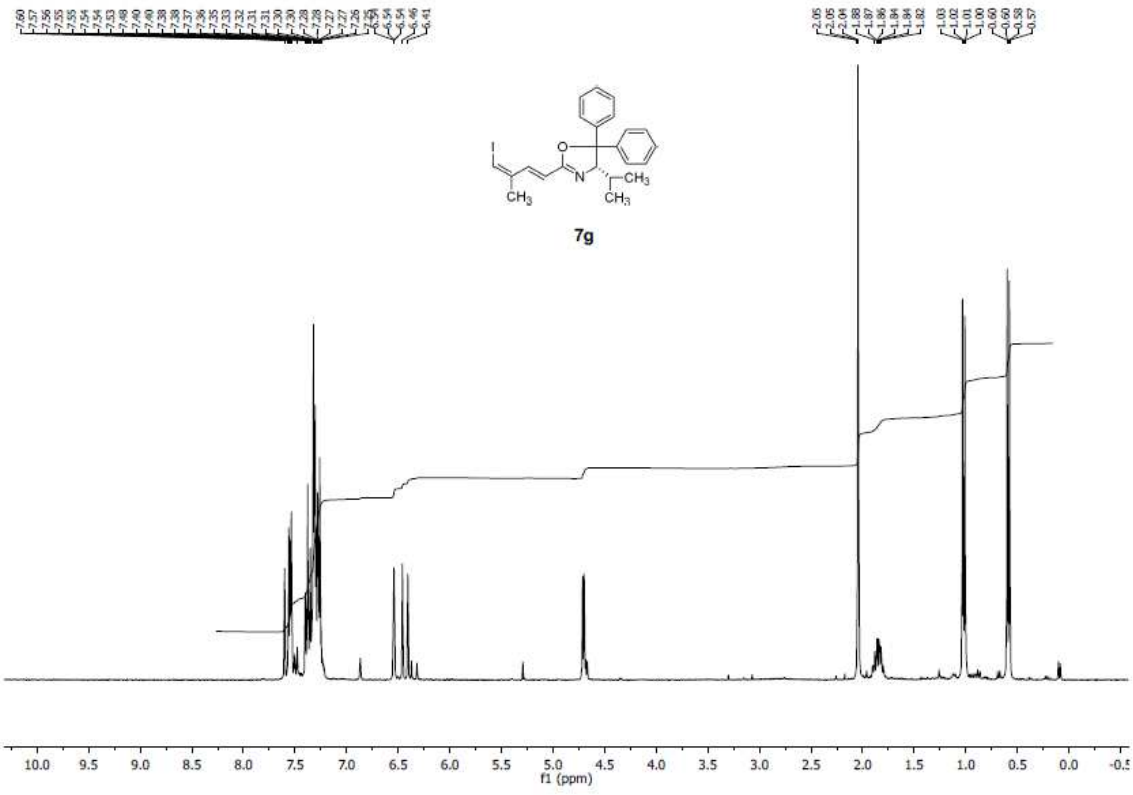

166.31
145.95
145.89
137.74
136.81
136.03
128.94
128.79
128.64
127.70
127.27
117.39
77.96
77.91
77.21
76.89
62.81
62.71
42.07
41.99
12.76
12.68
mesylate
f1 (ppm)

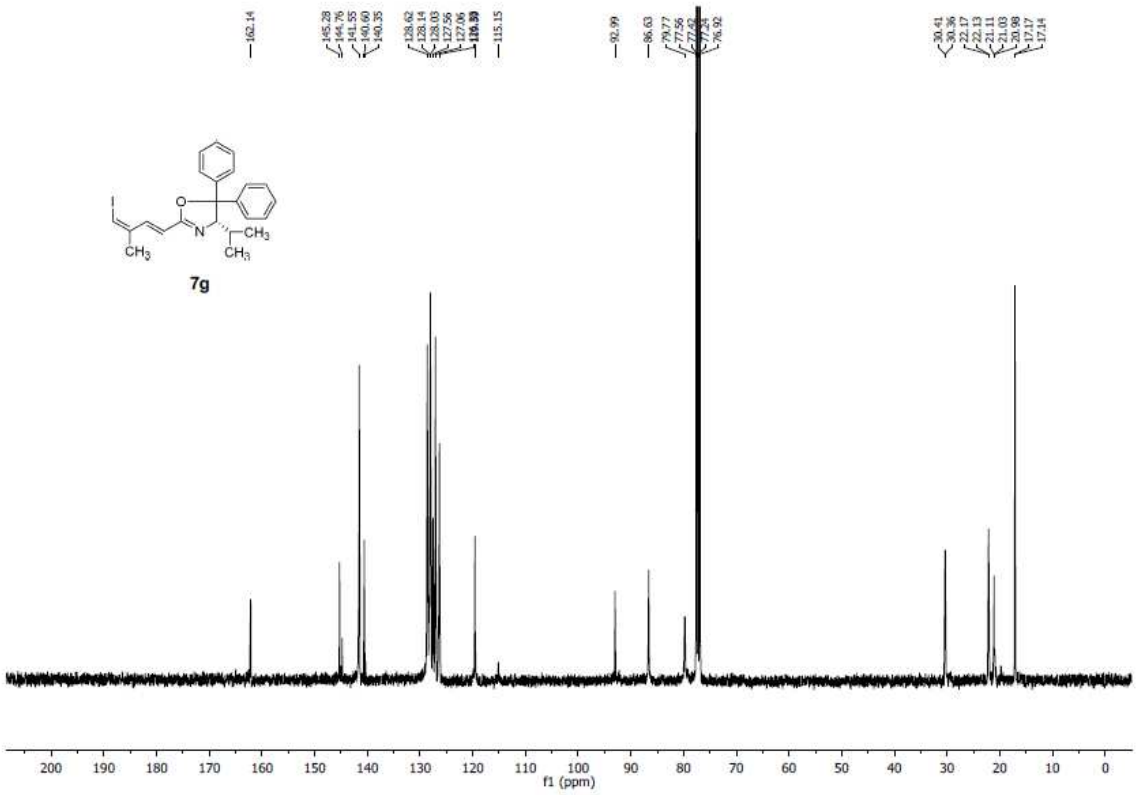

7.54
7.50
7.42
7.41
7.41
7.40
7.39
7.39
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.25
7.25
7.24
7.23
6.57
6.52
6.48
5.36
5.34
5.28
5.14
5.12
3.07
2.06
2.00
7f
f1 (ppm)

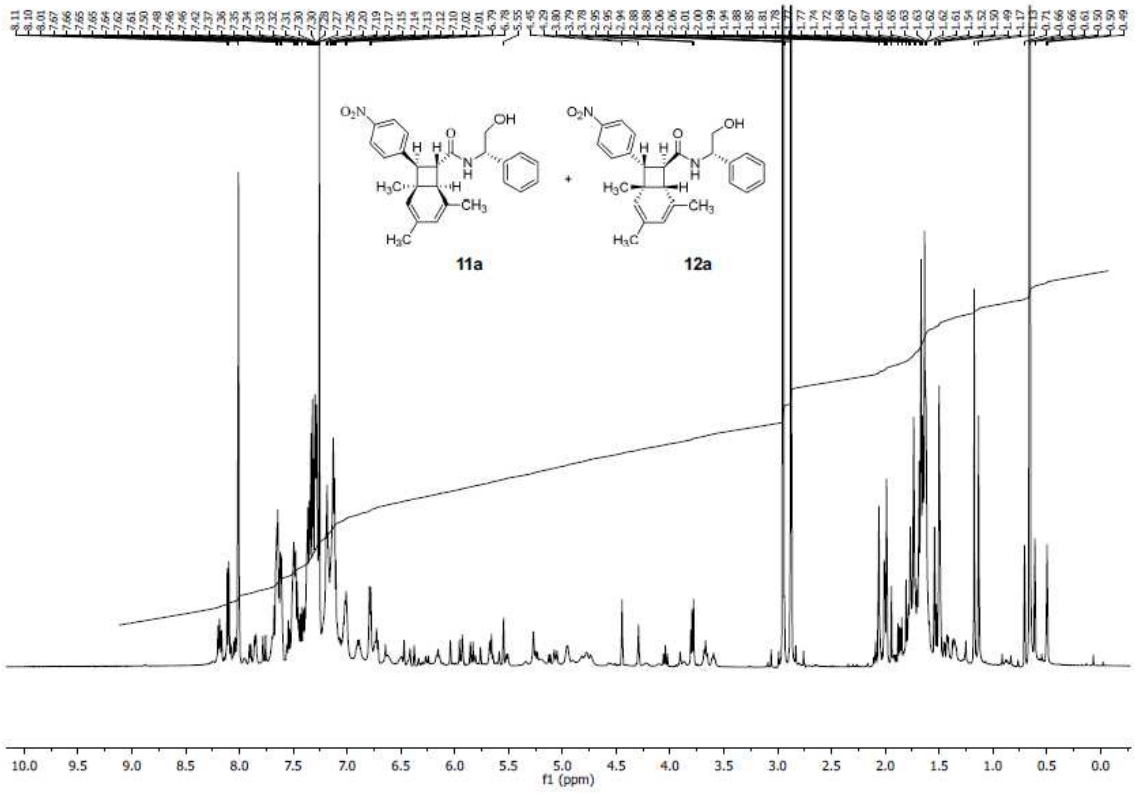

7f
f1 (ppm)

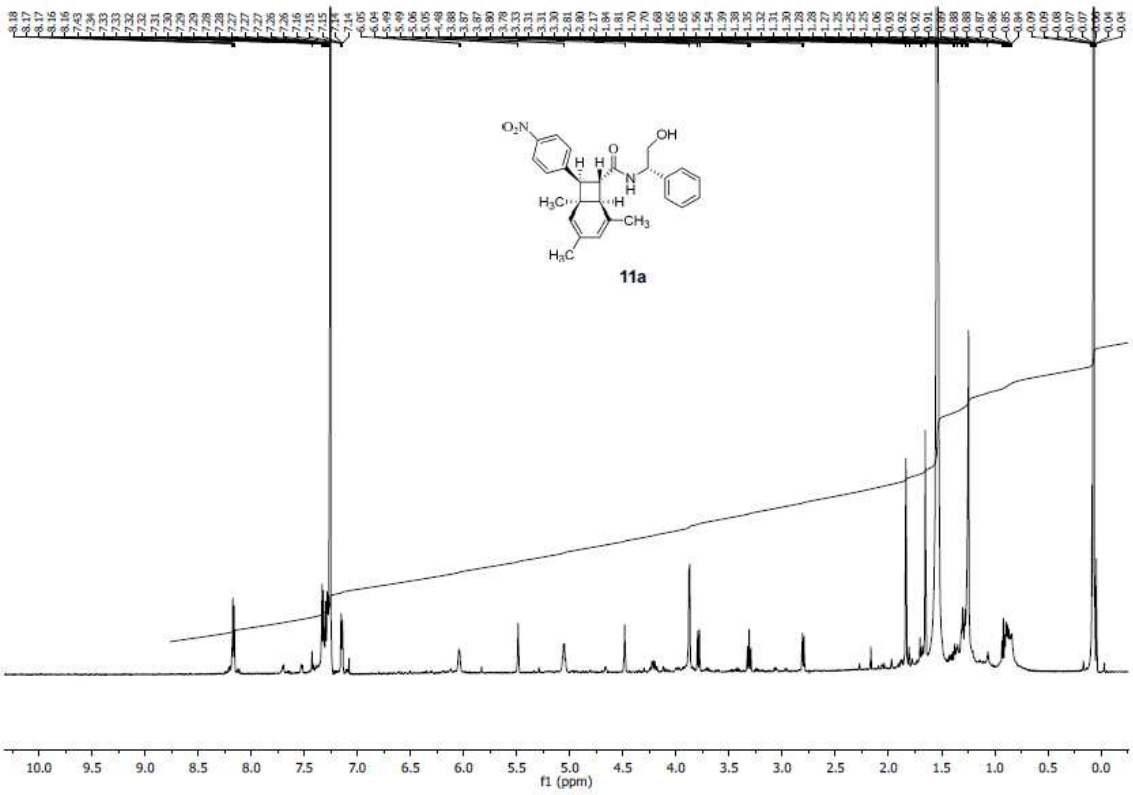

20
f1 (ppm)

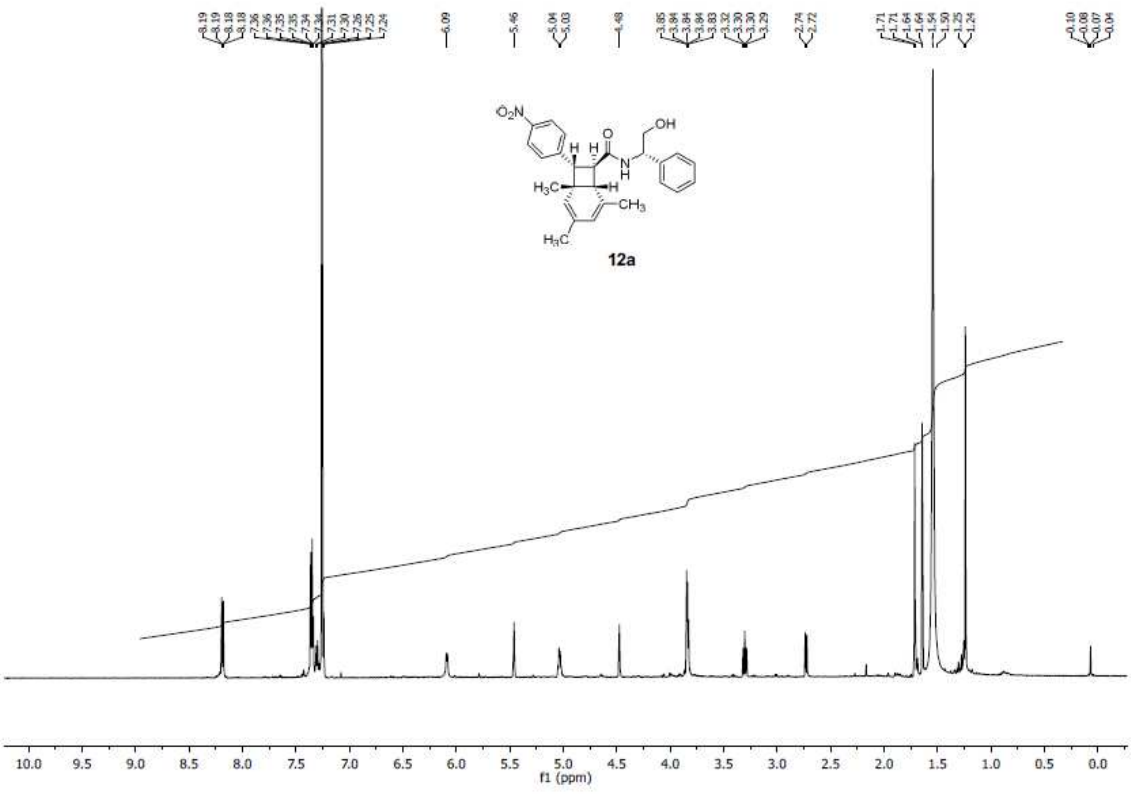

166.13
146.61
145.67
141.34
140.80
128.70
128.57
127.12
126.99
125.62
125.49
87.02
82.43
77.56
77.24
76.92
58.36
29.45
23.18
21.27
21.18
18.11
HO
O
N
I
CH3
CH3
CH3
20
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

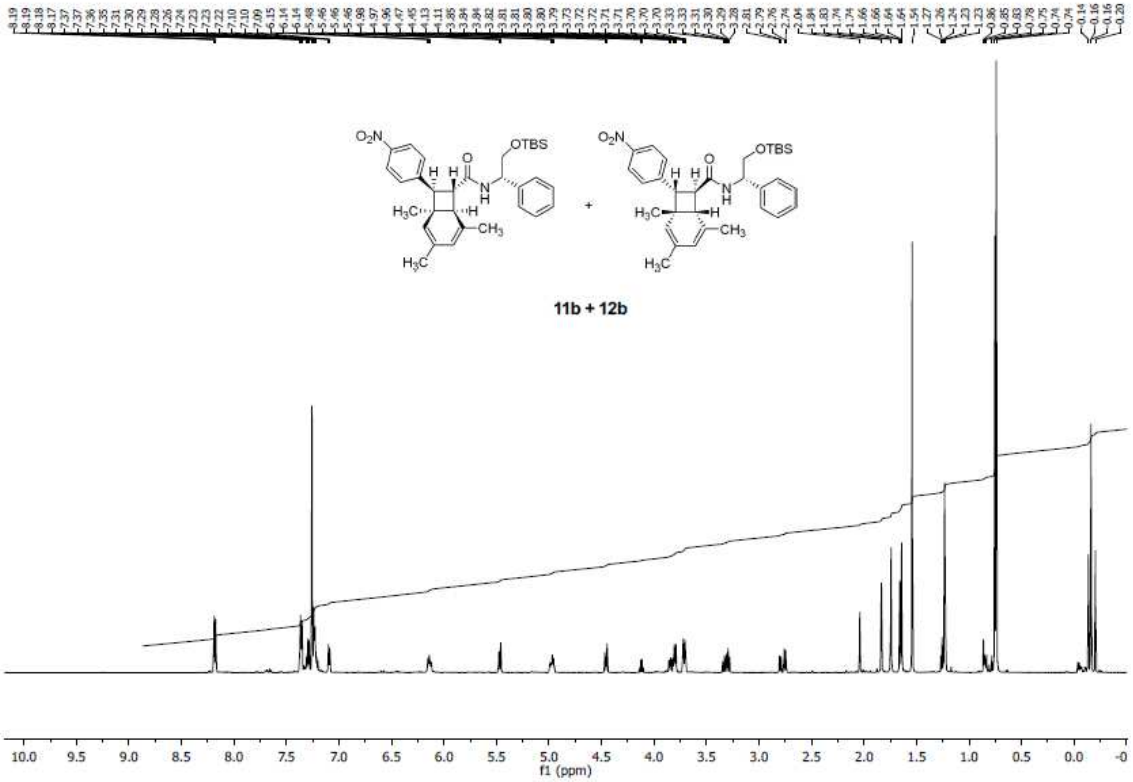

7.60
7.57
7.56
7.55
7.55
7.54
7.54
7.53
7.48
7.40
7.40
7.38
7.38
7.37
7.36
7.35
7.33
7.32
7.31
7.31
7.30
7.30
7.28
7.28
7.27
7.27
7.26
6.55
6.54
6.54
6.46
6.41
2.05
2.05
2.04
1.88
1.87
1.86
1.84
1.84
1.82
1.03
1.02
1.01
1.00
0.60
0.60
0.58
0.57
O
N
I
CH3
CH3
CH3
7g
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

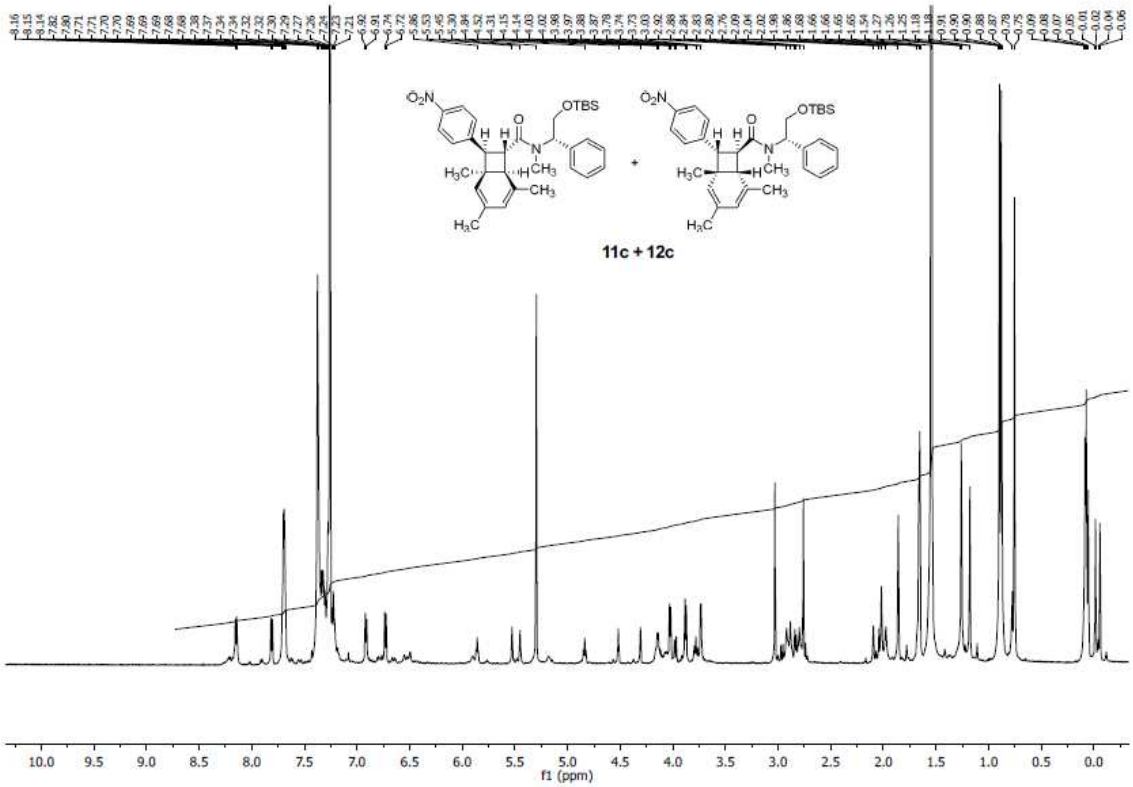

7g
f1 (ppm)

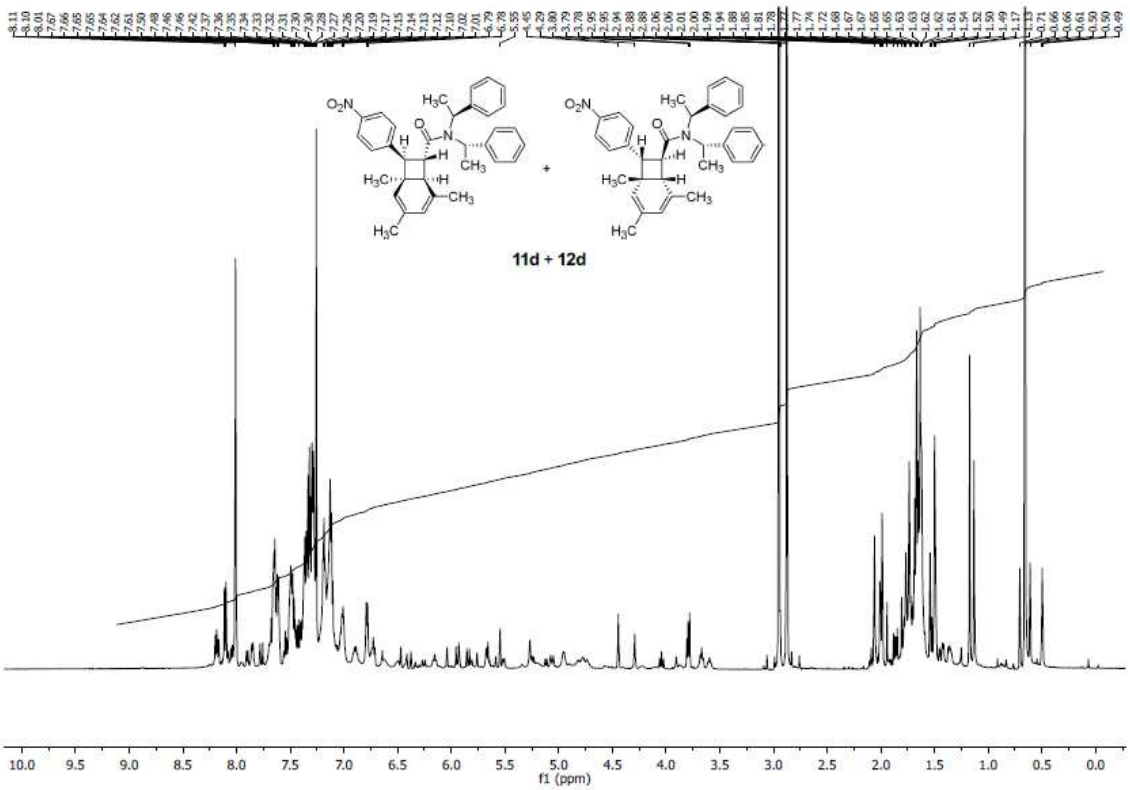

11a
12a
f1 (ppm)

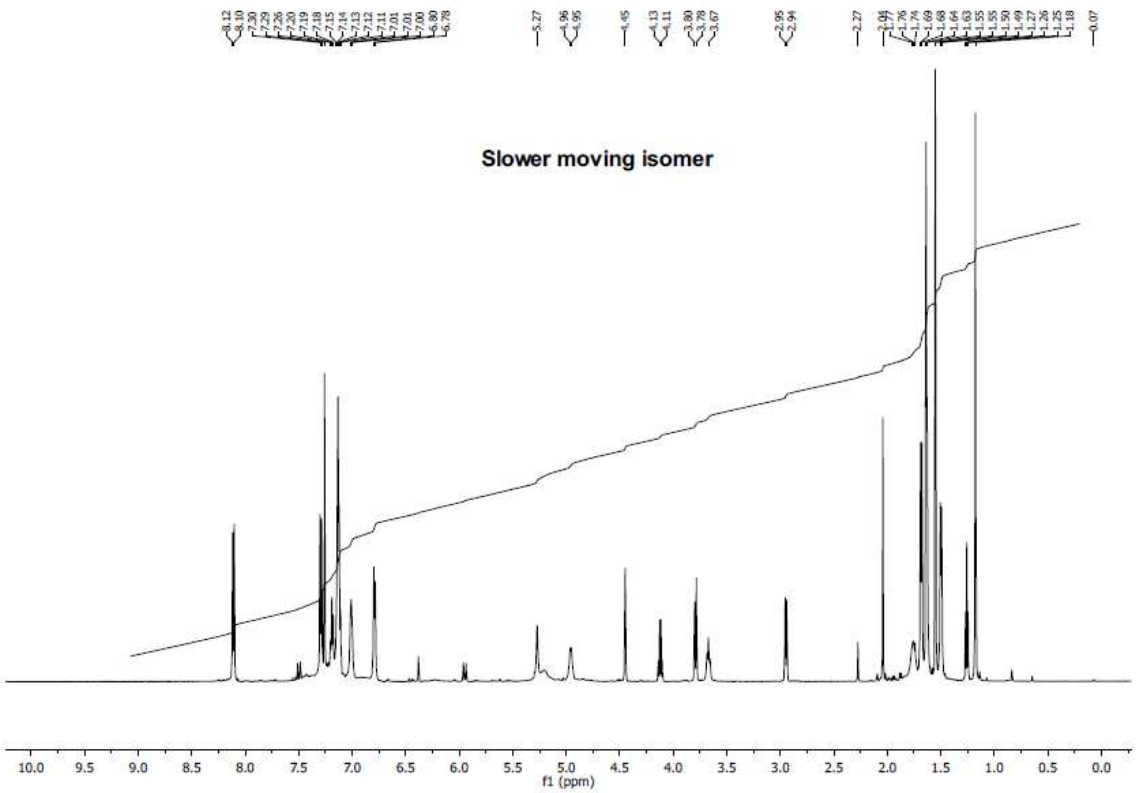

11a
f1 (ppm)


12a
f1 (ppm)

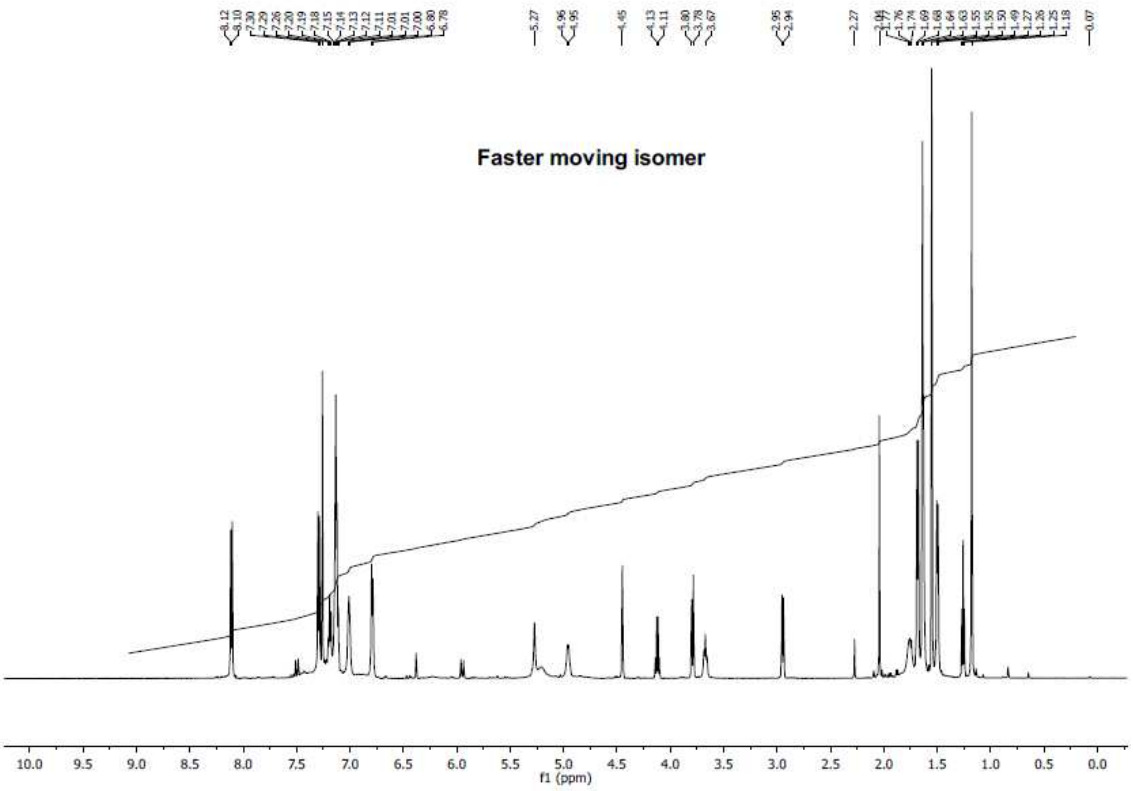

11b + 12b
f1 (ppm)


11c + 12c
f1 (ppm)

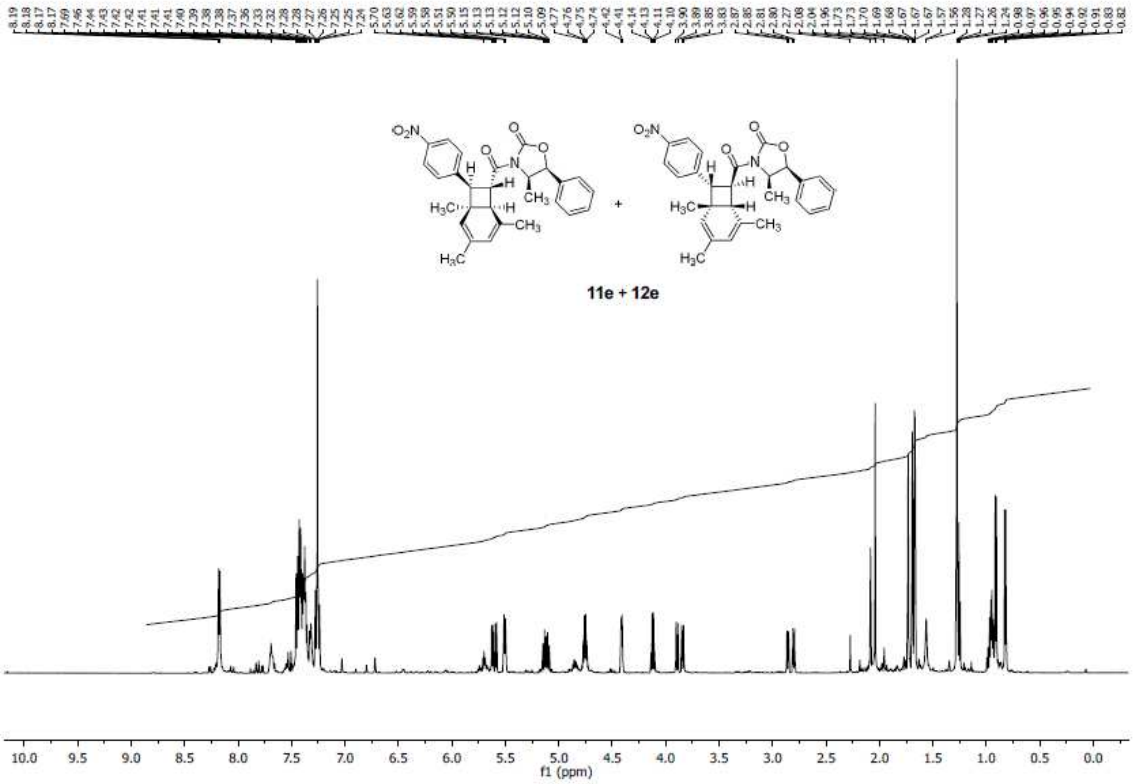


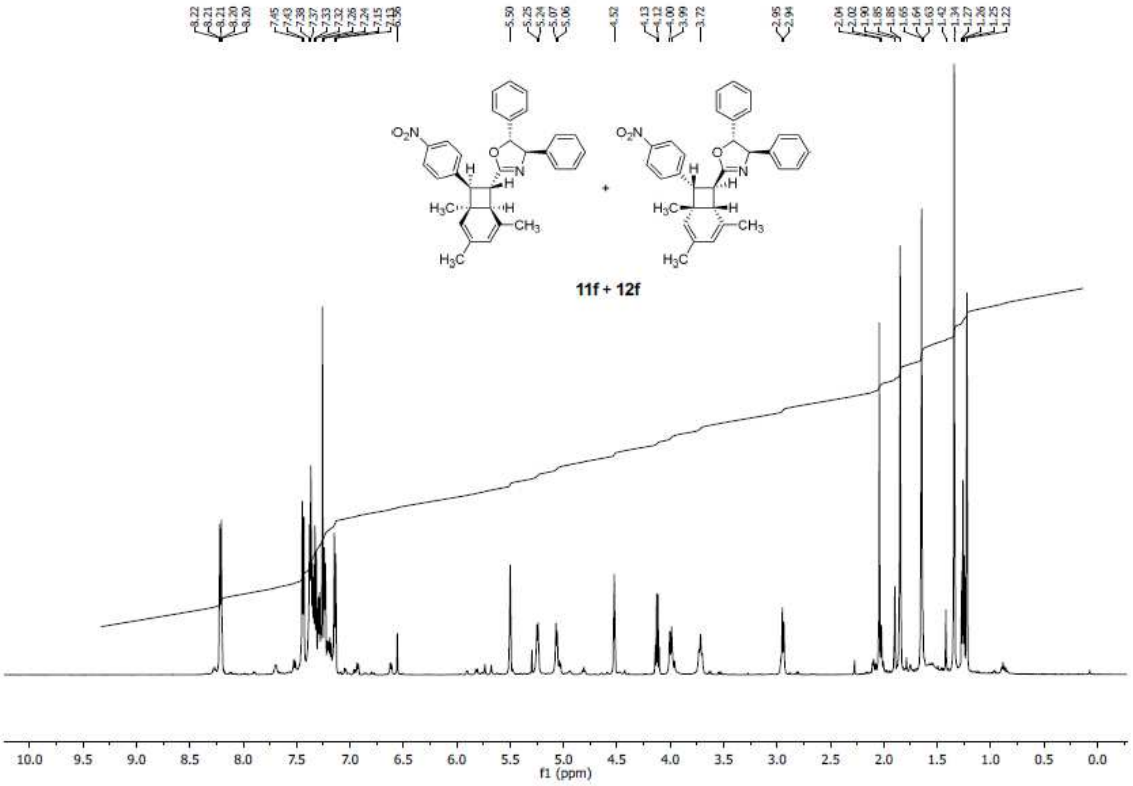


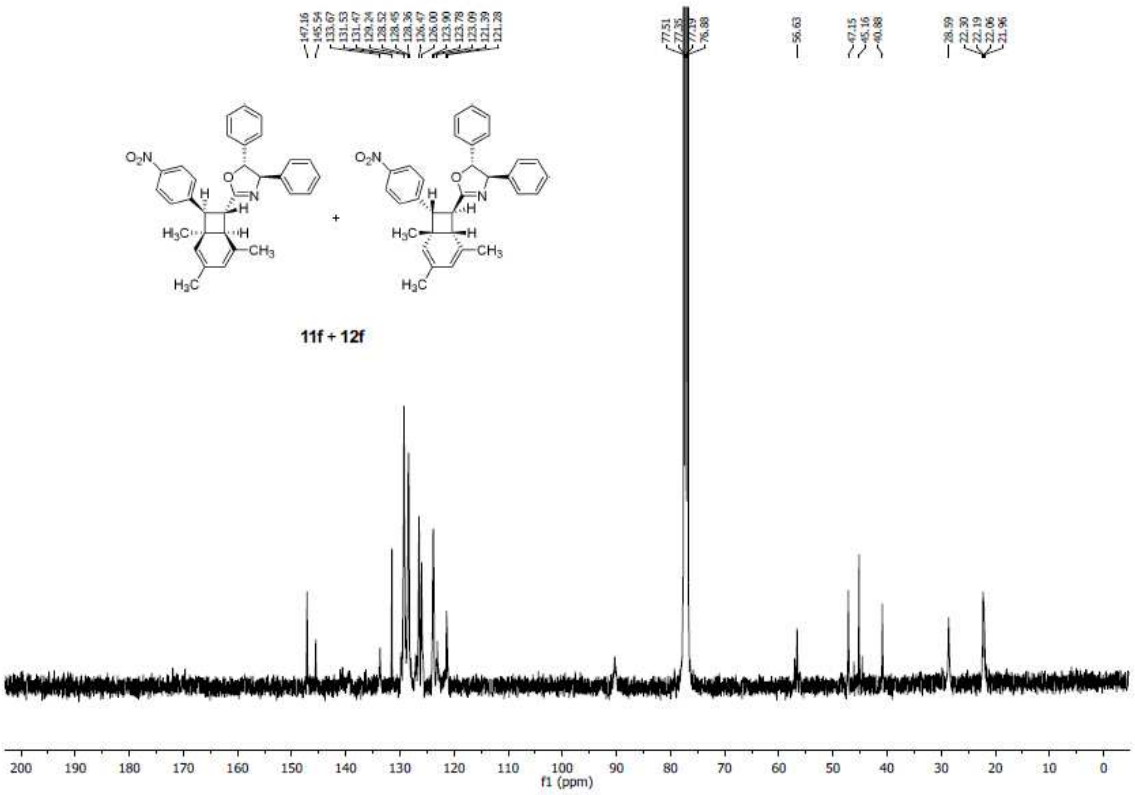
component of 11d + 12d mixture

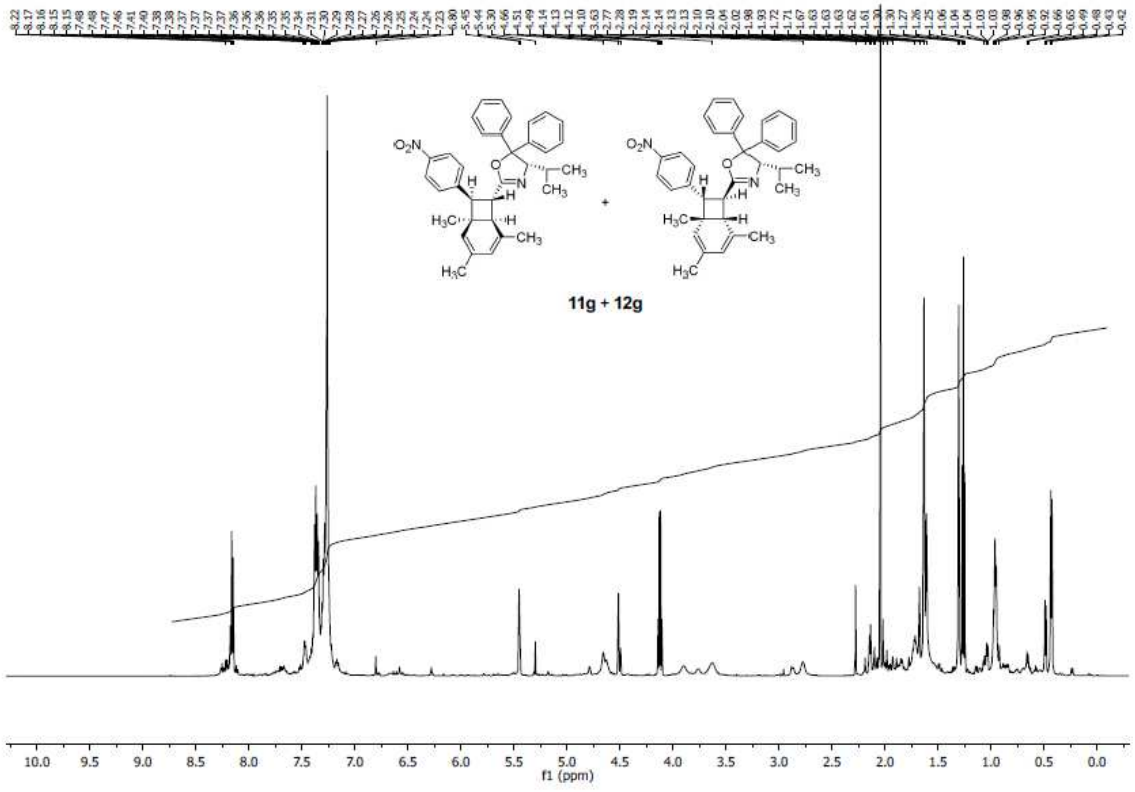


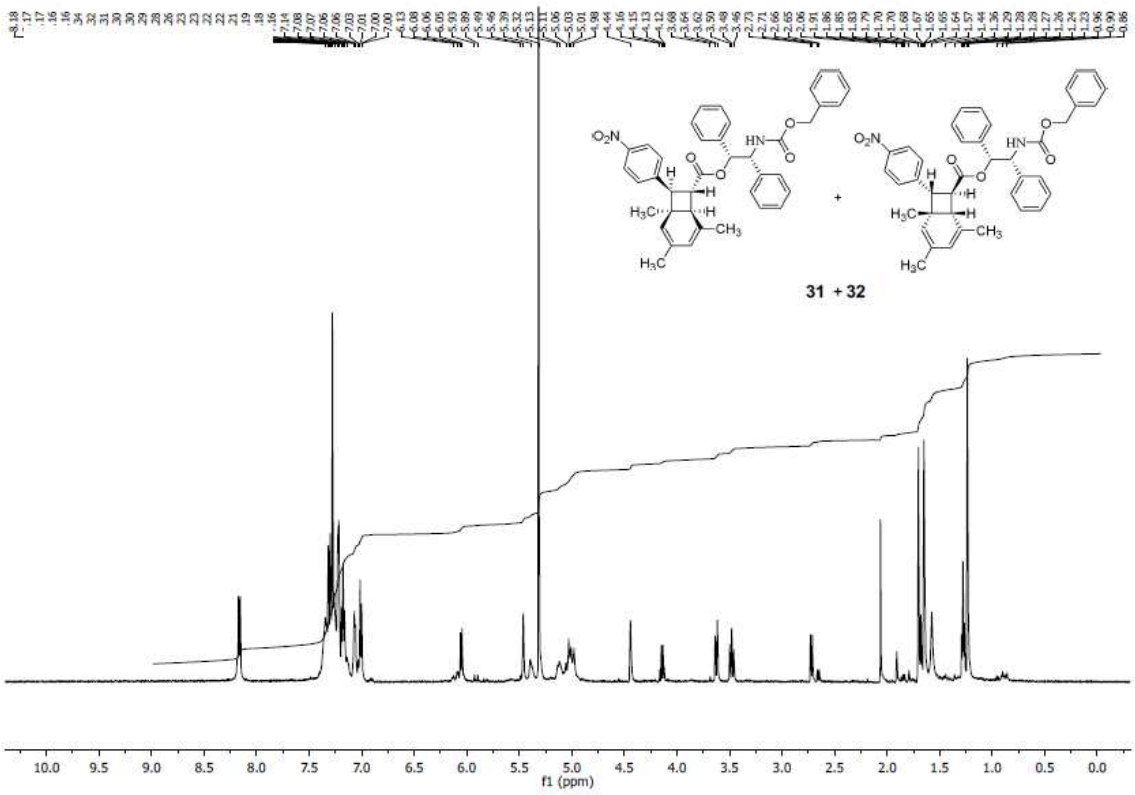
component of 11d + 12d mixture

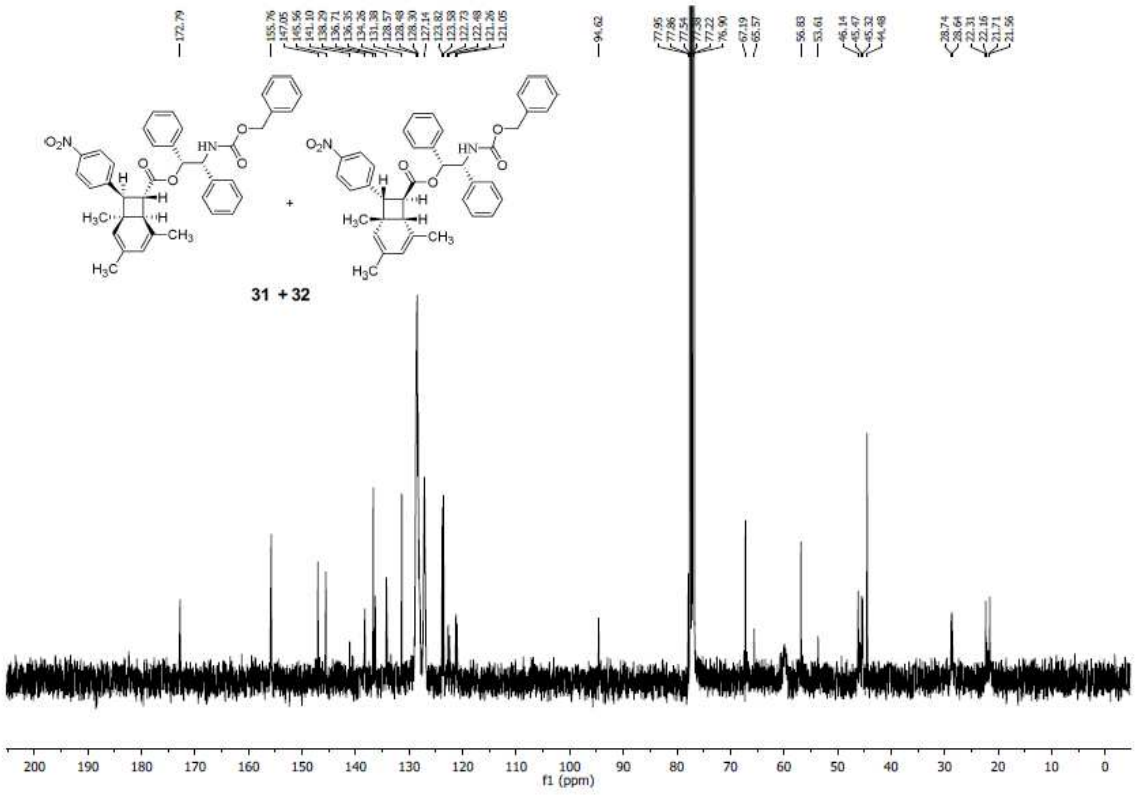

11e + 12e
f1 (ppm)

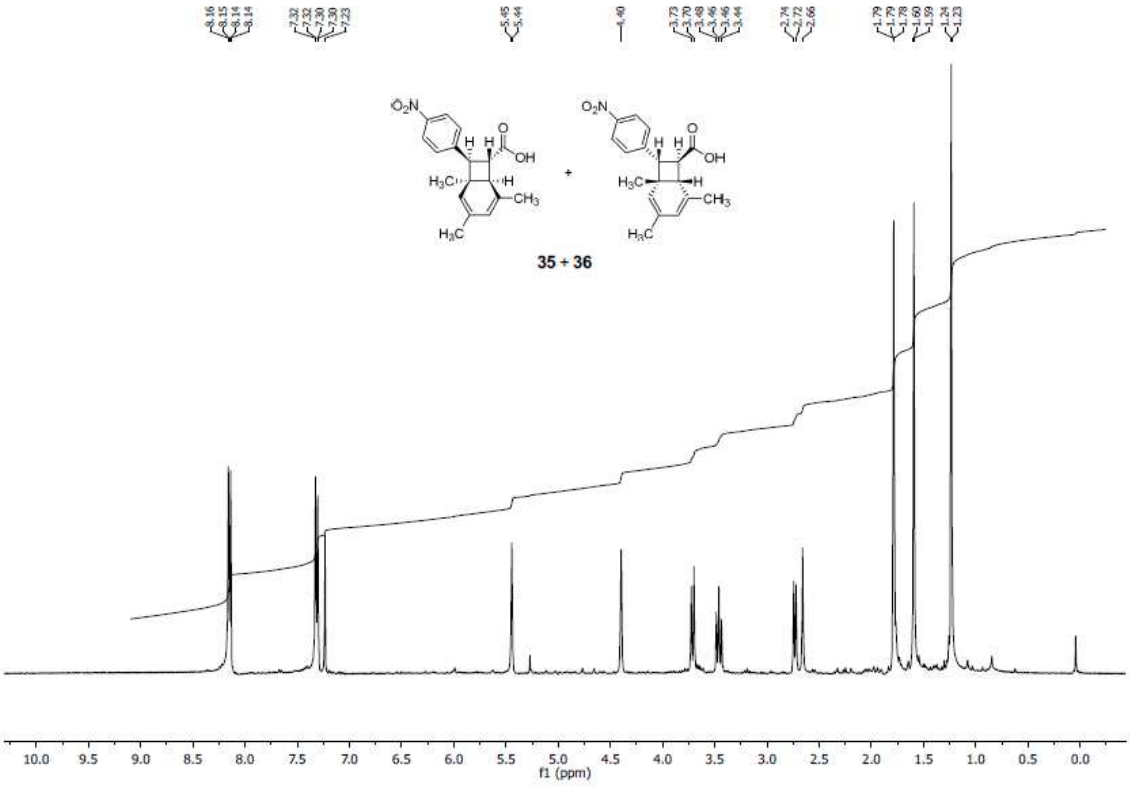

11f + 12f
f1 (ppm)

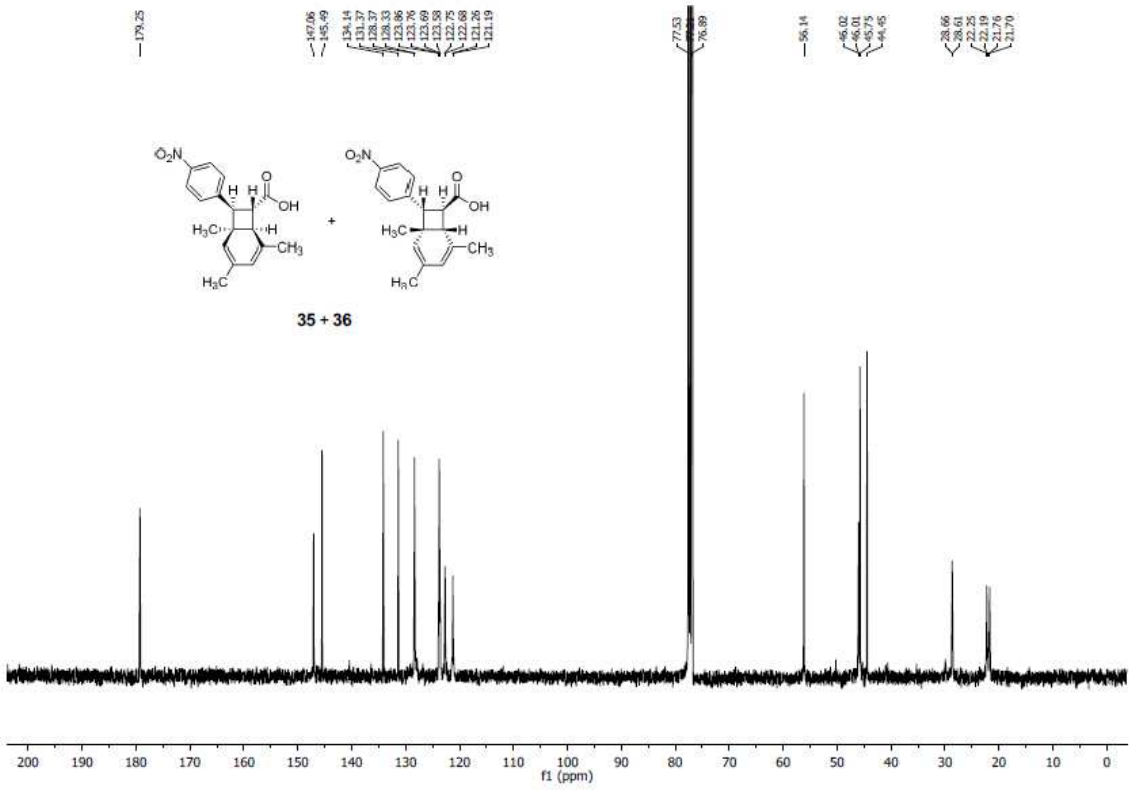

11f + 12f
f1 (ppm)

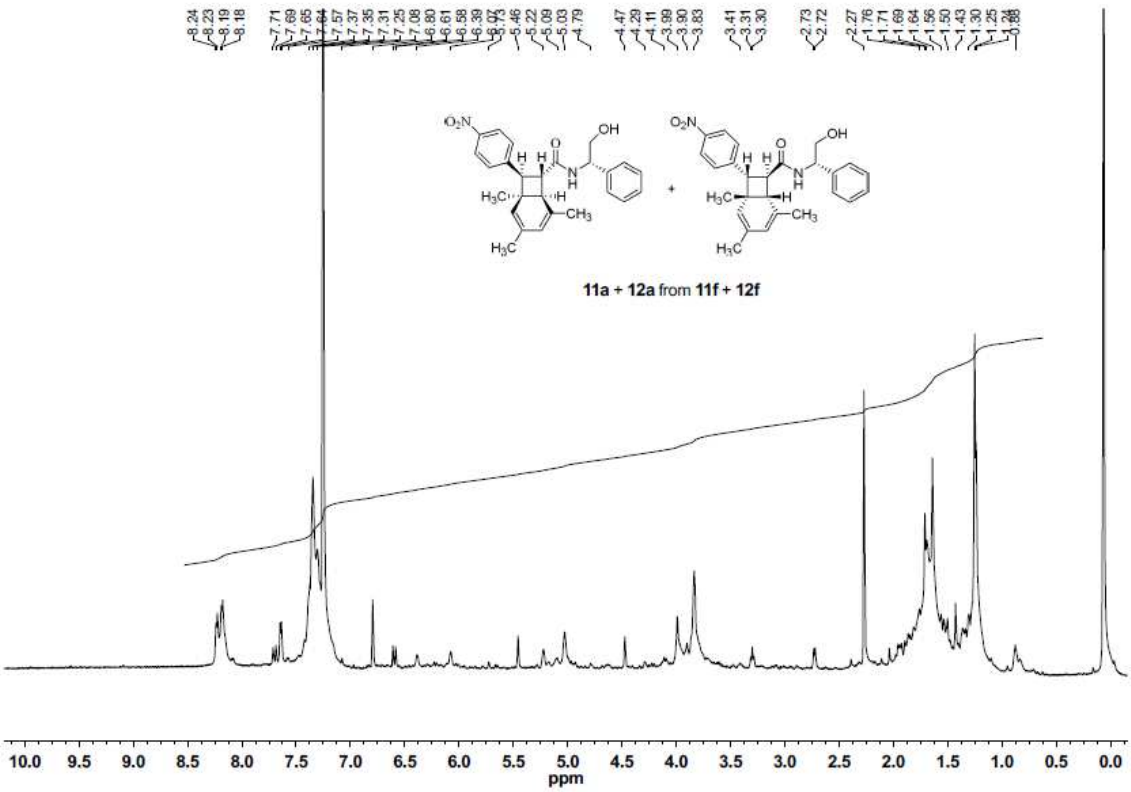

11g + 12g
f1 (ppm)

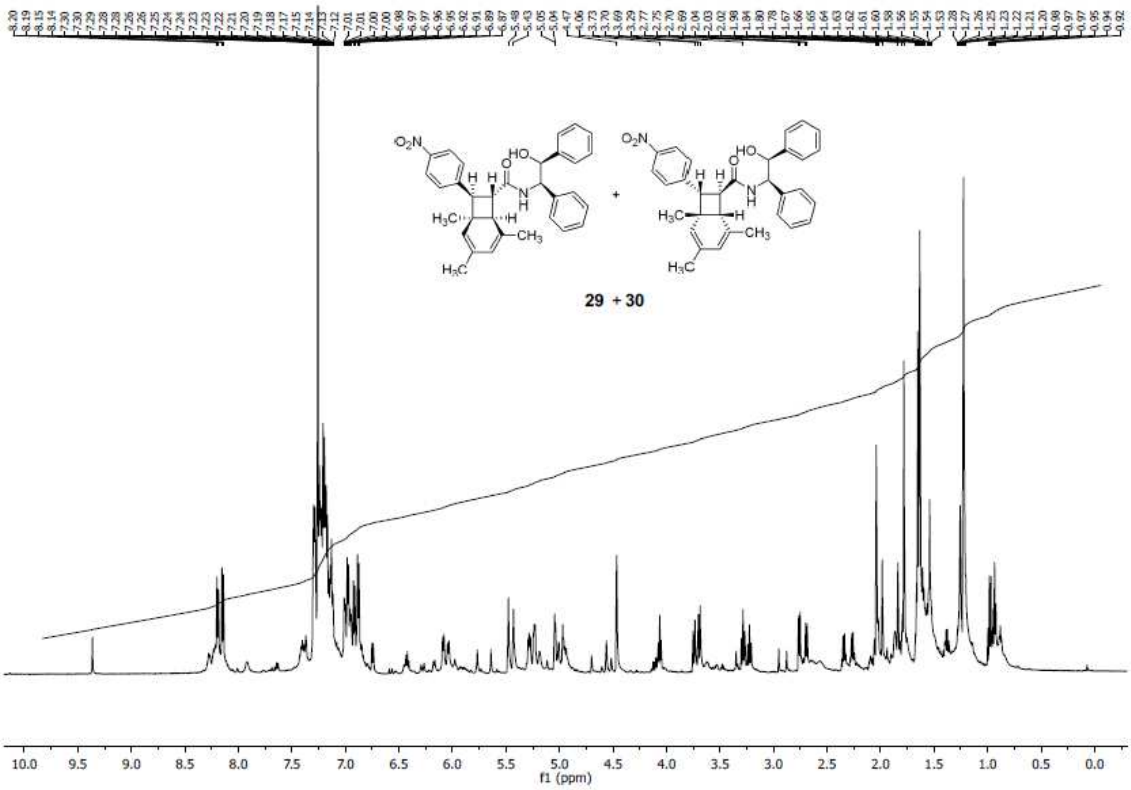

31 + 32
f1 (ppm)

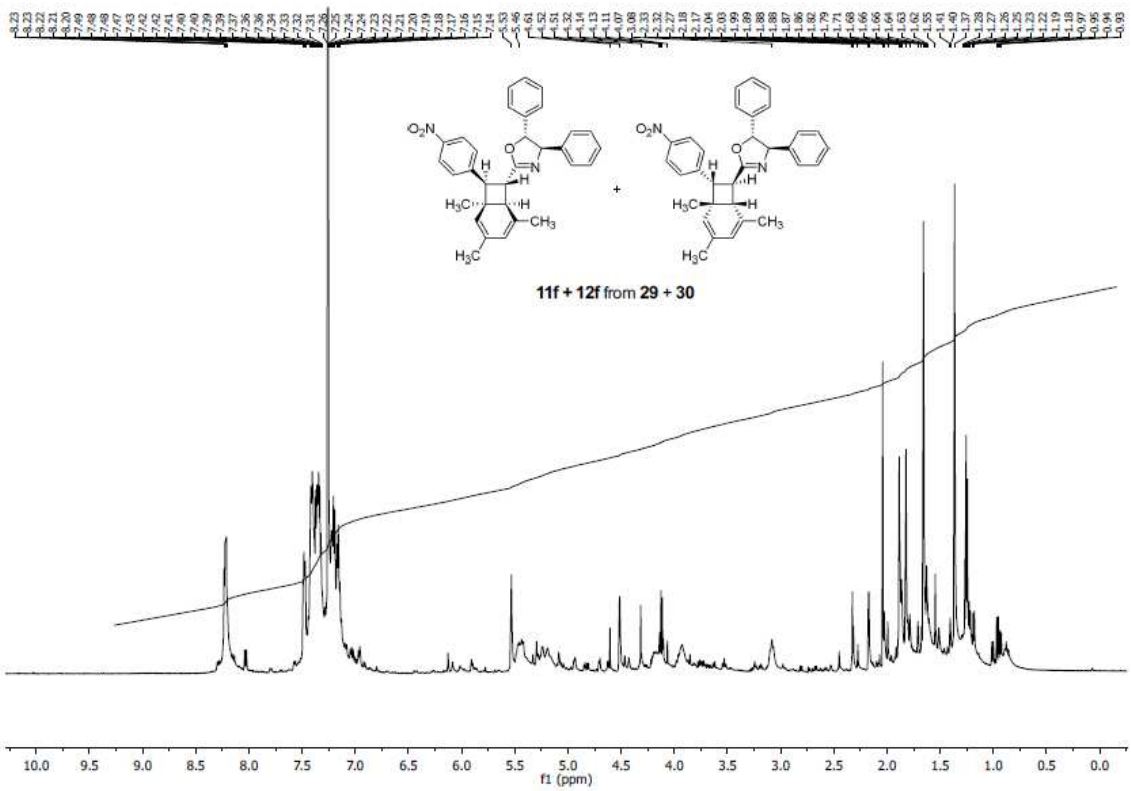

31 + 32
f1 (ppm)

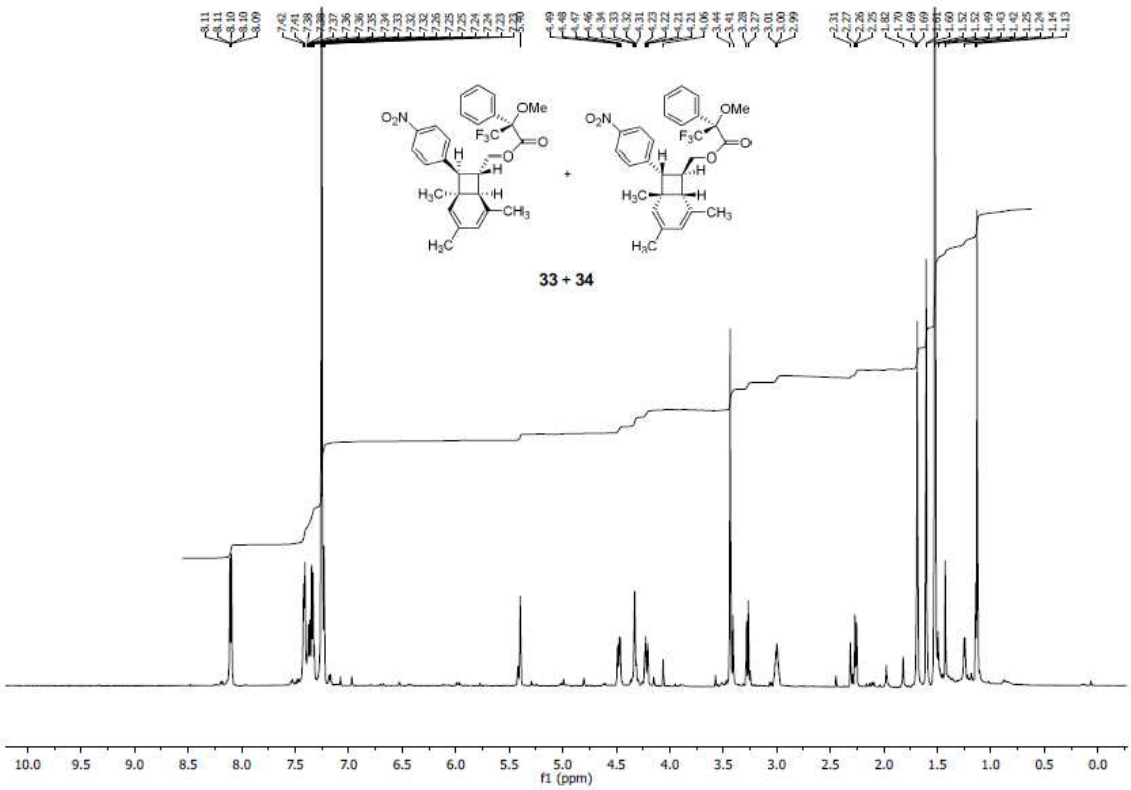

8.16
8.15
8.14
8.14
7.32
7.32
7.30
7.30
7.23
5.45
5.44
4.40
3.73
3.70
3.48
3.46
3.46
3.44
2.74
2.72
2.66
1.79
1.79
1.78
1.60
1.59
1.24
1.23
35 + 36
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


179.25
147.06
145.49
134.14
131.37
128.37
128.33
123.86
123.76
123.69
123.58
122.75
121.98
121.76
121.19
77.53
77.28
76.89
56.14
46.02
46.01
45.75
44.45
28.66
28.61
22.25
22.19
21.76
21.70
35 + 36
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


11a + 12a from 11f + 12f
ppm


29 + 30
f1 (ppm)


11f + 12f from 29 + 30
f1 (ppm)


33 + 34
f1 (ppm)