

Development of a Redox-Free Mitsunobu Reaction Exploiting

Phosphine Oxides as Phosphorus(V) Reagent Precursors

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1.0 General remarks

Glassware was dried in an oven overnight before use. Thin layer chromatography was carried out on Poligram SIL G/UV254 silica-aluminium plates and plates were visualised using ultra-violet light (254 nm) and KMnO₄ solution. For flash column chromatography Fluorochem silica gel 60, 35- 70 μ was used. NMR data was collected at either 270, or 400 MHz. Data was manipulated directly from the spectrometer or *via* a networked PC with appropriate software. All samples were analysed in CDCl₃ unless otherwise stated. Multiplicities for coupled signals designated using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, sex=sextet, br=broad signal, ap=apparent and are given in Hz. ¹³C multiplicities were assigned using a DEPT sequence. Where appropriate, COSY, HMQC and HMBC experiments were performed to aid assignment. High-resolution mass spectrometric data are quoted to four decimal places (0.1 mDa) with error limits for acceptance of +/-5.0 ppm (defined as calcd./found mass 10⁻⁶). Mass spectra were acquired on a VG micromass 70E, VG autospec or micromass LCTOF. Infrared spectra were recorded on a Pelkin-Elmer 1600 FTIR instrument as dilute chloroform solutions or via analysis of neat samples using an ATR accessory. All solvents and reagents were used as supplied. Triphenylphosphine oxide, polymer-supported, 1.2-1.8 mmol/g on polystyrene was purchased from Alfa Aesar. Known compounds were characterized by comparison with reported literature data.

2.0 Synthesis of Dioxyphosphoranes

General Procedure

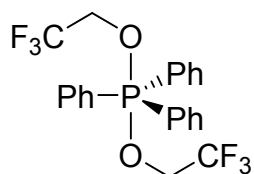
To a dry nitrogen flushed Schlenk flask was added triphenylphosphine oxide (835 mg, 3.00 mmol) followed by chloroform (5 mL). Oxalyl chloride (0.25 mL, 3.00 mmol) was then added over 1 minute to the resulting solution and vigorous elution of gas was observed. To a separate dry nitrogen flushed

Schlenk flask was added 2,2,2-trifluoroethanol (0.65 mL, 9.00 mmol) followed by anhydrous Et₂O (20 mL). To the resulting cooled (0 °C) solution was added *n*BuLi (5.60 mL, 9 mmol of a 1.6 M solution in hexane) dropwise over 1 minute. The resulting alkoxide solution was transferred via cannula to the above described, cooled (-78 °C), solution of chlorotriphenylphosphonium chloride. The reaction mixture was warmed to room temperature and stirred for a further 2 hours. After which the resulting dioxyphosphorane solution was transferred to a final Schlenk flask via filter cannula. The solution was then concentrated in vacuo and the dioxyphosphorane re-dissolved in anhydrous EtOAc to give a stock solution which was used for the coupling reactions.

The concentration of the stock solution was determined via ¹⁹F NMR as follows. A 0.5 mL aliquot of the stock solution was added to a solution of α,α,α-trifluorotoluene (25 μL, 0.2 mmol) in CDCl₃ (0.2 mL). The concentration was calculated based on the relative size of the ¹⁹F integrals.

2.1 Characterization of dioxyphosphoranes

Dioxyphosphoranes are unstable with respect to hydrolysis to afford the corresponding phosphine oxide. Therefore, they are characterised via multinuclear NMR in solution. Yields were determined via ¹⁹F NMR using α,α,α-trifluorotoluene as an internal standard.



Dioxyphosphorane **3a**¹

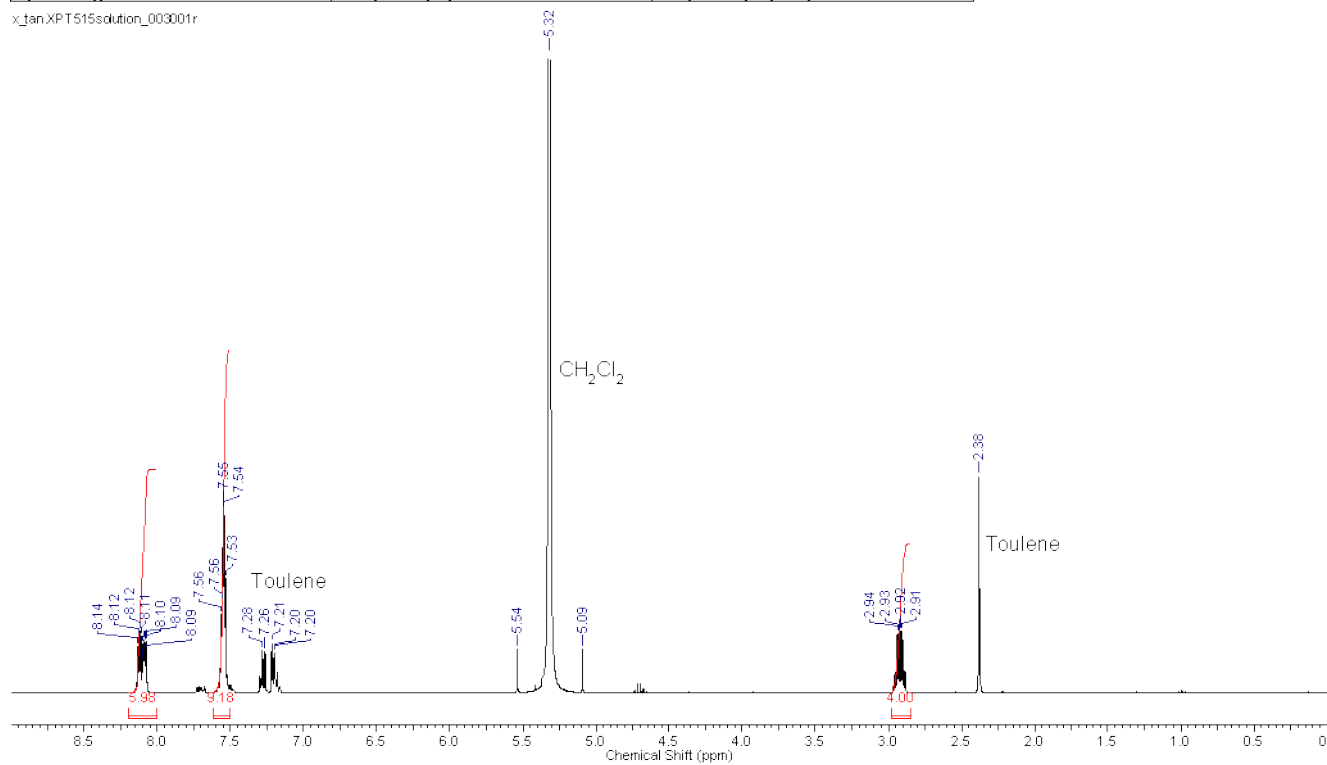
The product was obtained as a solution in 93% yield. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.02 - 8.21 (6 H, m, ArH), 7.46 - 7.63 (9 H, m, ArH), 2.92 (4 H, qd, *J*=2.0 and 4.3, 4 H). ¹³C NMR (100 MHz, CDCl₃) δ ppm 134.8 (d, *J*=174 Hz, C_q), 132.7 (d, *J*=9.9 Hz, C_{Ar}), 130.6 (d, *J*=3.8 Hz, C_{Ar}), 128.5 (d, *J*=15.3 Hz,

¹ . Kubota, S. Miyashita, T. Kitaxume and N. Ishikawa, *J. Org. Chem.* 1980, **45**, 50

C_{Ar} , 60.4 (dq, $J=6.0$ and 34.2 Hz CH_2). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -74.3 (t, $J=9.0$ Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ ppm -58.2.

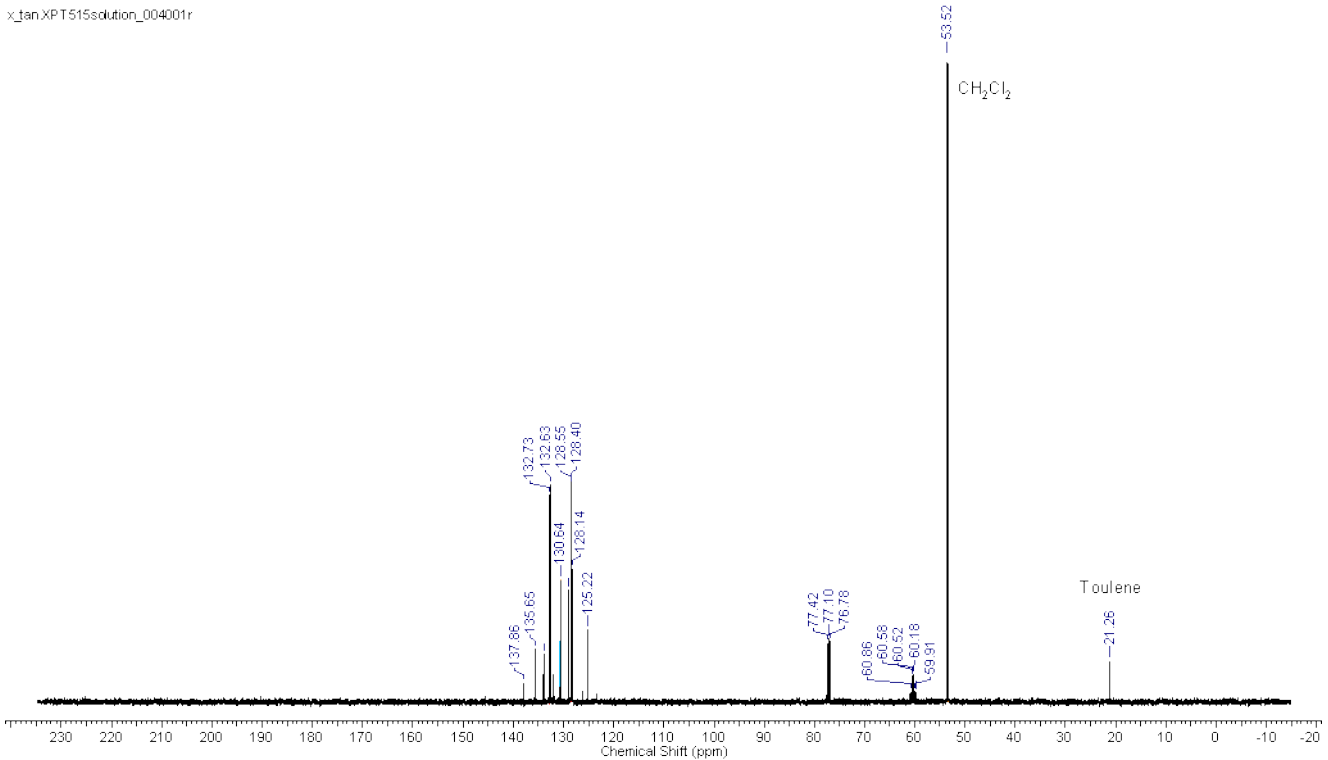
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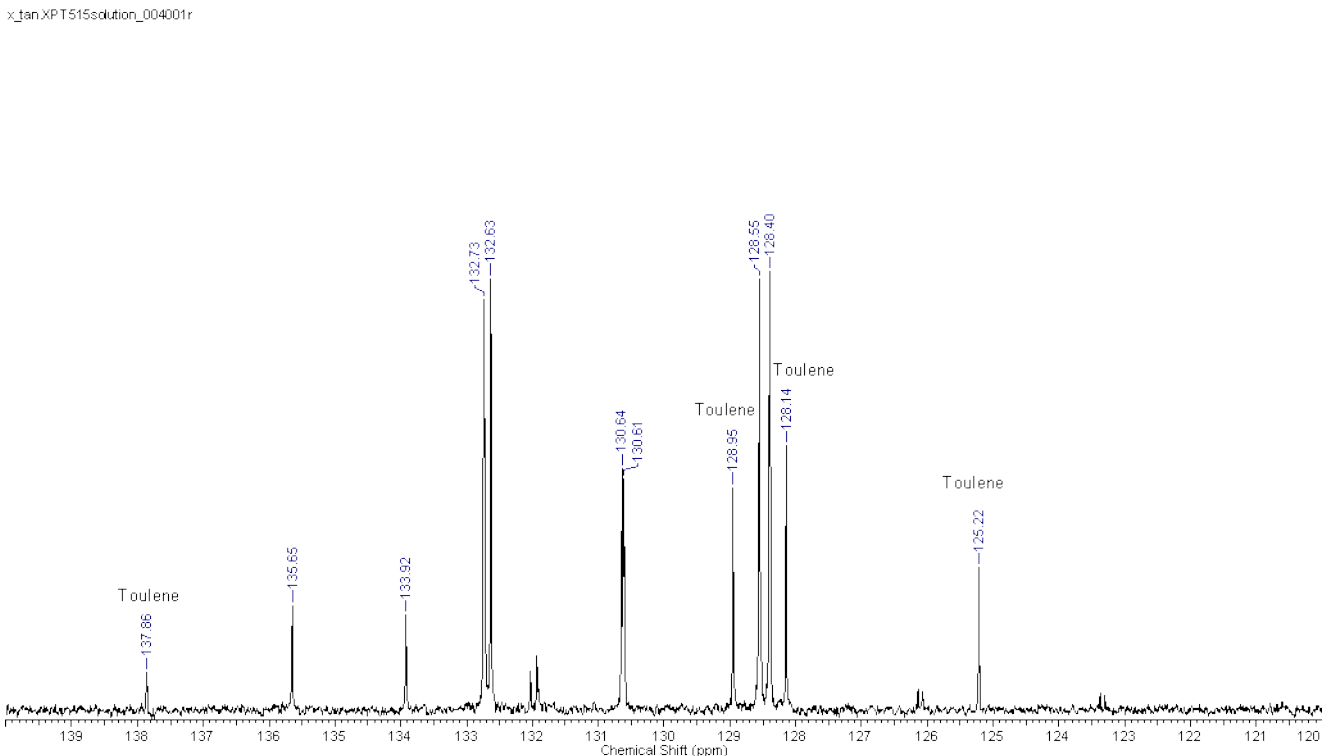
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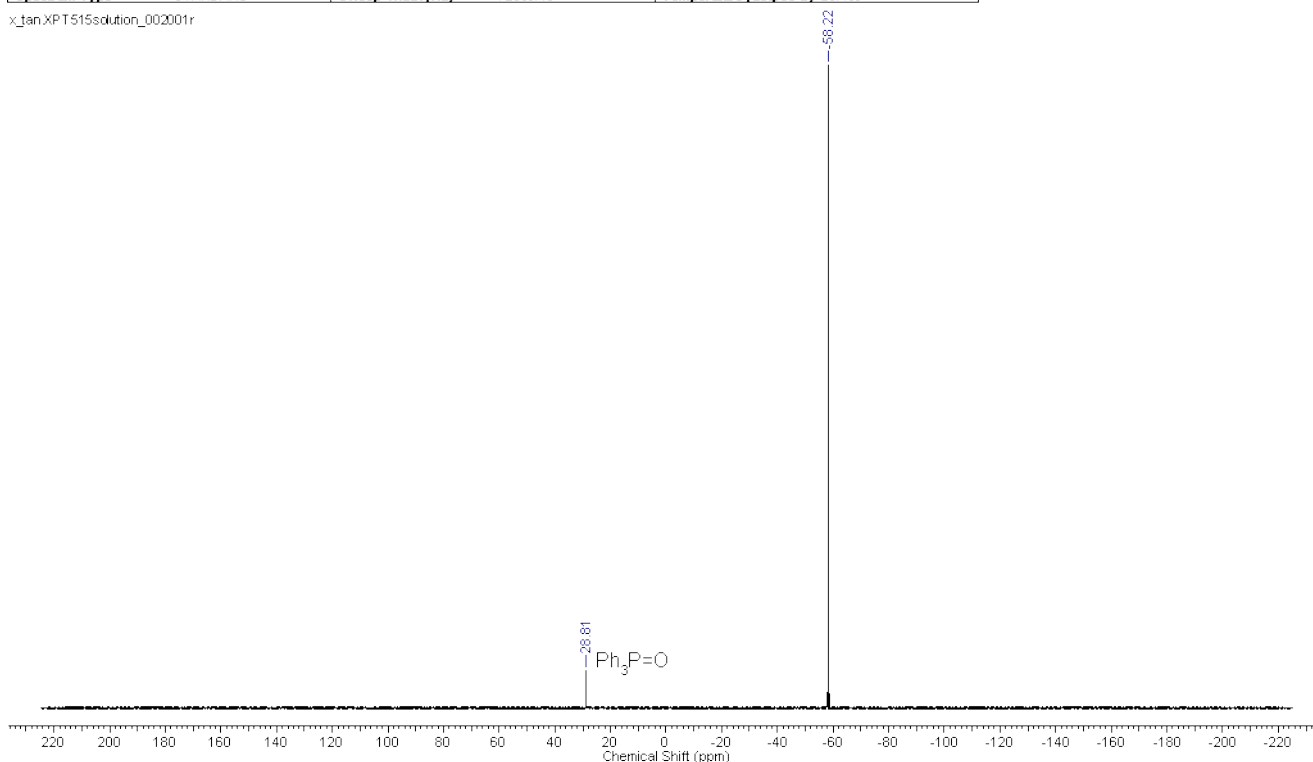
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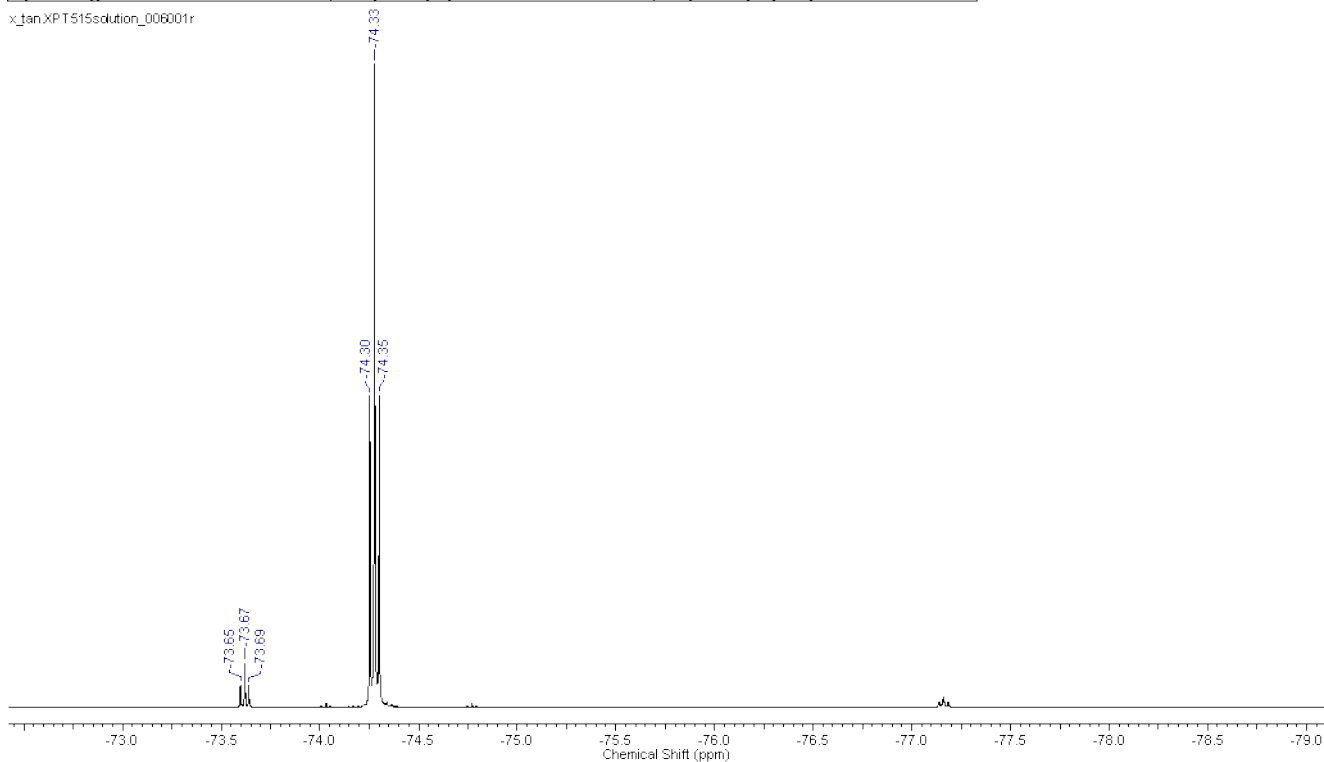
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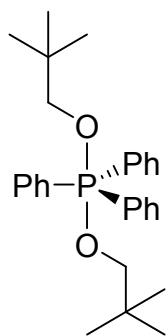
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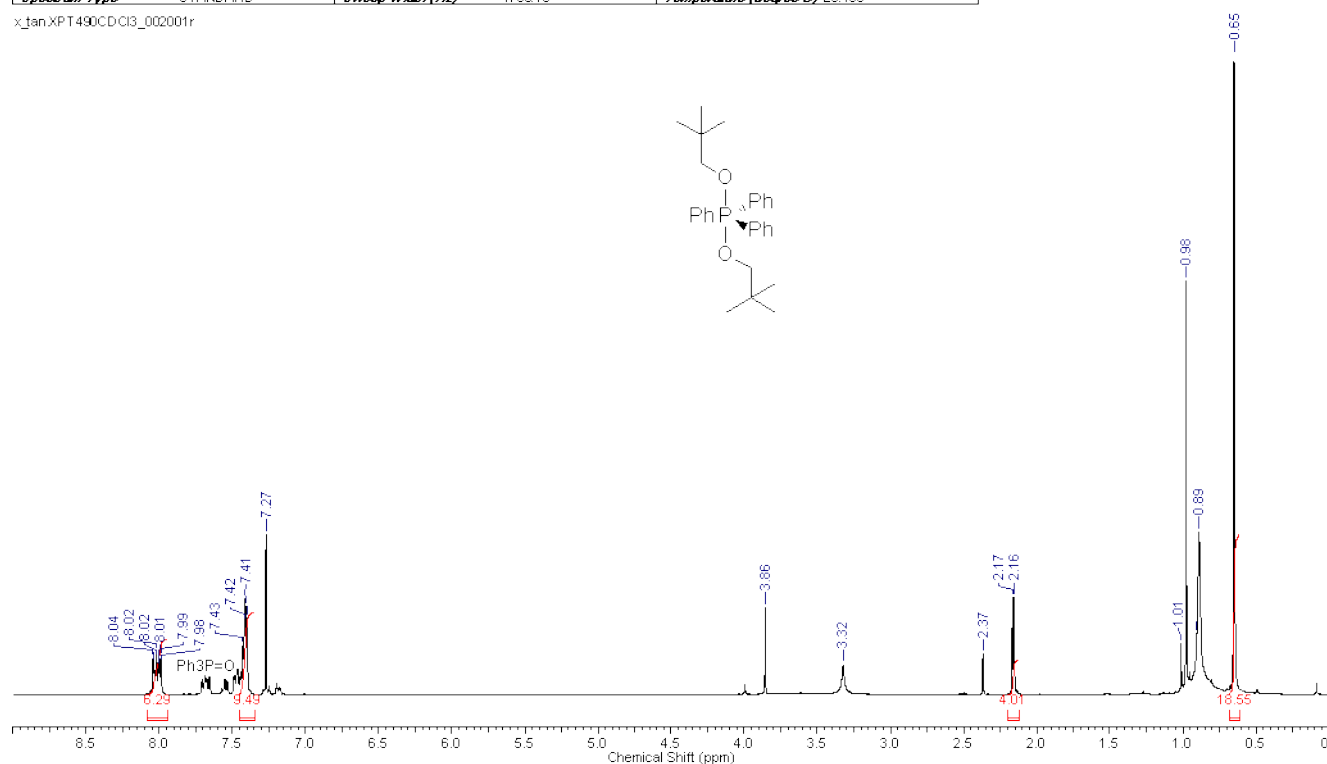


Dioxo phosphorane **3b²**

¹H NMR (400 MHz, CDCl₃) δ ppm 7.93 - 8.12 (6 H, m, ArH), 7.34 - 7.46 (9 H, m, ArH), 2.16 (4 H, d, *J* = 4.1 Hz, 4 H, CH₂), 0.65 (s, 18 H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ ppm 138.5 (d, *J* = 176 Hz, C_q), 132.7 (d, *J* = 9.5 Hz, C_{Ar}), 129.0 (d, *J* = 2.9 Hz, C_{Ar}), 127.4 (d, *J* = 15.3 Hz, C_{Ar}), 71.2 (d, *J* = 8.8 Hz, CH₂), 32.7 (d, *J* = 5.1 Hz, C_q), 27.1 (s, CH₃). ³¹P NMR (162 MHz, CDCl₃) δ ppm -58.1.

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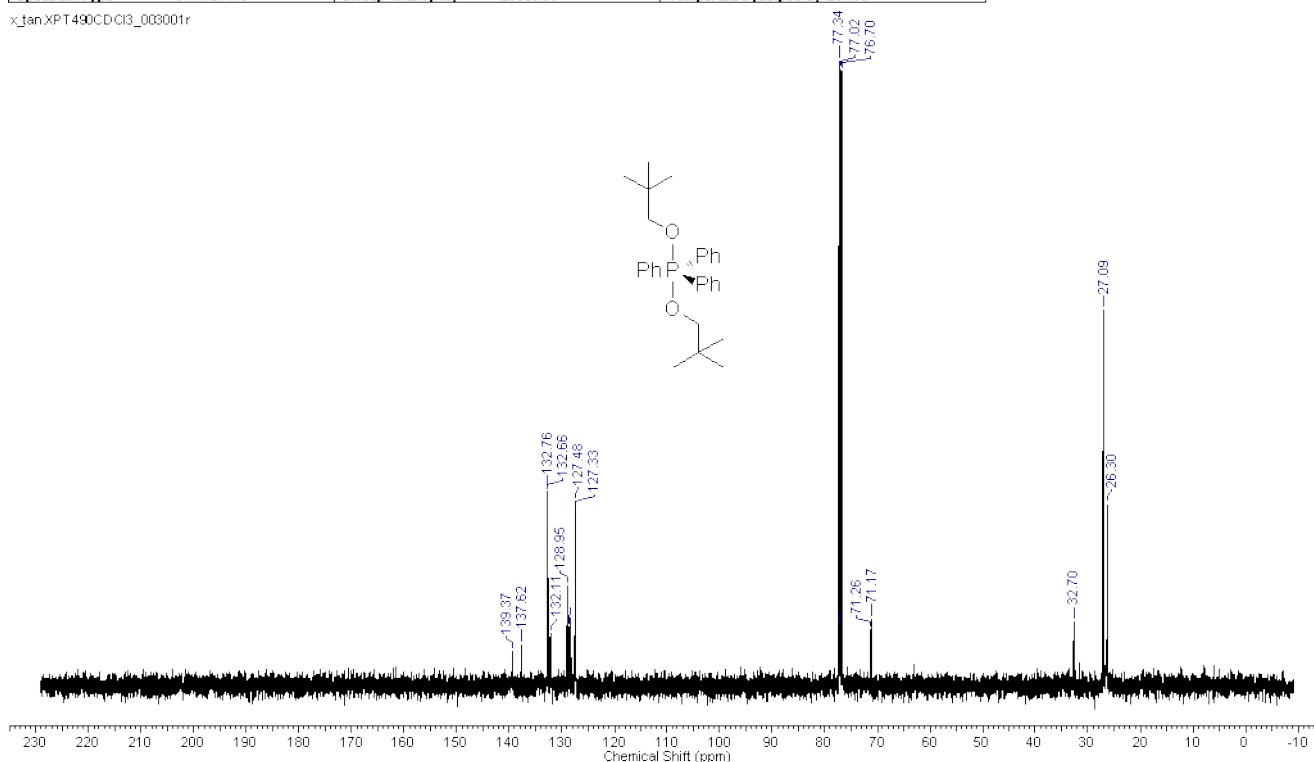
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² J.W. Kelly and S.A. Evans *J. Org. Chem.* 1980, **51**, 5492.

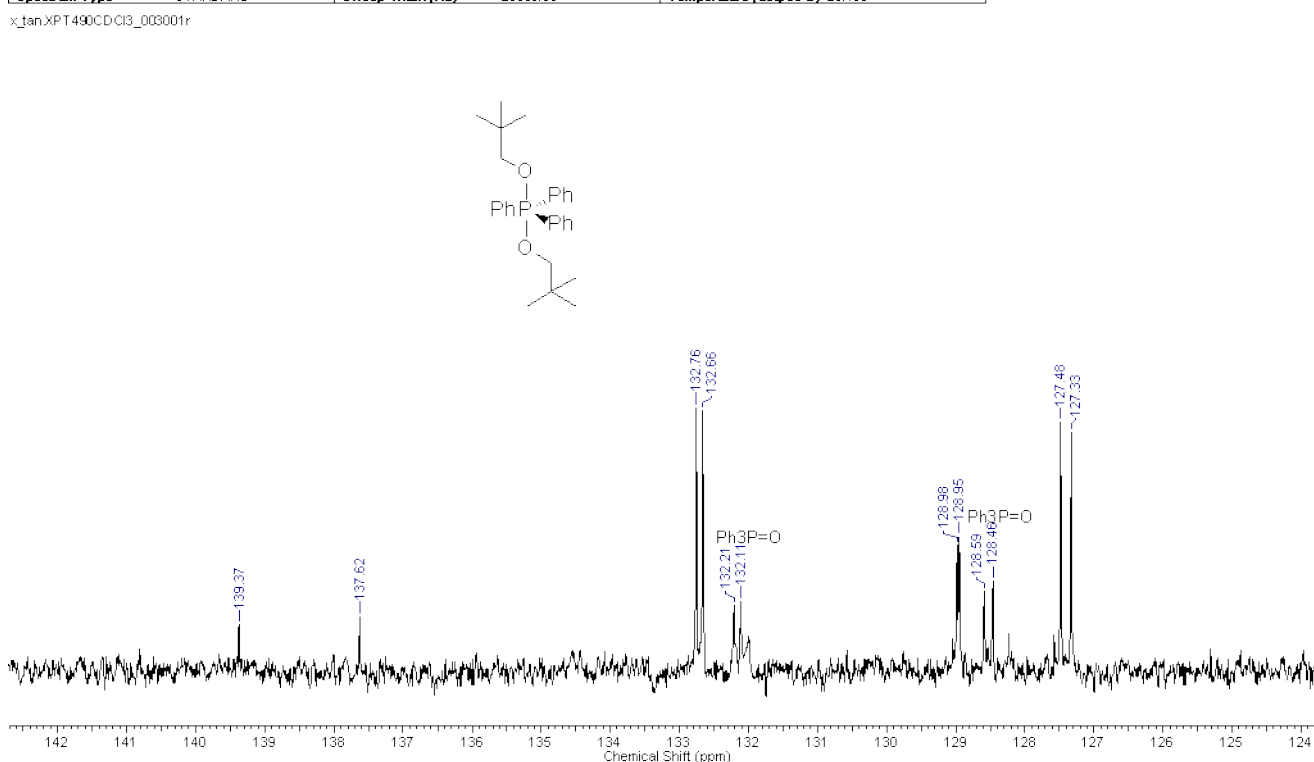
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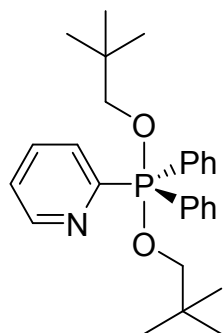
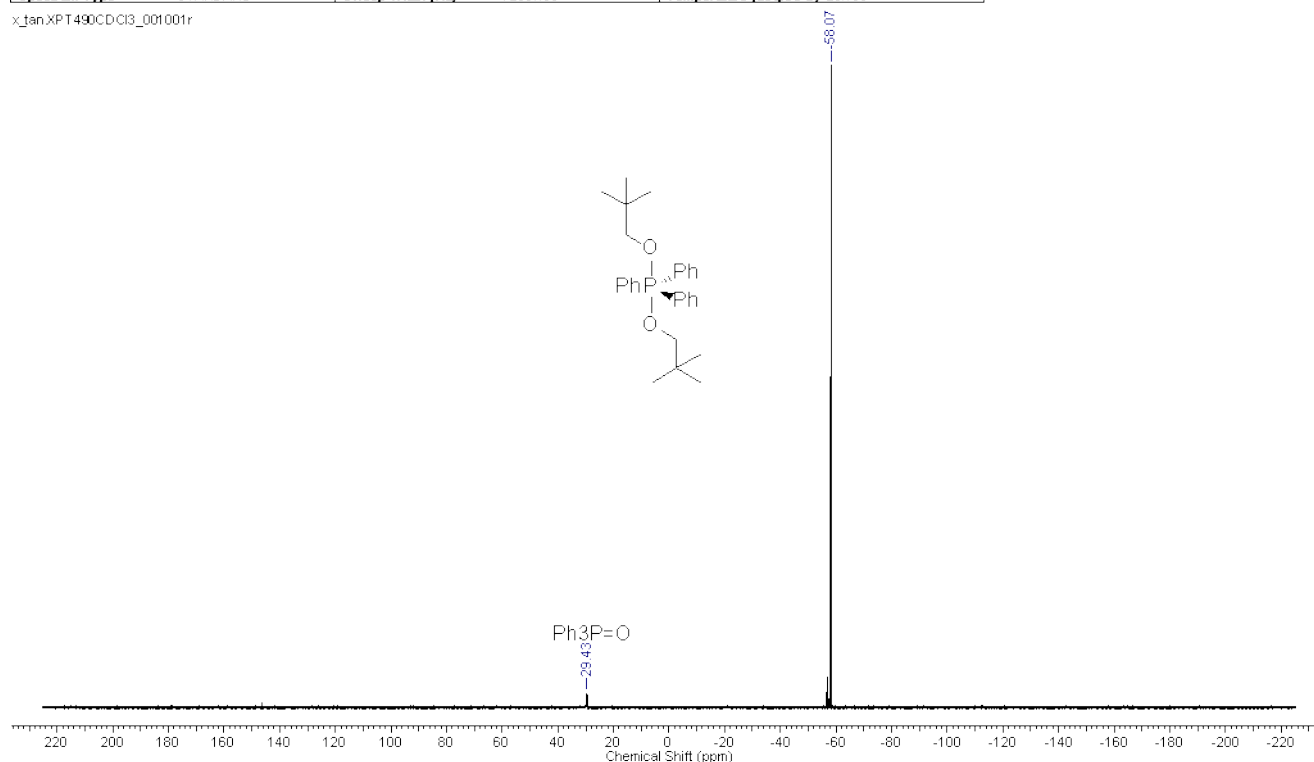
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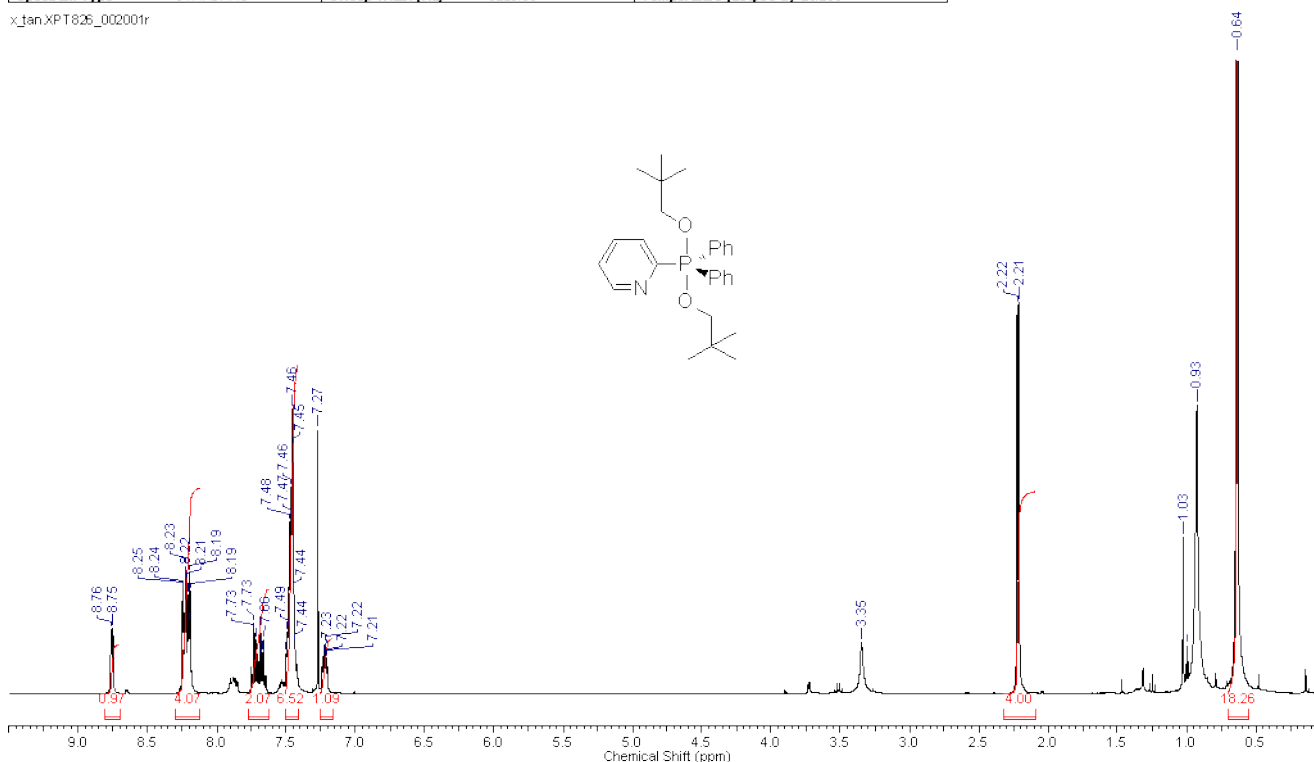


Dioxiphosphorane **3c**

¹H NMR (400 MHz, CDCl₃) δ ppm 8.76 (1 H, d, *J*=4.8 Hz, ArH), 8.13 - 8.30 (4 H, m, ArH), 7.62 - 7.77 (2 H, 2 H, ArH), 7.40 - 7.51 (6 H, m, ArH), 7.16 - 7.25 (1 H, m, ArH), 2.22 (4 H, d, *J*=4.4 Hz, CH₂), 0.64 (18 H, s, CH₃). **¹³C NMR** (100 MHz, CDCl₃) δ ppm 161.6 (d, *J*=219 Hz, C_q), 148.5 (d, *J*=25 Hz, C_{Ar}), 137.6 (d, *J*=177 Hz, C_q), 134.6 (d, *J*=13.0 Hz, C_{Ar}), 133.9 (d, *J*=9.9 Hz, C_{Ar}), 129.4 (d, *J*=3.1 Hz, C_{Ar}), 127.4 (d, *J*=15.3 Hz, C_{Ar}), 123.6 (d, *J*=26 Hz, C_{Ar}), 122.4 (d, *J*=3.8 Hz, C_{Ar}), 71.7 (d, *J*=8.4 Hz, CH₂), 32.6 (d, *J*=5.4 Hz, C_q), 27.0 (s, CH₃). **³¹P NMR** (162 MHz, CDCl₃) δ ppm -59.5.

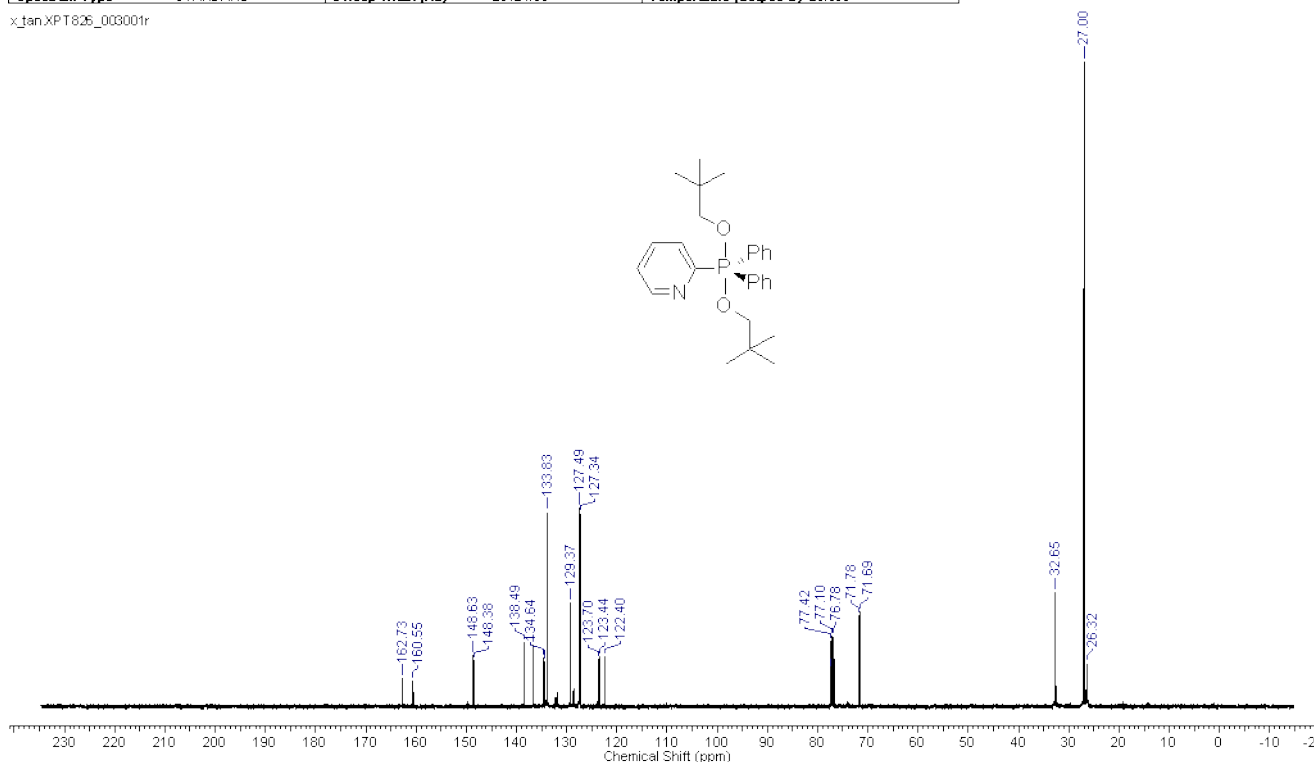
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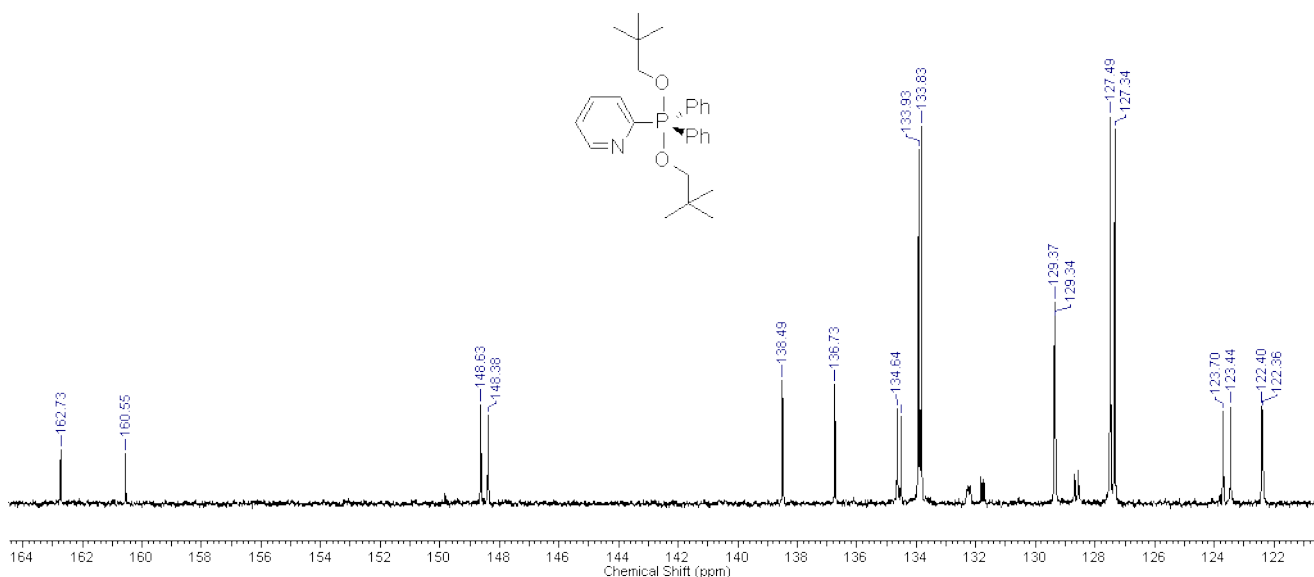
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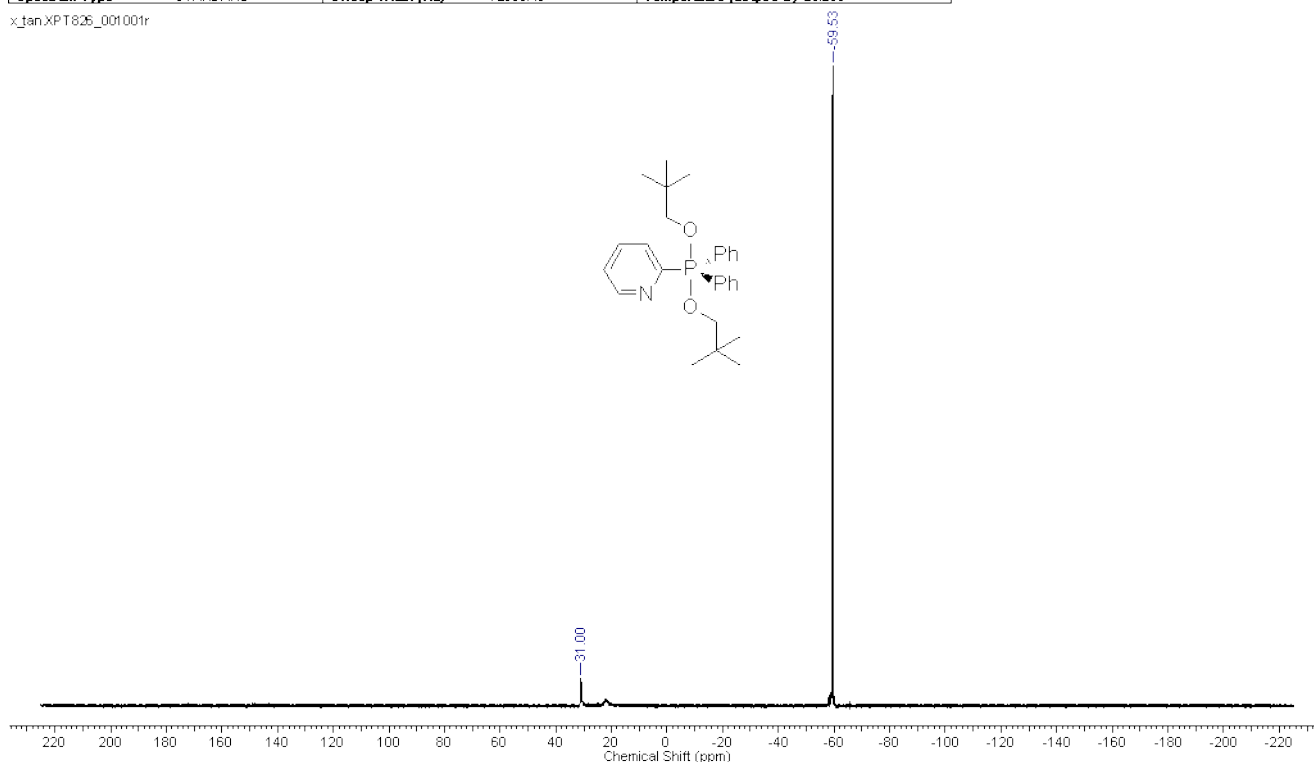
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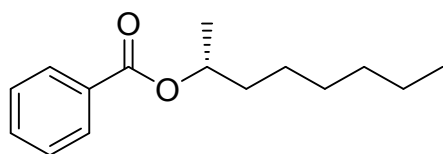
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x_tan.XPT826_001001r



General procedure for Mitsunobu reaction

To a phosphorane **3a** in EtOAc was added the appropriate acid (2.0 equiv.) and alcohol (1.0 equiv.) at 78 °C. The reaction mixture was then heated at 70 °C for 18 hours. The cooled reaction mixture was quenched with H₂O and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give crude products which were purified by flash column chromatography on normal phase silica gel.



(*R*)-Octan-2-yl benzoate **6a**³

(*S*)-2-Octanol (0.16 mL, 1.0 mmol) and benzoic acid (244 mg, 2.00 mmol) were combined with phosphorane **3a** according to the general procedure. The product was obtained as colourless oil after purification (172 mg, 73% yield).

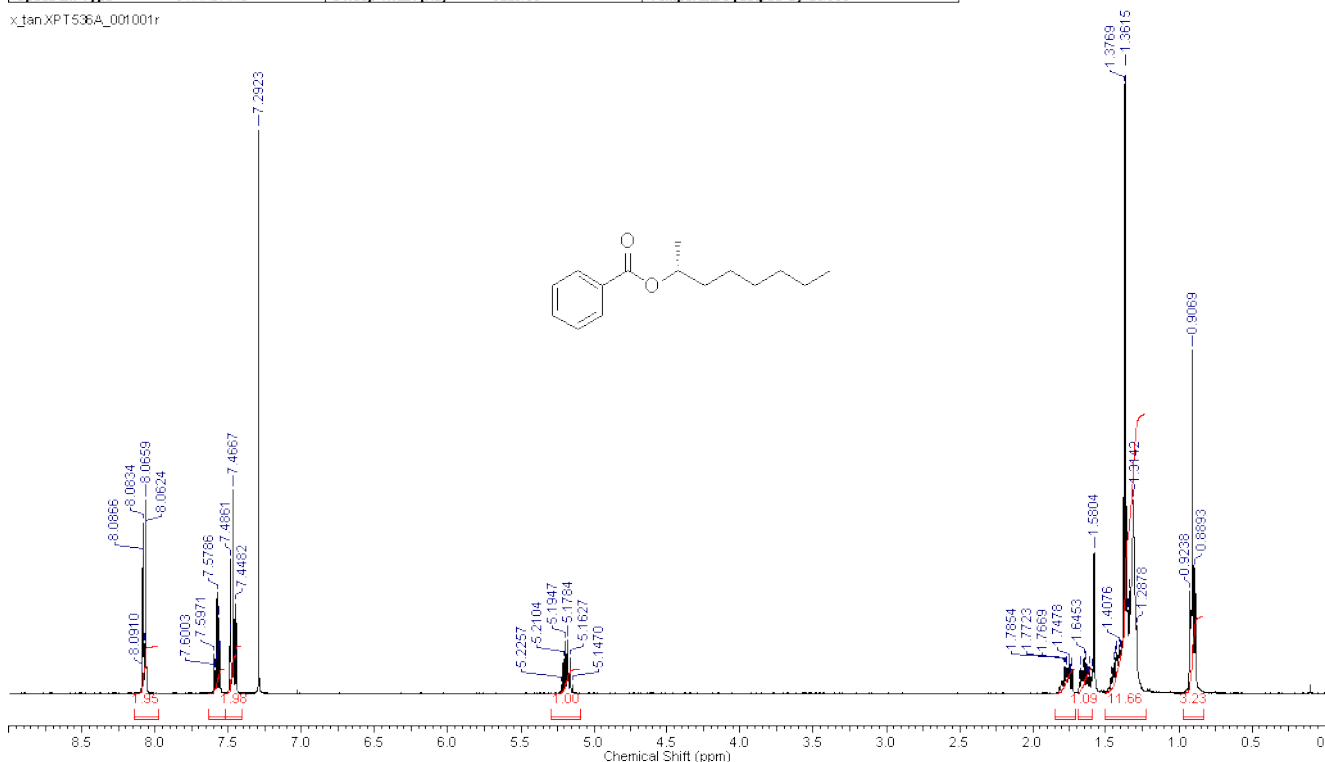
Large scale reaction. (*S*)-2-Octanol (2.38 mL, 15.0 mmol) and benzoic acid (3.66 mg, 30.0 mmol) were combined with phosphorane **3a** according to the general procedure. The product was obtained as colourless oil after purification (1.95 g, 73% yield). Triphenylphosphine oxide (3.59 g, 86%) was also recovered (and was used again for a subsequent phosphorane synthesis).

¹H NMR (400 MHz, CDCl₃) δ ppm 8.04 - 8.11 (2 H, m, ArH), 7.54 - 7.61 (1, H, m, ArH), 7.43 - 7.51 (2 H, m, ArH), 5.19 (1 H, sept., *J* = 6.3 Hz, CH), 1.73 - 1.82 (m, 1 CH₂), 1.59 - 1.68 (1 H, m, 1 H, CH₂), 1.46 - 1.28 (11, m, CH₃ and 4xCH₂), 0.91 (3 H, t, *J* = 6.8 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm 166.2, 132.7, 131.0, 130.0, 128.3, 71.8, 36.1, 31.7, 29.2, 25.4, 22.6, 20.1, 14.1.

³ J. D. Moore, R. J. Byrne, P. Vedantham, D. L. Flynn and P. R. Hanson, *Org. Lett.*, 2003, **5**, 4241-4244.

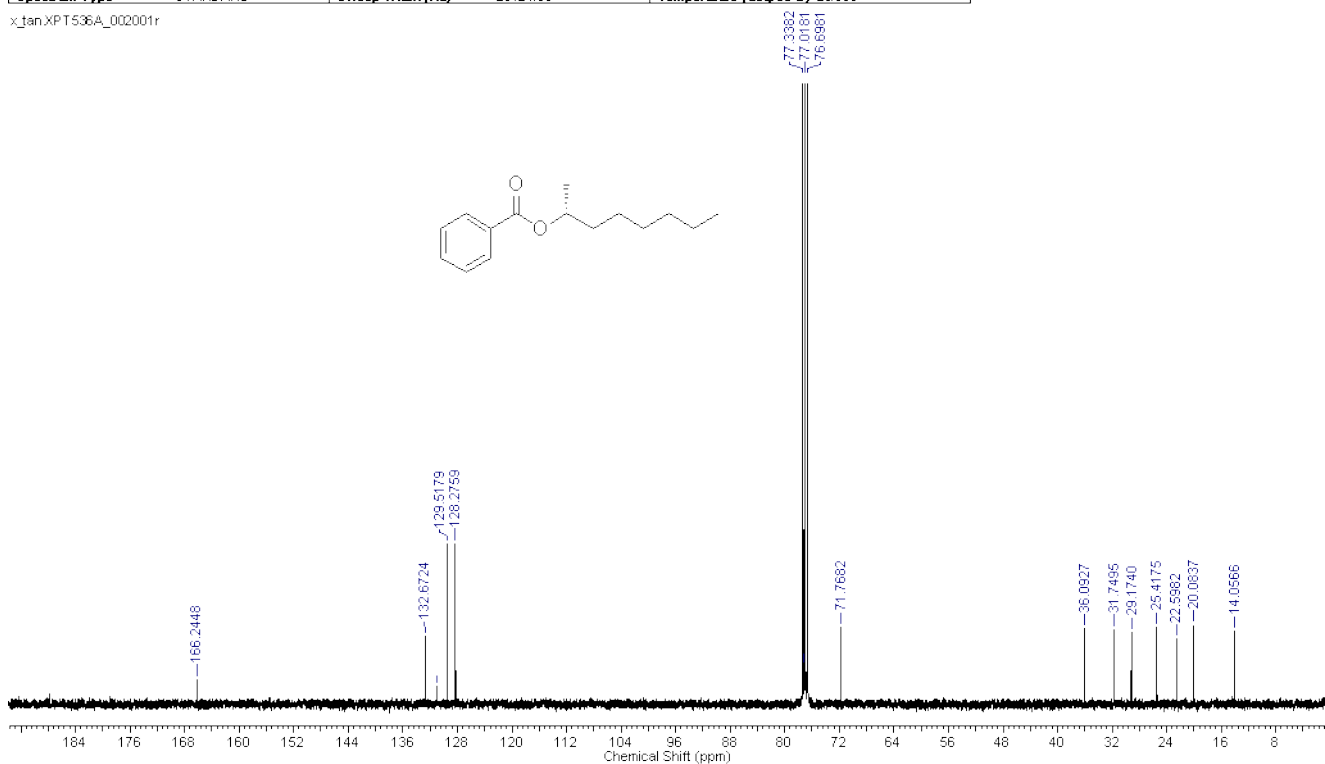
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				Spectrum Offset (Hz)	2471.2361

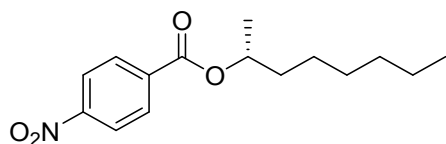
x_tan.XPT536A_001001r



Acquisition Time (sec)	0.6521	Comment	Slot No. 14 Sample ID: XPT536A SupervisorID: rderi Lab Phone No. 13540 UserID: x_tan		
Date	16 Apr 2012 20:03:28	Date Stamp	16 Apr 2012 20:03:28		
File Name	C:\Documents and Settings\Denton\My Documents\@Personal folders\X.TANG\NMR\NMR (Denton)\601-600\%_tan.XPT536A\2\data\1\1r				
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Original Points Count	16384	Owner	nmruser	Points Count	32768
Receiver Gain	7238.20	SW (cyclical) (Hz)	25125.63	Solvent	CHLOROFORM-d
Spectrum Type	STANDARD	Sweep Width (Hz)	25124.86	Temperature (degree C)	25.000
				Origin	dpq400
				Pulse Sequence	zqpg30
				Spectrum Offset (Hz)	11069.3428

x_tan.XPT536A_002001r





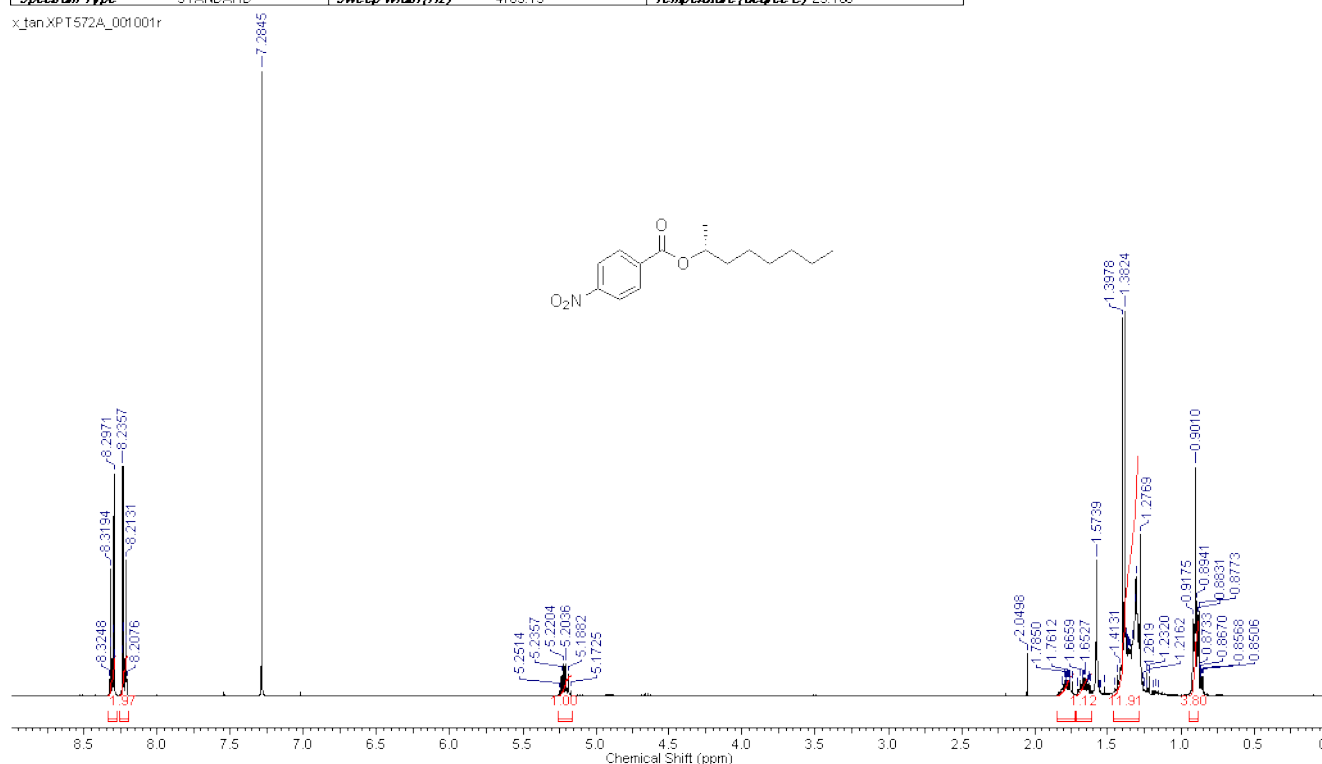
(*R*)-octan-2-yl 4-nitrobenzoate **6b⁴**

(*S*)-2-Octanol (0.16 mL, 1.0 mmol) and 4-nitrobenzoic acid (334 mg, 2.00 mmol) were combined with phosphorane **3a** according to the general procedure. The product was obtained as yellow oil after purification (195 mg, 70% yield).

¹H NMR (400 MHz, CDCl₃) δ ppm 8.29 - 8.33 (2 H, m, ArH), 8.21 - 8.25 (2 H, m, ArH), 5.21 (1 H, sept., *J* = 6.1 Hz, CH), 1.74 - 1.83 (1 H, m, CH₂), 1.62 - 1.70 (1 H, m, CH₂), 1.39 (d, *J* = 6.1 Hz, 3 H), 1.30 - 1.46 (2 H, m, 8 H), 0.90 (3 H, t, *J* = 6.6 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm 164.3, 150.4, 136.3, 130.6, 123.5, 73.2, 36.0, 31.7, 29.1, 25.4, 22.6, 20.0, 14.1.

Acquisition Time (sec)	3.4210	Comment	UserID: x_tan_SampleID: XPT572A_SupervisorID: rident_LabPhone: No. 000_Slot Number 19
Date	27 Jun 2012 03:48:32	Date Stamp	27 Jun 2012 03:48:32
File Name	C:\Documents and Settings\Denton\My Documents\6@Personal folders\Y.TANG\NMR\NMR (Denton)\501-600\%_tan.XPT572A\1\data\1\1r		
Frequency (MHz)	400.13	Nucleus	¹ H
Original Points Count	16384	Owner	nmruser
Receiver Gain	512.00	SW (cyclical) (Hz)	4789.27
Spectrum Type	STANDARD	Sweep Width (Hz)	4789.13
		Number of Transients	16
		Points Count	32768
		Solvent	CHLOROFORM-d
		Temperature (degree C)	25.160
		Origin	av400
		Pulse Sequence	zg30
		Spectrum Offset (Hz)	2200.7131

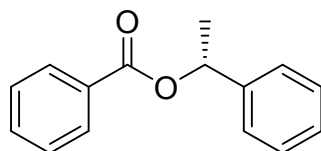
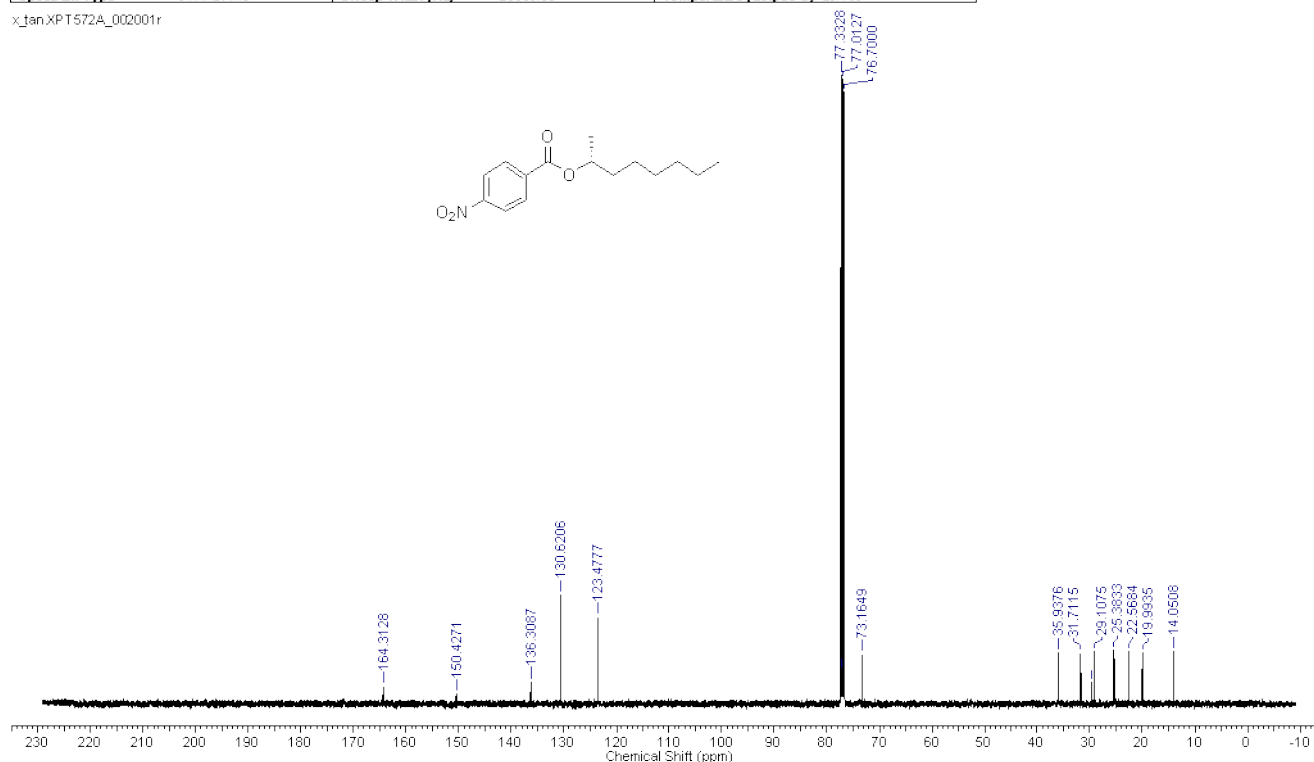
x_tan.XPT572A_001001r



⁴ A. Chighine, S. Crosignani, M.-C. Arnal, M. Bradley and B. Linclau, *J. Org. Chem.*, 2009, **74**, 4753-5762.

Acquisition Time (sec)	0.6832	Comment	UserID x_tan_SampleID:XPT572A_SupervisorID:rdent_Lab Phone No. 000_Slot Number 19
Date	27 Jun 2012 04:50:24	Date Stamp	27 Jun 2012 04:50:24
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Frequency (MHz)	100.61	Nucleus	¹³ C
Original Points Count	16384	Owner	nmruser
Receiver Gain	20642.50	SW (cyclical) (Hz)	23980.81
Spectrum Type	STANDARD	Sweep Width (Hz)	23980.08
		Solvent	CHLOROFORM-d
		Temperature (degree C)	25.180
		Origin	av400
		Pulse Sequence	zgpg30
		Spectrum Offset (Hz)	11065.5117

x_tan.XPT572A_002001r



(*R*)-1-phenylethyl benzoate **6d**⁵

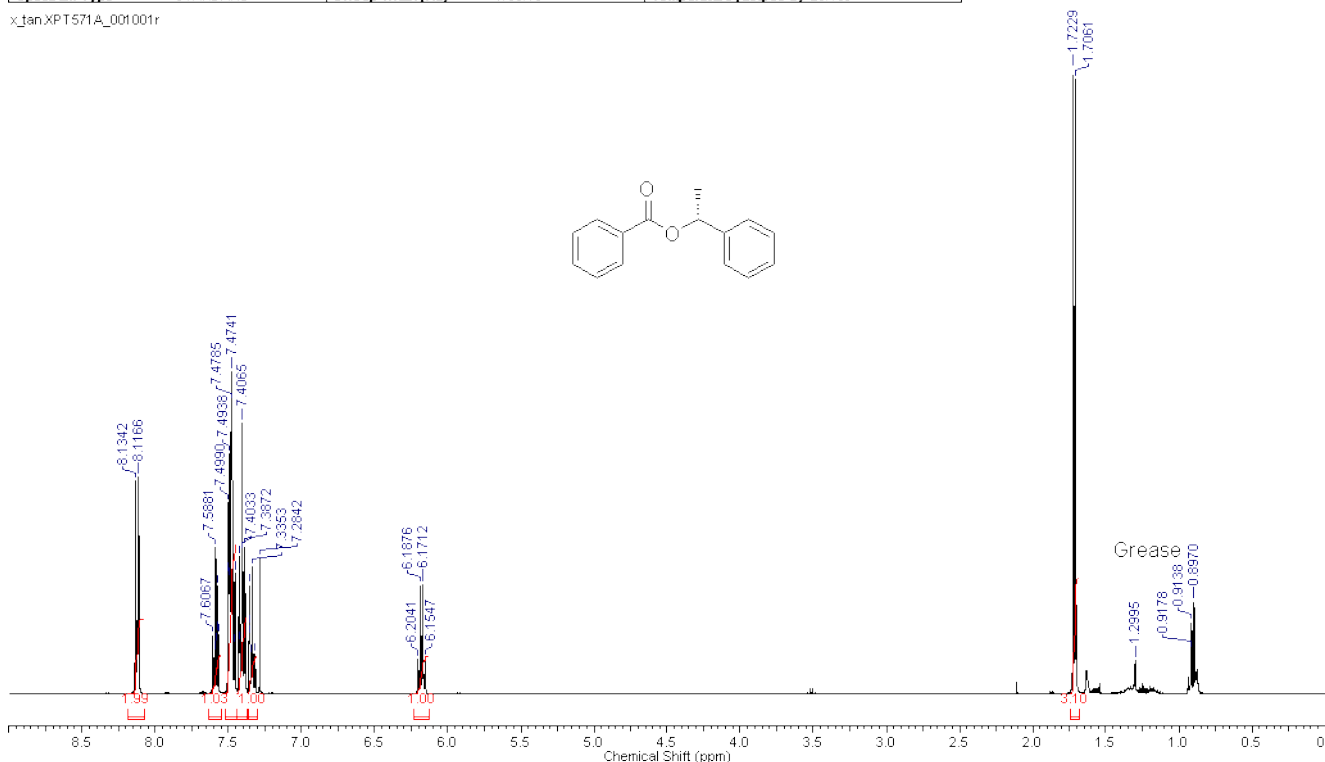
(*S*)-1-Phenylethanol (0.12 mL, 1.0 mmol) and benzoic acid (244 mg, 2.00 mmol) were combined with phosphorane **3a** according to the general procedure. The product was obtained as colourless oil after purification (178 mg, 79% yield).

¹H NMR (400 MHz, CDCl₃) δ ppm 8.10 - 8.14 (2 H, m, H_{Ar}), 7.57 - 7.61 (1 H, m, H_{Ar}), 7.45 - 7.51 (4 H, m, H_{Ar}), 7.39 - 7.43 (2 H, m, H_{Ar}), 7.31 - 7.36 (1 H, m, H_{Ar}), 6.17 (1 H, q, *J* = 6.7 Hz, CH), 1.72 (3 H, t, *J* = 6.7 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm 165.8, 141.8, 132.9, 130.6, 129.7, 128.6, 128.4, 127.9, 126.1, 72.9, 22.4.

⁵ S. T. Heller, T. Fu and R. Sarpong, *Org. Lett.*, 2012, **14**, 1970-1973.

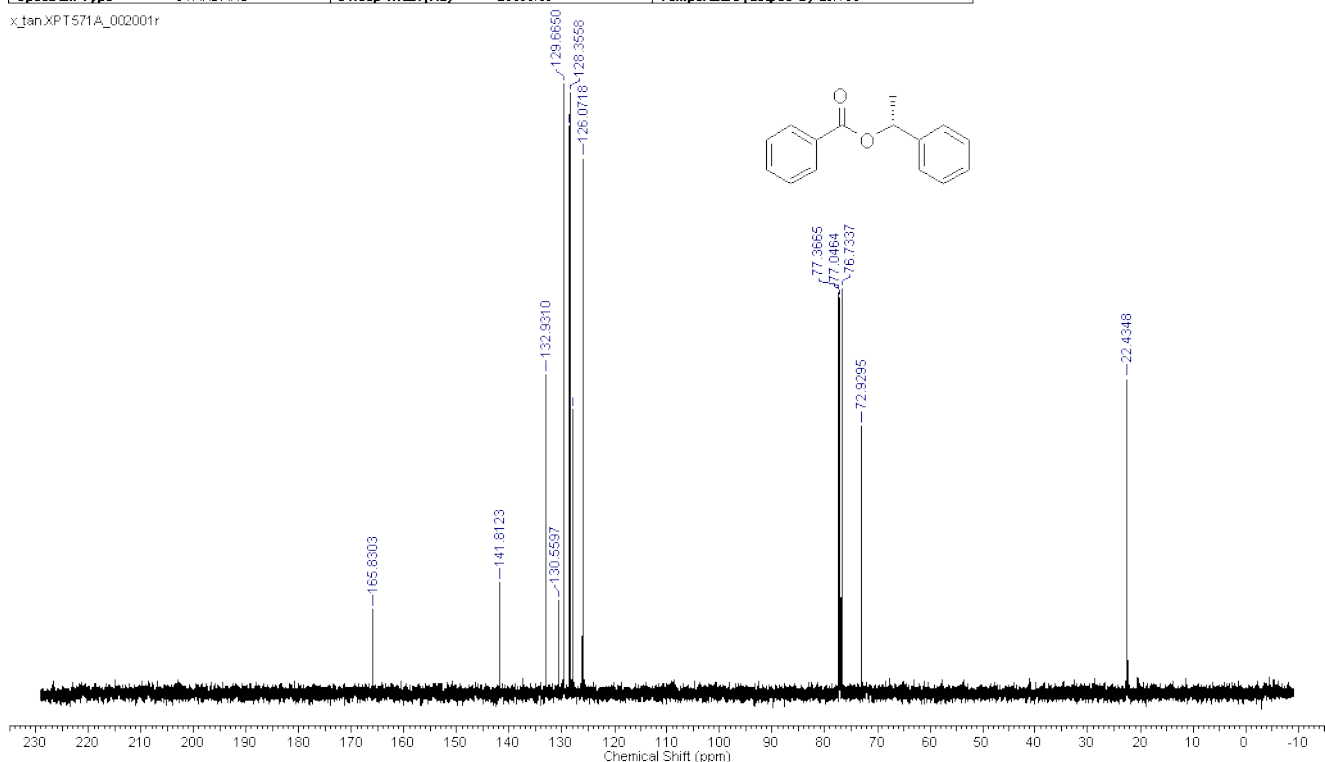
Acquisition Time (sec)	3.4210	Comment	UserID: x_tan_SampleID: XPT571A_SupervisorID: rderi_LabPhone No: 000_Slot Number: 14
Date	27 Jun 2012 15:43:12	Date Stamp	27 Jun 2012 15:43:12
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Frequency (MHz)	400.13	Nucleus	¹ H
Original Points Count	16384	Owner	nmruser
Receiver Gain	114.00	SW (cyclical) (Hz)	4789.27
Spectrum Type	STANDARD	Sweep Width (Hz)	4789.13
		Number of Transients	16
		Points Count	32768
		Solvent	CHLOROFORM-d
		Temperature (degree C)	25.160
		Origin	av400
		Pulse Sequence	zg30
		Spectrum Offset (Hz)	2200.7131

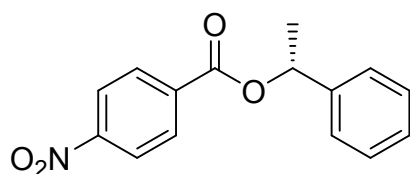
x_tan.XPT571A_001001r



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Frequency (MHz)	100.61	Nucleus	¹³ C
Original Points Count	16384	Owner	nmruser
Receiver Gain	20642.50	SW (cyclical) (Hz)	23980.81
Spectrum Type	STANDARD	Sweep Width (Hz)	23980.08
		Number of Transients	128
		Points Count	32768
		Solvent	CHLOROFORM-d
		Temperature (degree C)	25.160
		Origin	av400
		Pulse Sequence	zgpg30
		Spectrum Offset (Hz)	11065.9756

x_tan.XPT571A_002001r





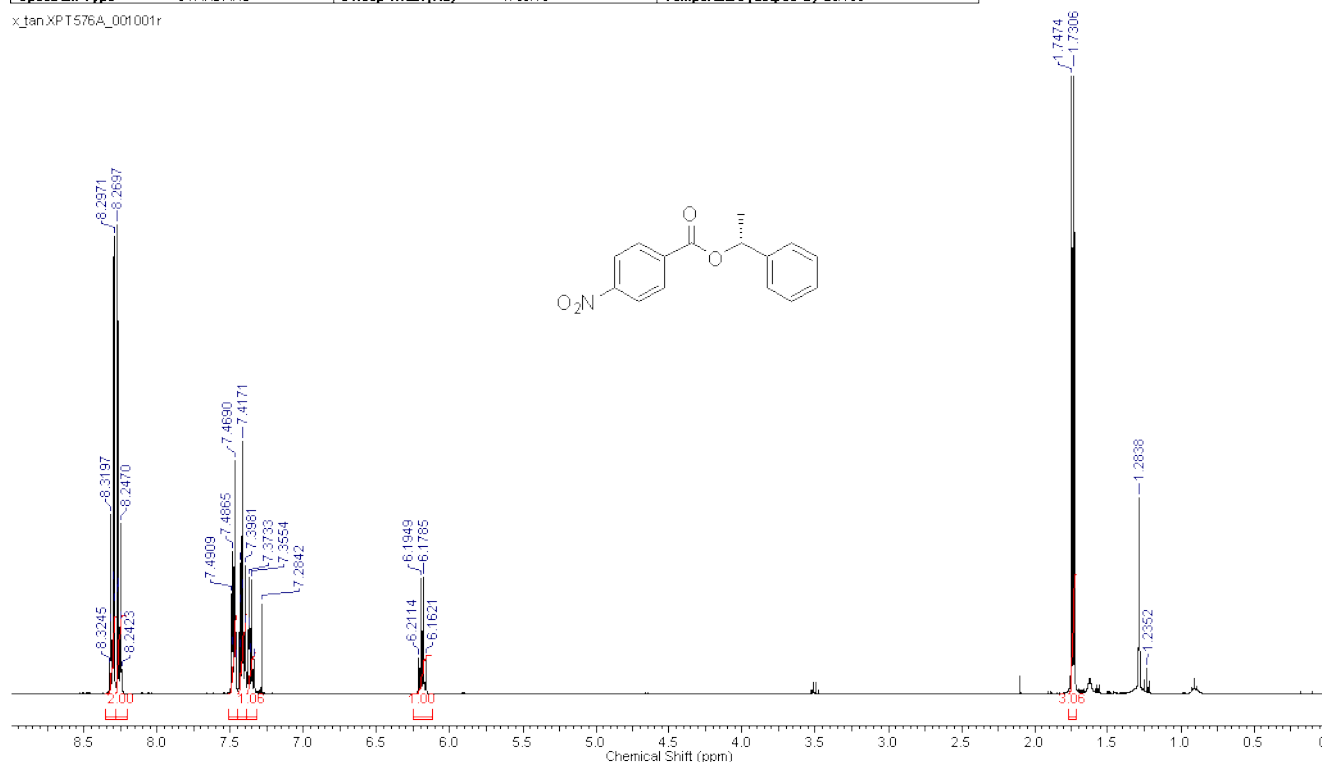
(*R*)-1-phenylethyl 4-nitrobenzoate **6c⁶**

(*S*)-1-Phenylethanol (61 μ L, 0.50 mmol) and 4-nitrobenzoic acid (167 mg, 1.00 mmol) were combined with phosphorane **3a** according to the general procedure. The product was obtained as yellow oil after purification (121 mg, 90% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.29 - 8.33 (2 H, m, ArH), 8.24 - 8.27 (2 H, m, ArH), 7.46 - 7.49 (2 H, m, ArH), 7.39 - 7.44 (2 H, m, ArH), 7.34 - 7.38 (1 H, m, ArH), 6.19 (1 H, q, *J* = 6.7 Hz, CH), 1.74 (3 H, d, *J* = 6.7 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm 164.0, 150.6, 141.0, 136.0, 130.8, 128.7, 128.3, 126.2, 123.6, 74.3, 22.3.

Acquisition Time (sec)	3.4210	Comment	UserID: x_tan_SampleID: XPT576A_SupervisorID: ident_LabPhoneNo: 000_Slot Number: 36
Date	17 Jul 2012 06:22:08	Date Stamp	17 Jul 2012 06:22:08
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Frequency (MHz)	400.13	Nucleus	¹ H
Original Points Count	16384	Number of Transients	16
Receiver Gain	128.00	Points Count	32768
Spectrum Type	STANDARD	Solvent	CHLOROFORM-d
		Sweep Width (Hz)	4789.13
		Temperature (degree C)	25.160
		Origin	av400
		Pulse Sequence	zg30
		Spectrum Offset (Hz)	2200.7131

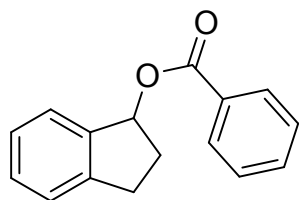
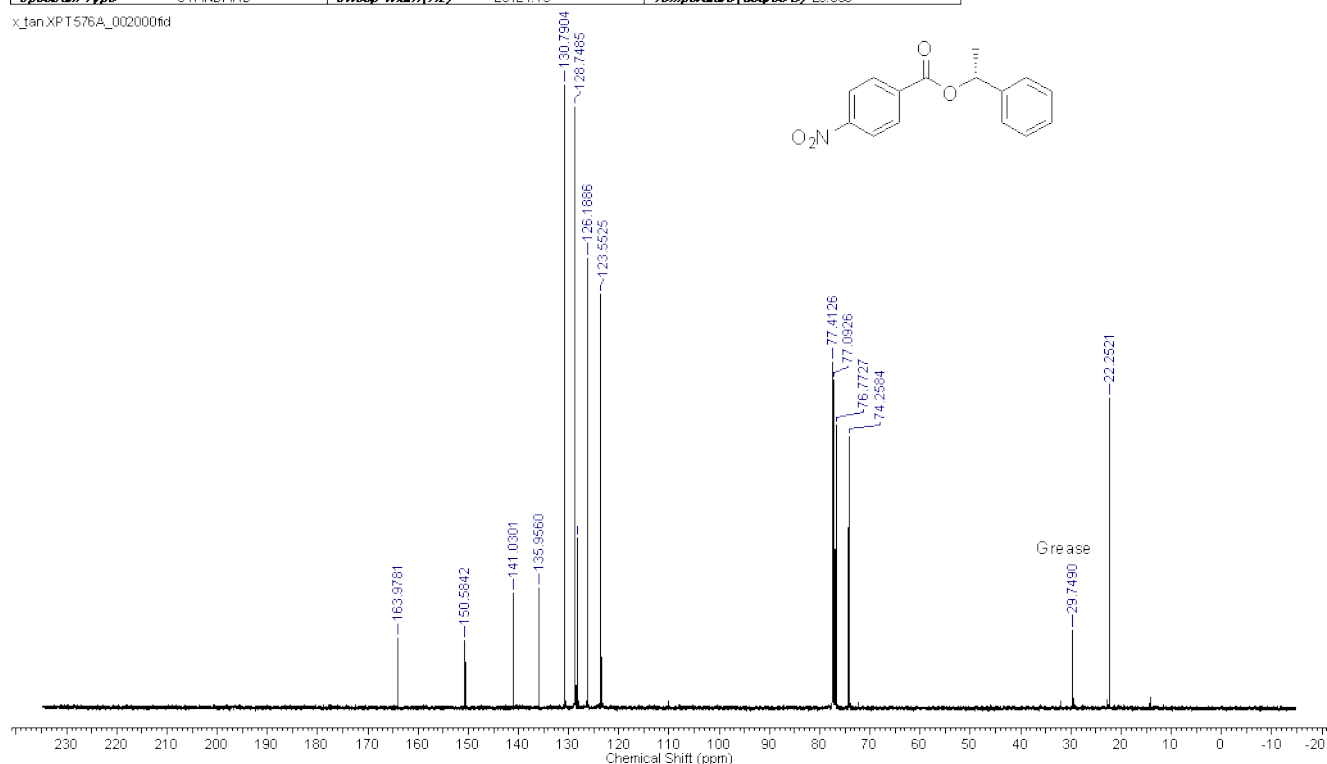
x_tan.XPT576A_001001r



⁶ T. Y. S. But and P. H. Toy, *J. Am. Chem. Soc.*, 2006, **128**, 9636-9637.

Acquisition Time (sec)	0.6521	Comment	Slot No. 4 Sample ID XPT576A SupervisorID rident Lab Phone No. 13540 UserID x_tan		
Date	06 Jul 2012 22:05:04	Date Stamp	06 Jul 2012 22:05:04		
File Name	C:\Documents and Settings\Denton\My Documents\Y@@ Personal folders\Y. TANG\NMR\NMR (Denton)\501-600\X_tan.XPT576A\2fid				
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Original Points Count	16384	Owner	nmtuser	Points Count	16384
Receiver Gain	5732.60	SW (cyclical) (Hz)	25125.63	Solvent	CHLOROFORM-d
Spectrum Type	STANDARD	Sweep Width (Hz)	25124.10	Temperature (degree C)	25.000

x_tan.XPT576A_002000fid



2,3-dihydro-1H-inden-1-yl benzoate **6f**⁷

2,3-dihydro-1H-inden-1-ol (67 mg, 0.50 mmol) and benzoic acid (122 mg, 1.00 mmol) were combined with phosphorane **3a** according to the general procedure. The product was obtained as white solid after purification (86 mg, 72% yield).

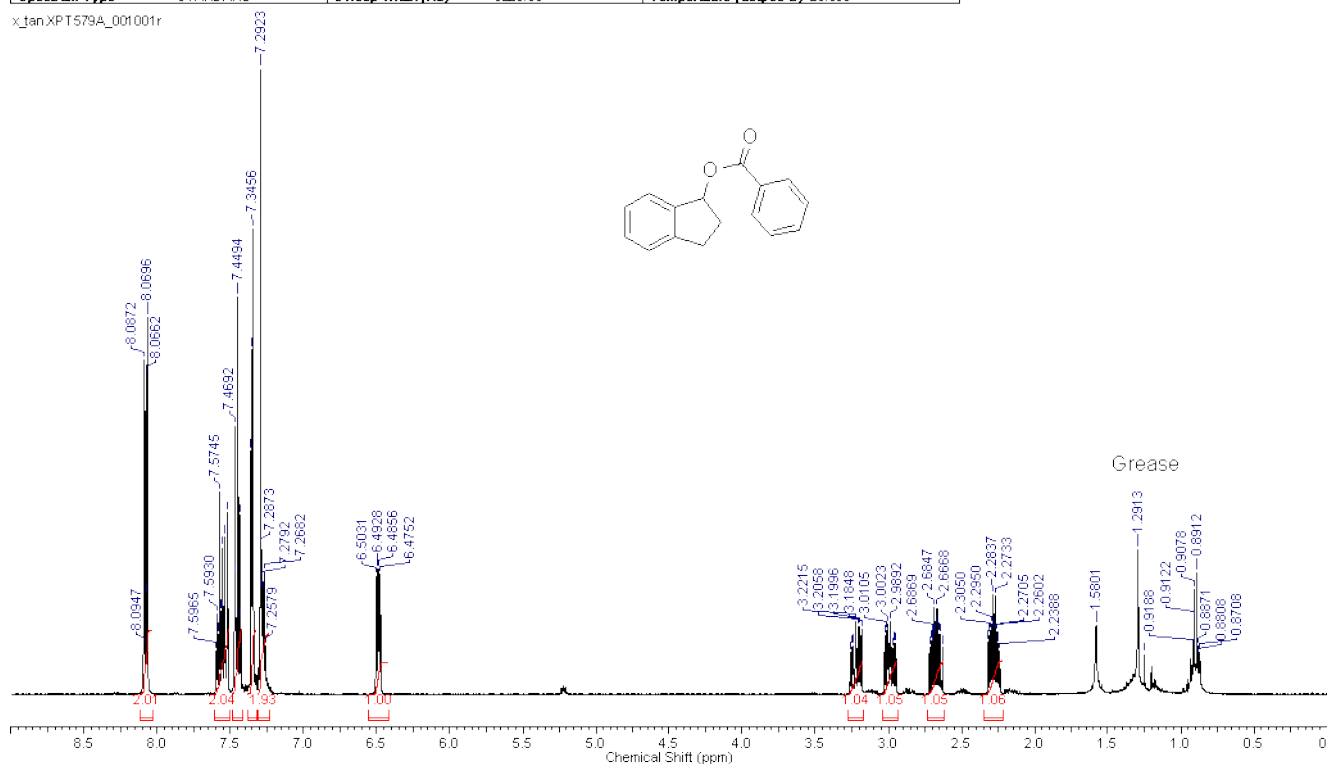
¹H NMR (400 MHz, CDCl₃) δ 8.04 - 8.10 (2 H, m, ArH), 7.51 - 7.60 (2 H, m, ArH), 7.43 - 7.47 (2 H, m, ArH), 7.33 - 7.36 (2 H, m, ArH), 7.25 - 7.30 (1 H, m, ArH), 6.49 (dd, *J*=7.0 and 4.1 Hz, 1 H), 3.18 - 3.26 (m, 1 H), 2.99 (m, 1 H), 2.63 - 2.72 (m, 1 H), 2.23 - 2.32 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 166.6, 144.4, 141.1, 132.9, 130.5, 129.7, 129.0, 128.3, 126.8, 125.7, 124.8, 79.0, 32.5, 30.3. HRMS (ESI)

⁷ T. Ohshima, T. Iwasaki, Y. Maegawa, A. Yoshiyama and K. Mashima, *J. Am. Chem. Soc.*, 2008, **130**, 2944-2945.

(m/z): [M+Na]⁺ calcd for C₁₆H₁₄NaO₂ 261.0886; found 261.0888 **IR** ν_{max}(ATR): 2918, 2850, 1702(C=O), 1461, 1251, 1100, 761, 708. **m.p.**: 48-51 °C

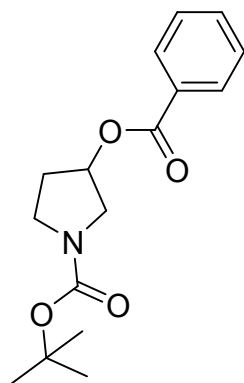
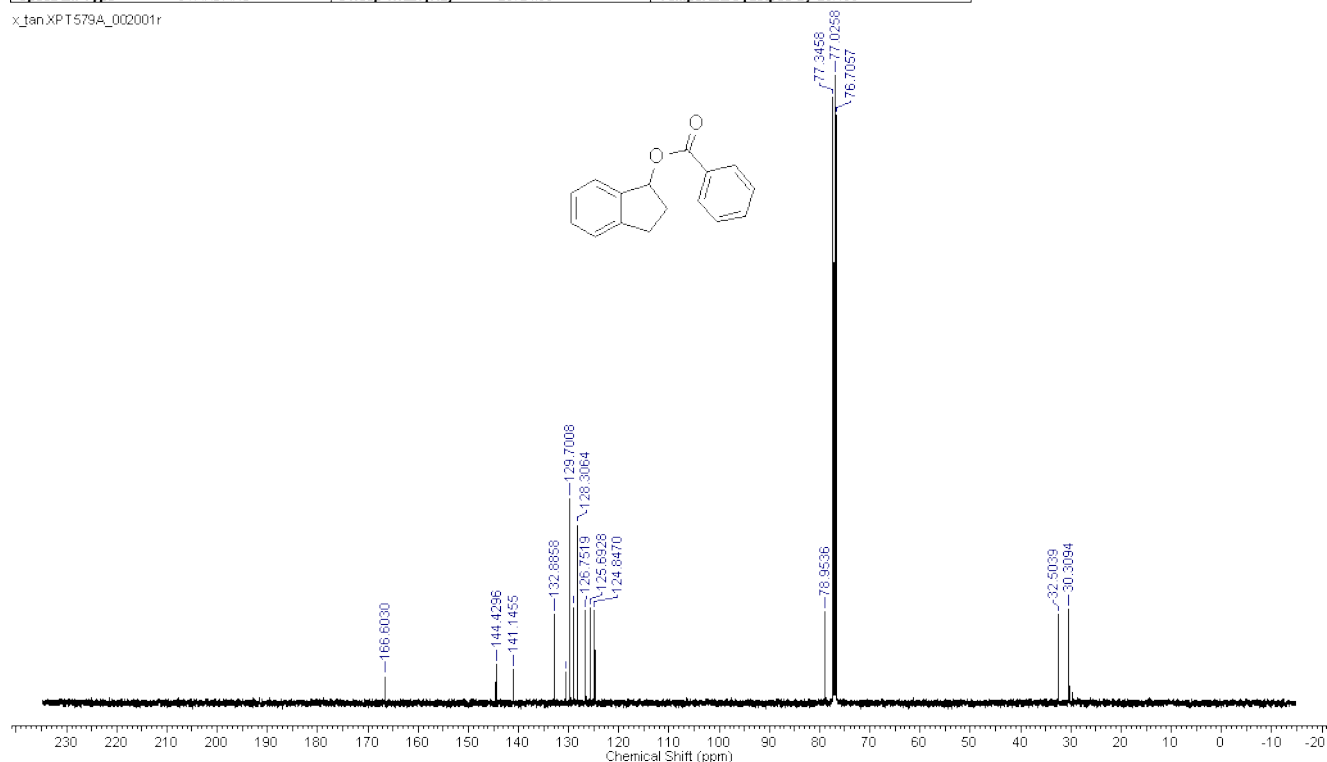
Acquisition Time (sec)	3.9946	Comment	Slot No. 24, Sample ID: XPT579A, Supervisor: D rident, Lab Phone No. 13540, User ID: x_tan				
Date	16 Jul 2012 18:31:44	Date Stamp	16 Jul 2012 18:31:44				
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Frequency (MHz)	400.20	Nucleus	¹ H	Number of Transients	16	Origin	dx400
Original Points Count	32768	Owner	nmruser	Points Count	65536	Pulse Sequence	zg30
Receiver Gain	645.10	SW (cyclical) (Hz)	8223.68	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2471.2361
Spectrum Type	STANDARD	Sweep Width (Hz)	8223.56	Temperature (degree C)	25.000		

x_tan.XPT579A_001001r



Acquisition Time (sec)	0.6521	Comment	Slot No. 24 Sample ID: XPT579A Supervisor: D rident Lab Phone No. 13540 User ID: x_tan		
Date	17 Jul 2012 06:00:48	Date Stamp	17 Jul 2012 06:00:48		
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Frequency (MHz)	100.63	Nucleus	¹³ C	Number of Transients	2048
Original Points Count	16384	Owner	nmluser	Points Count	32768
Receiver Gain	5160.60	SW (cyclical) (Hz)	25125.63	Solvent	CHLOROFORM-d
Spectrum Type	STANDARD	Sweep Width (Hz)	25124.86	Temperature (degree C)	25.100
				Origin	dcx400
				Pulse Sequence	zgpg30
				Spectrum Offset (Hz)	11069.3428

x_tan.XPT579A_002001r



tert-Butyl 3-(benzoyloxy)pyrrolidine-1-carboxylate **6e⁸**

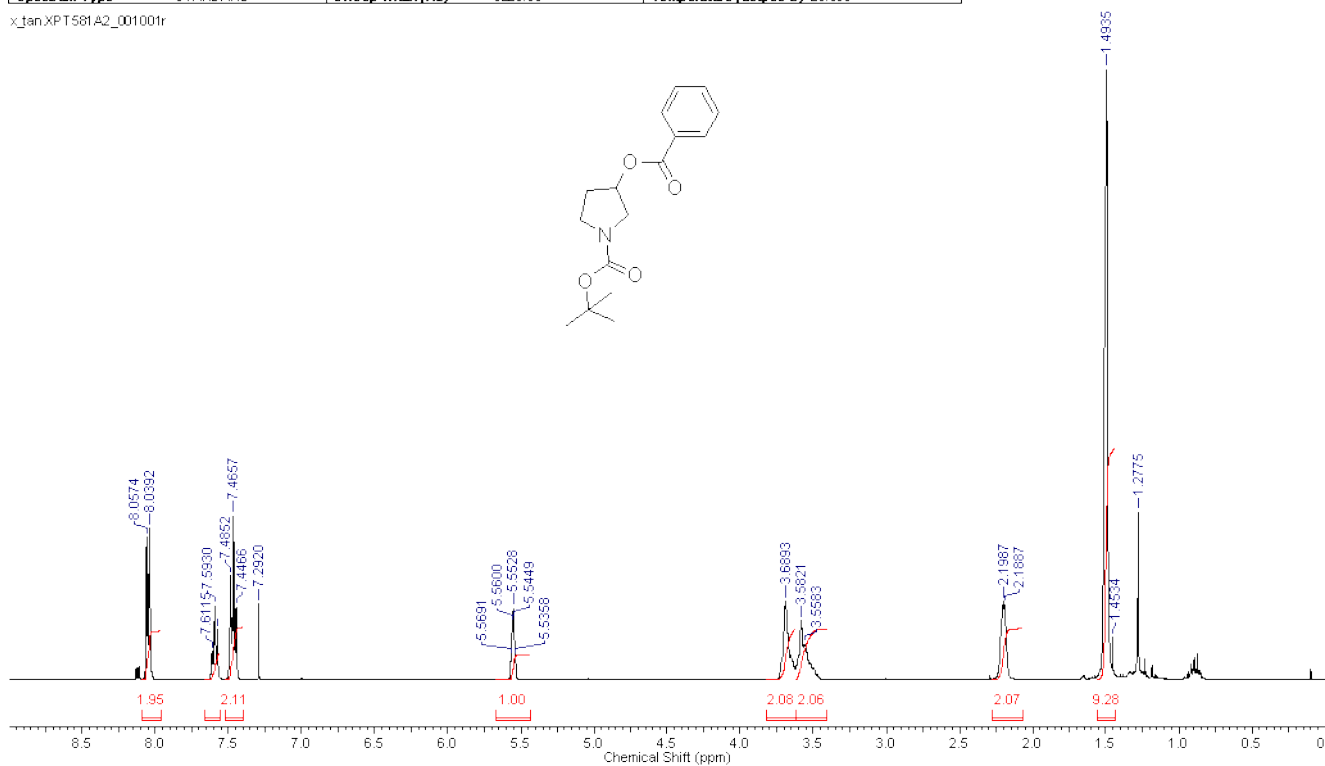
tert-Butyl 3-hydroxypyrrolidine-1-carboxylate (94 mg, 0.50 mmol) and benzoic acid (122 mg, 1.00 mmol) were combined with phosphorane **3a** according to the general procedure. The product was obtained white solid after purification (110 mg, 76% yield).

⁸ Astrazeneca AB Patent: WO2004/5295 A1, 2004

¹H NMR (400 MHz, CDCl₃) δ 8.05 (2 H, m, ArH), 7.60 (1 H, m, ArH), 7.47 (2 H, m, ArH), 5.55 (1 H, m, CH), 3.63-3.75 (2 H, br. m, CH₂), 3.43 - 3.62 (2 H, br. m, CH₂), 2.15-2.25 (2 H, br. m, CH₂), 1.49 (9 H, s, 3xCH₃); ¹³C NMR (100 MHz, CDCl₃) (mixture of rotamers) δ ppm 166.1, 154.5, 133.2, 130.1, 129.7, 128.4, 79.6, 74.4, 73.7, 52.0, 51.5, 44.2, 43.8, 31.8, 30.9, 29.7, 28.5. HRMS (ESI) (m/z): [M+H]⁺ calcd for C₁₆H₂₂NO₄ 292.1543; found 292.1538. IR ν_{max}(CHCl₃): 2982, 1689(CO), 1414, 1274, 1168, 1116, 909. m.p.:84-86 °C.

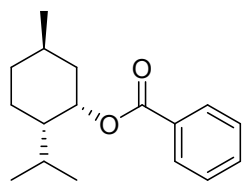
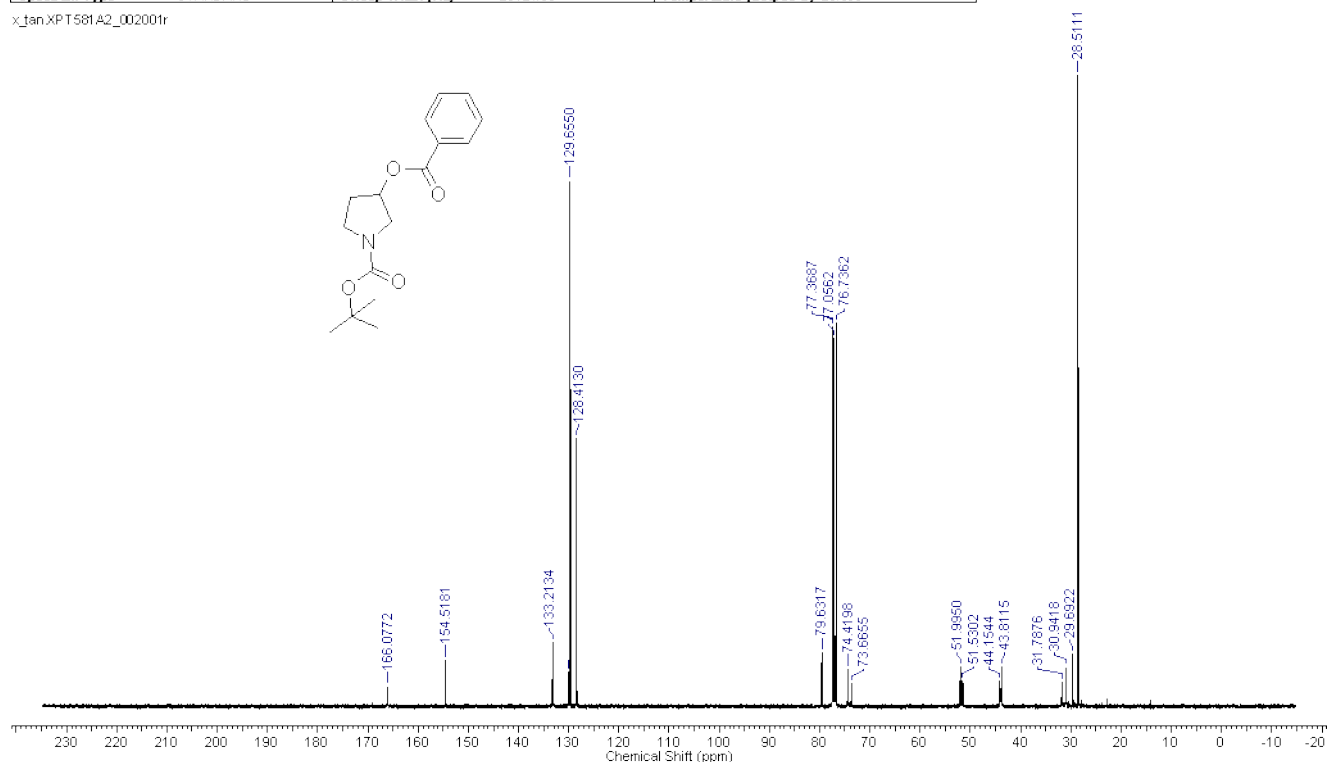
Acquisition Time (sec)	3.9946	Comment	Slot No. 18 Sample ID: XPT581A2 Supervisor ID: rident Lab Phone No. 13540 UserID: x_tan		
Date	09 Oct 2013 10:46:40	Date Stamp	09 Oct 2013 10:46:40		
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Frequency (MHz)	400.20	Nucleus	¹ H	Number of Transients	16
Original Points Count	32768	Owner	nmruser	Points Count	65536
Receiver Gain	143.70	SW (cyclical) (Hz)	8223.68	Solvent	CHLOROFORM-d
Spectrum Type	STANDARD	Sweep Width (Hz)	8223.96	Temperature (degree C)	25.000
				Origin	dcw400
				Pulse Sequence	zg30
				Spectrum Offset (Hz)	2471.2361

x_tan.XPT581A2_001001r



Acquisition Time (sec)	0.6521	Comment	Std No. 18 Sample ID: XPT581A2 Supervisor: D rderit Lab Phone No. 13540 User: D x tan				
Date	10 Oct 2013 06:28:32	Date Stamp	10 Oct 2013 06:28:32				
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Frequency (MHz)	100.63	Nucleus	¹³ C	Number of Transients	4096	Origin	dpw400
Original Points Count	16384	Owner	nmruser	Points Count	32768	Pulse Sequence	zgpg30
Receiver Gain	11585.20	SW (cyclical) (Hz)	25125.63	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	11069.3428
Spectrum Type	STANDARD	Sweep Width (Hz)	25124.86	Temperature (degree C)	25.000		

x_tan.XPT581A2_002001r



(1*S**,2*S**,5*R**)-2-isopropyl-5-methylcyclohexyl benzoate **6j**⁹

(1*R**,2*S**,5*R**)-2-isopropyl-5-methylcyclohexan-1-ol (156 mg, 1.00 mmol) and benzoic acid (244 mg, 2.00 mmol) were combined with phosphorane **3a** according to the general procedure. The product was obtained as colourless oil after purification (71 mg, 27% yield).

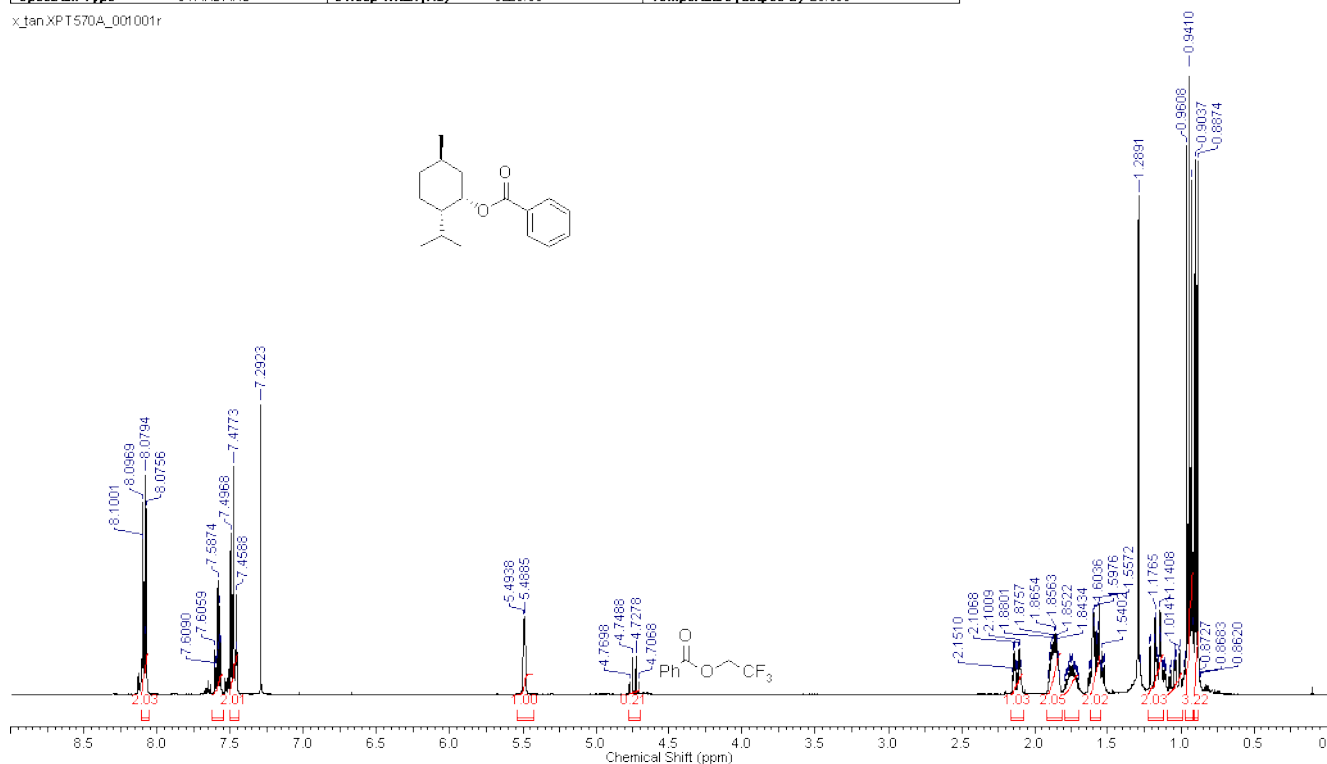
¹H NMR (400 MHz, CDCl₃) δ 8.08 - 8.10 (2 H, m, 2 H, ArH), 7.56 - 7.61 (1 H, m, 1 H, ArH), 7.45 - 7.50 (2 H, m, ArH), 5.49 (1 H, br. d, *J* = 2.1 Hz, CH), 2.09 - 2.15 (1 H, m, CH), 1.82 - 1.90 (2 H, m), 1.69 - 1.79 (1 H, m), 1.55 - 1.61 (2 H, m), 1.13 - 1.21 (2 H, m), 1.00 - 1.08 (1 H, m), 0.94 (3 H, d, *J* = 6.8 Hz,

⁹ J. A. Dodge, J. I. Trujillo and M. J. Presnell, *J. Org. Chem.*, 1994, **59**, 234-236.

CH₃), 0.93 (3 H, d, J=6.8 Hz, CH₃), 0.90 (3 H, d, J=6.5 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm 165.9, 132.7, 131.1, 129.5, 128.4, 71.8, 47.1, 39.3, 34.9, 29.4, 26.8, 25.4, 22.2, 21.0, 20.8.

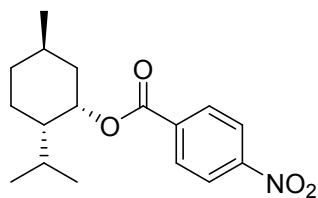
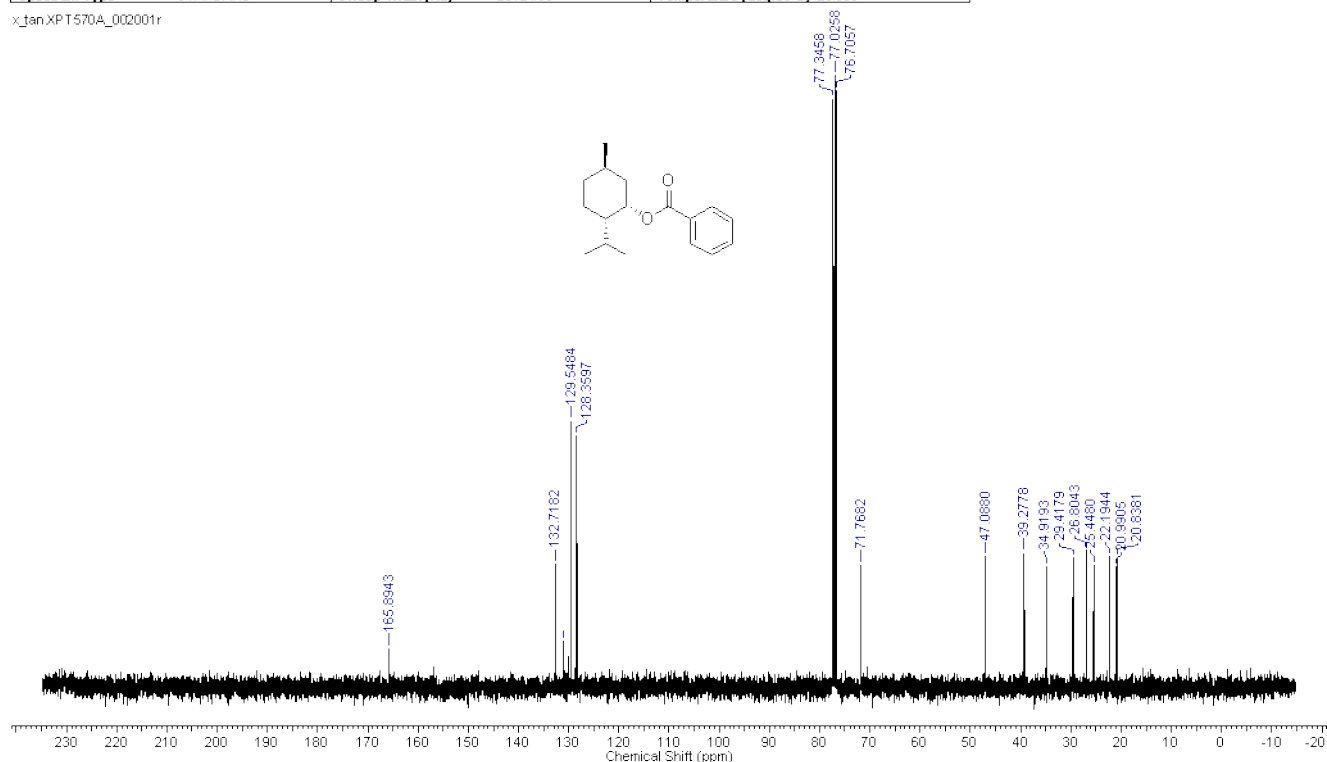
Acquisition Time (sec)	3.9946	Comment	Slot No. 1 Sample ID: XPT570A Supervisor ID: ident Lab Phone No. 13540 User ID: x_tan		
Date	26 Jun 2012 16:28:00	Date Stamp	26 Jun 2012 16:28:00		
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Frequency (MHz)	400.20	Nucleus	¹ H	Number of Transients	16
Original Points Count	32768	Owner	nmruser	Points Count	65536
Receiver Gain	256.00	SW (cyclical) (Hz)	8223.68	Solvent	CHLOROFORM-d
Spectrum Type	STANDARD	Sweep Width (Hz)	8223.56	Temperature (degree C)	25.000
				Origin	djv400
				Pulse Sequence	zg30
				Spectrum Offset (Hz)	2471.2361

x_tan.XPT570A_001001r



Acquisition Time (sec)	0.6521	Comment	Slot No. 1 Sample ID: XPT570A Supervisor ID: rident Lab Phone No. 13540 UserID: x_tan		
Date	26 Jun 2012 16:32:16	Date Stamp	26 Jun 2012 16:32:16		
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Frequency (MHz)	100.63	Nucleus	¹³ C	Number of Transients	128
Original Points Count	16384	Owner	nmtuser	Points Count	32768
Receiver Gain	4096.00	SW (cycles) (Hz)	25125.63	Solvent	CHLOROFORM-d
Spectrum Type	STANDARD	Sweep Width (Hz)	25124.86	Temperature (degree C)	25.000

x_tan.XPT570A_002001r



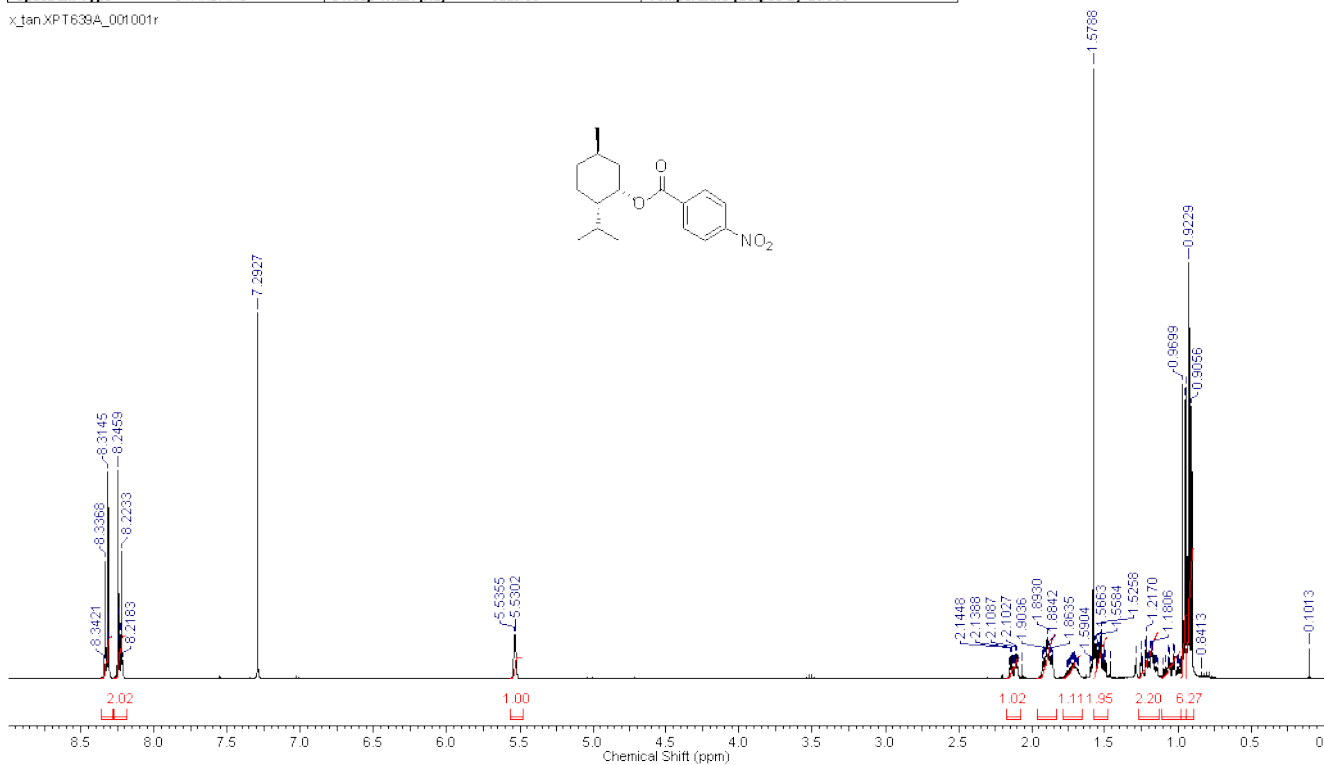
(1S,2S,5R)-2-isopropyl-5-methylcyclohexyl 4-nitrobenzoate⁷

(1R*,2S*,5R*)-2-isopropyl-5-methylcyclohexan-1-ol (156 mg, 1.00 mmol) and 4-nitrobenzoic acid (334 mg, 2.00 mmol) were combined with phosphorane **3a** according to the general procedure. The product was obtained as a yellow solid after purification (91 mg, 30% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.31 - 8.34 (2 H, m, ArH), 8.22 - 8.25 (2 H, m, ArH), 5.54 (1 H, br. d, *J* = 1.3 Hz, CH), 2.10 - 2.16 (m, 1 H), 1.85 - 1.94 (m, 2 H), 1.72 (m, 1 H), 1.49 - 1.57 (m, 2 H), 1.14 - 1.25 (m, 2 H), 0.99 - 1.10 (m, 1 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.90 - 0.94 (m, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 164.0, 136.4, 130.6, 123.6, 73.2, 47.0, 39.1, 34.8, 29.5, 26.9, 25.4, 22.1, 20.9, 20.8. **m.p.**: 90-92 °C.

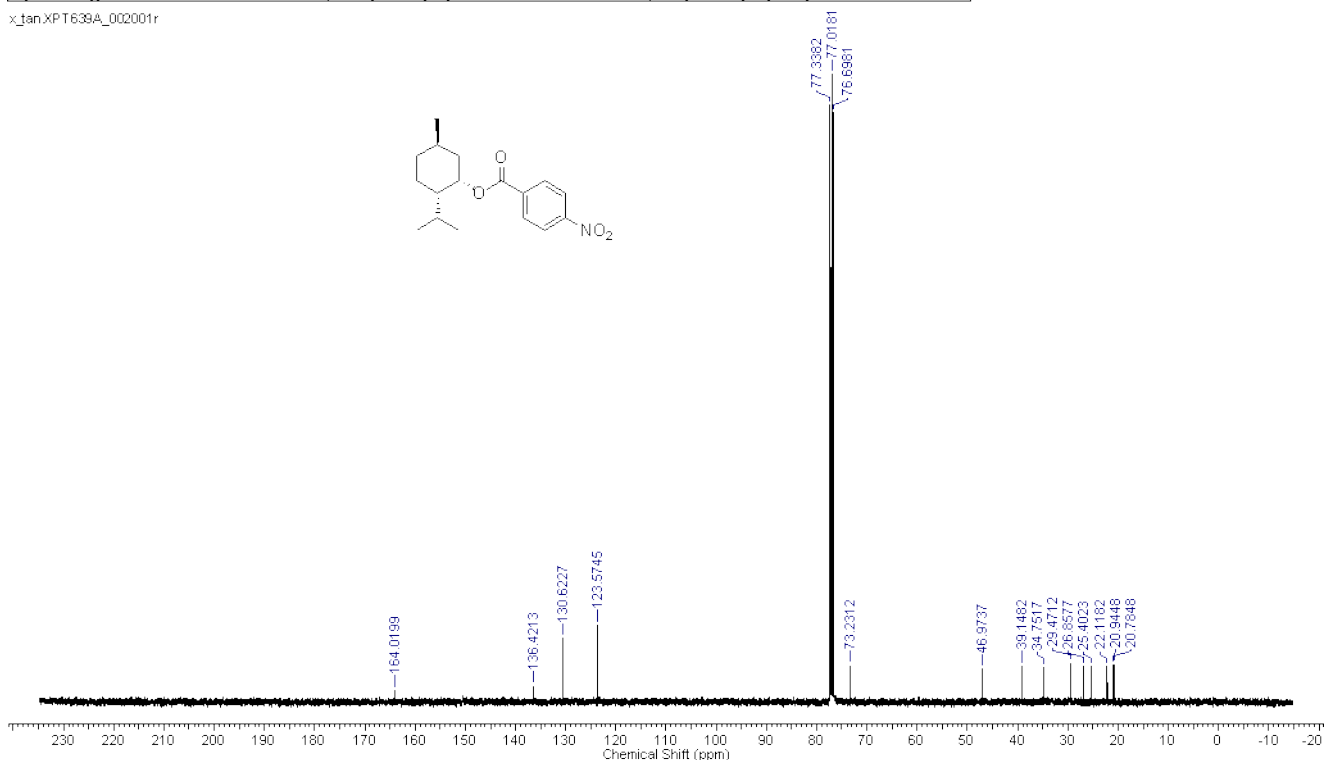
Acquisition Time (sec)	3.9846	Comment	Slot No. 51 Sample ID: XPT639A SupervisorID: rderk Lab Phone No. 13540 UserID: x_tan		
Date	30 Oct 2012 16:40:32	Date Stamp	30 Oct 2012 16:40:32		
File Name	C:\Documents and Settings\Denton\My Documents\@@ Personal folders\X.TANG\@NMR\NMR (Denton)\601-700\X_tan.XPT639A\1\pdata\1\1r				
Frequency (MHz)	400.20	Nucleus	¹ H	Number of Transients	16
Original Points Count	32768	Owner	nmtuser	Points Count	65536
Receiver Gain	812.70	SW (cyclical) (Hz)	8223.68	Solvent	CHLOROFORM-d
Spectrum Type	STANDARD	Sweep Width (Hz)	8223.56	Temperature (degree C)	25.000
				Origin	dpx400
				Pulse Sequence	zg30
				Spectrum Offset (Hz)	2471.2361

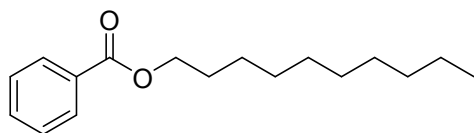
x_tan.XPT639A_001001r



Acquisition Time (sec)	0.6521	Comment	Slot No. 51 Sample ID: XPT639A SupervisorID: rderk Lab Phone No. 13540 UserID: x_tan		
Date	30 Oct 2012 23:40:48	Date Stamp	30 Oct 2012 23:40:48		
File Name	C:\Documents and Settings\Denton\My Documents\@@ Personal folders\X.TANG\@NMR\NMR (Denton)\601-700\X_tan.XPT639A\2\pdata\1\1r				
Frequency (MHz)	100.63	Nucleus	¹³ C	Number of Transients	2048
Original Points Count	16384	Owner	nmtuser	Points Count	32768
Receiver Gain	20642.50	SW (cyclical) (Hz)	25125.63	Solvent	CHLOROFORM-d
Spectrum Type	STANDARD	Sweep Width (Hz)	25124.86	Temperature (degree C)	25.000
				Origin	dpx400
				Pulse Sequence	zgpg30
				Spectrum Offset (Hz)	11069.3428

x_tan.XPT639A_002001r





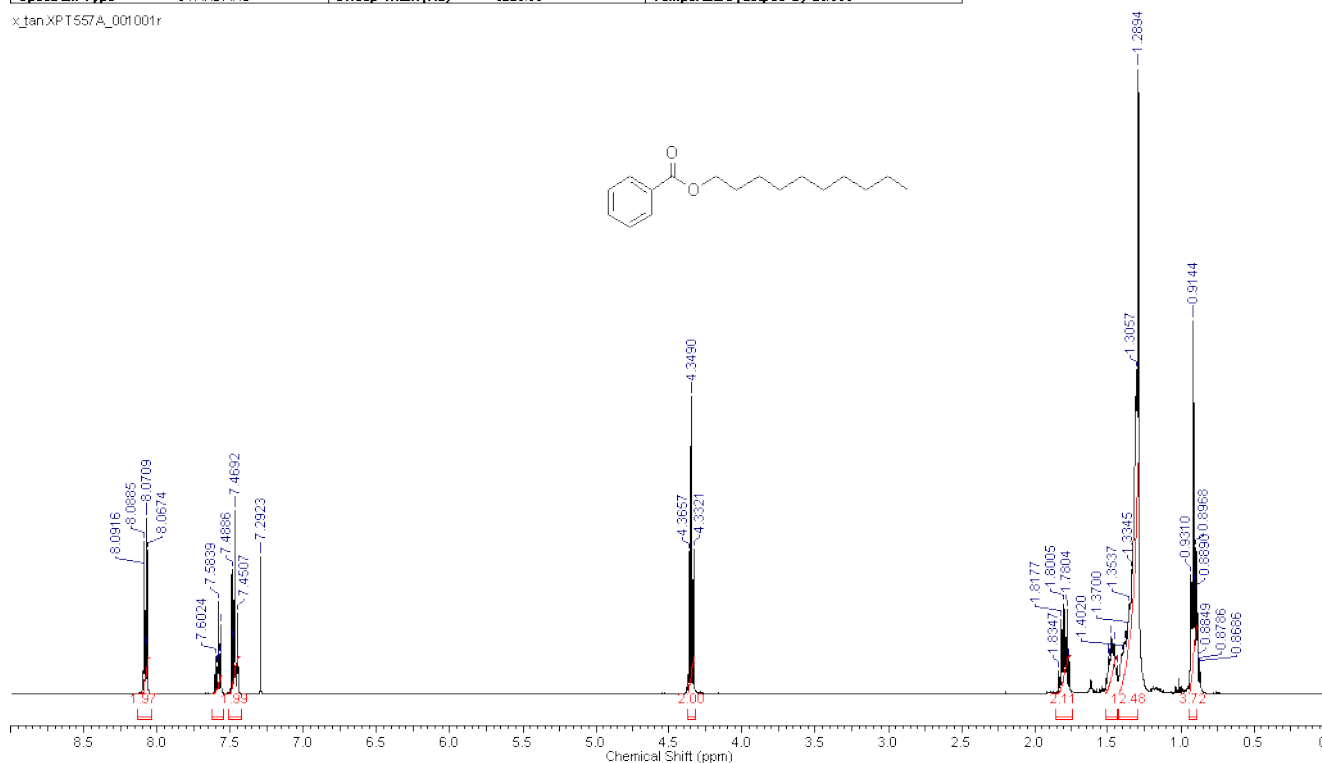
Decyl benzoate **6g**¹⁰

1-Decanol (0.10 mg, 0.50 mmol) and benzoic acid (122 mg, 1.00 mmol) were combined with phosphorane **3a** according to the general procedure. The product was obtained as colourless oil after purification (55 mg, 42% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.07 - 8.09 (2 H, m, ArH), 7.56 - 7.60 (1 H, m, ArH), 7.44 - 7.49 (2 H, m, ArH), 4.35 (2 H, t, *J* = 6.7 Hz, CH₂), 1.80 (2 H, quint., *J* = 6.7 Hz, CH₂), 1.44 - 1.51 (2 H, m, CH₂), 1.23 - 1.42 (12 H, m, 6xCH₂), 0.91 (3 H, t, *J* = 6.7 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm 166.7, 132.8, 130.6, 129.6, 128.3, 65.2, 31.9, 29.7, 29.6, 29.3 (2C), 28.8, 26.1, 22.7, 14.1.

Acquisition Time (sec)	3.9846	Comment	Slot No. 37 Sample ID:XPT557A SupervisorID:rdent Lab Phone No. 13540 UserID: x_tan		
Date	22 May 2012 17:40:32	Date Stamp	22 May 2012 17:40:32		
File Name	C:\Documents and Settings\Denton\My Documents\TANG\@Personal folders\TANG\@NMR\NMR (Denton)\601-600\XPT557A\1\data\1\1				
Frequency (MHz)	400.20	Nucleus	¹ H	Number of Transients	16
Original Points Count	32768	Owner	nmuser	Points Count	65536
Receiver Gain	181.00	SW(cyclical) (Hz)	8223.68	Solvent	CHLOROFORM-d
Spectrum Type	STANDARD	Sweep Width (Hz)	8223.56	Temperature (degree C)	25.000
				Origin	dpc400
				Pulse Sequence	zg30
				Spectrum Offset (Hz)	2471.2361

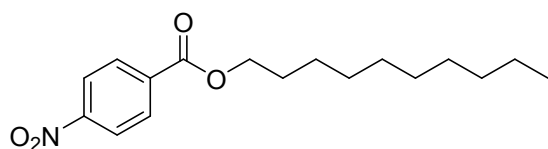
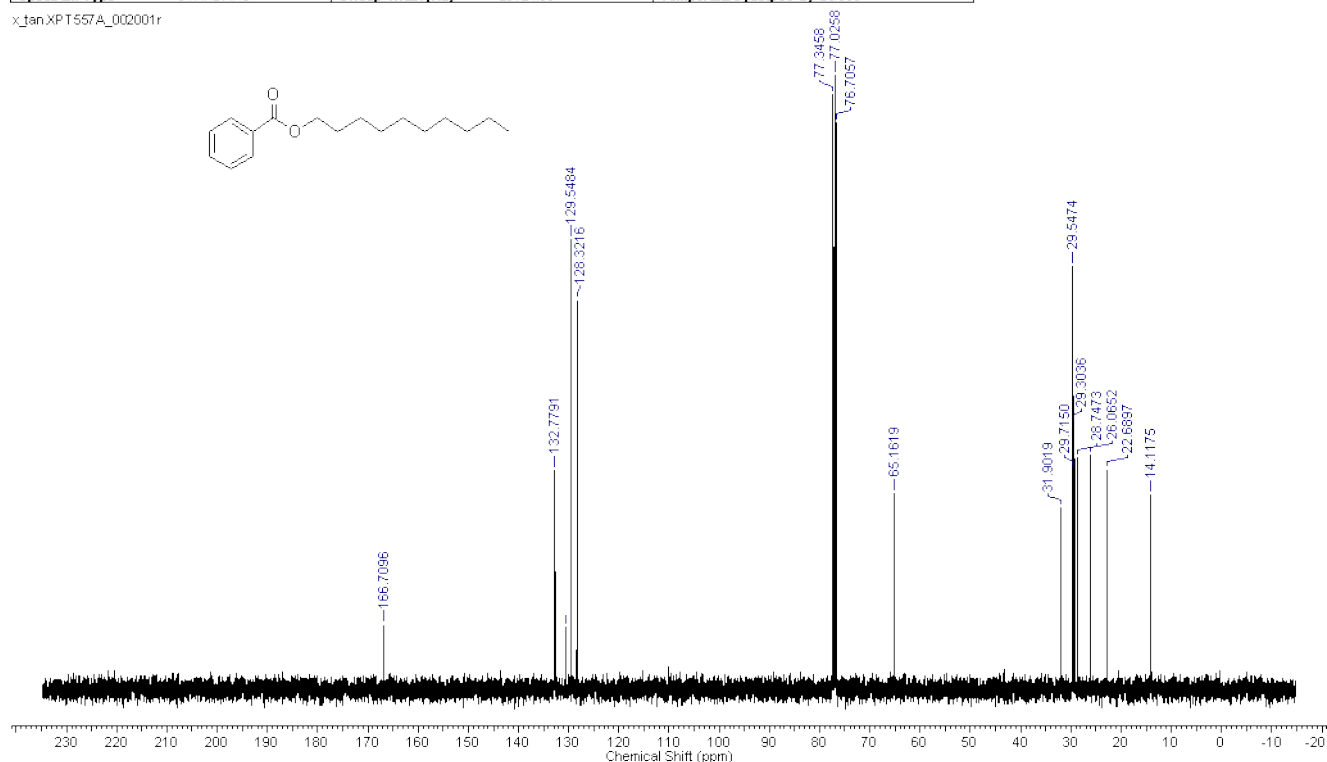
x_tan.XPT557A_001001r



¹⁰ M. Tamura, S. M. A. H. Siddiki and K. Shimizu, *Green Chem.*, 2013, **15**, 1641-1646.

Acquisition Time (sec)	0.6521	Comment	Slot No. 37 Sample ID: XPT557A Supervisor: rident Lab Phone No. 13540 UserID: x_tan		
Date	22 May 2012 17:44:48	Date Stamp	22 May 2012 17:44:48		
File Name	C:\Documents and Settings\Denton\My Documents\X\@ Personal folders\X\TANG\@NMR\NMR (Denton)\501-600\%_tan.XPT557A\2\data\1\1r				
Frequency (MHz)	100.63	Nucleus	¹³ C	Number of Transients	128
Original Points Count	16384	Owner	rntuser	Points Count	32768
Receiver Gain	18390.40	SW (cyclical) (Hz)	25125.63	Solvent	CHLOROFORM-d
Spectrum Type	STANDARD	Sweep Width (Hz)	25124.85	Temperature (degree C)	25.000
				Spectrum Offset (Hz)	11069.3428

x_tan.XPT557A_002001r



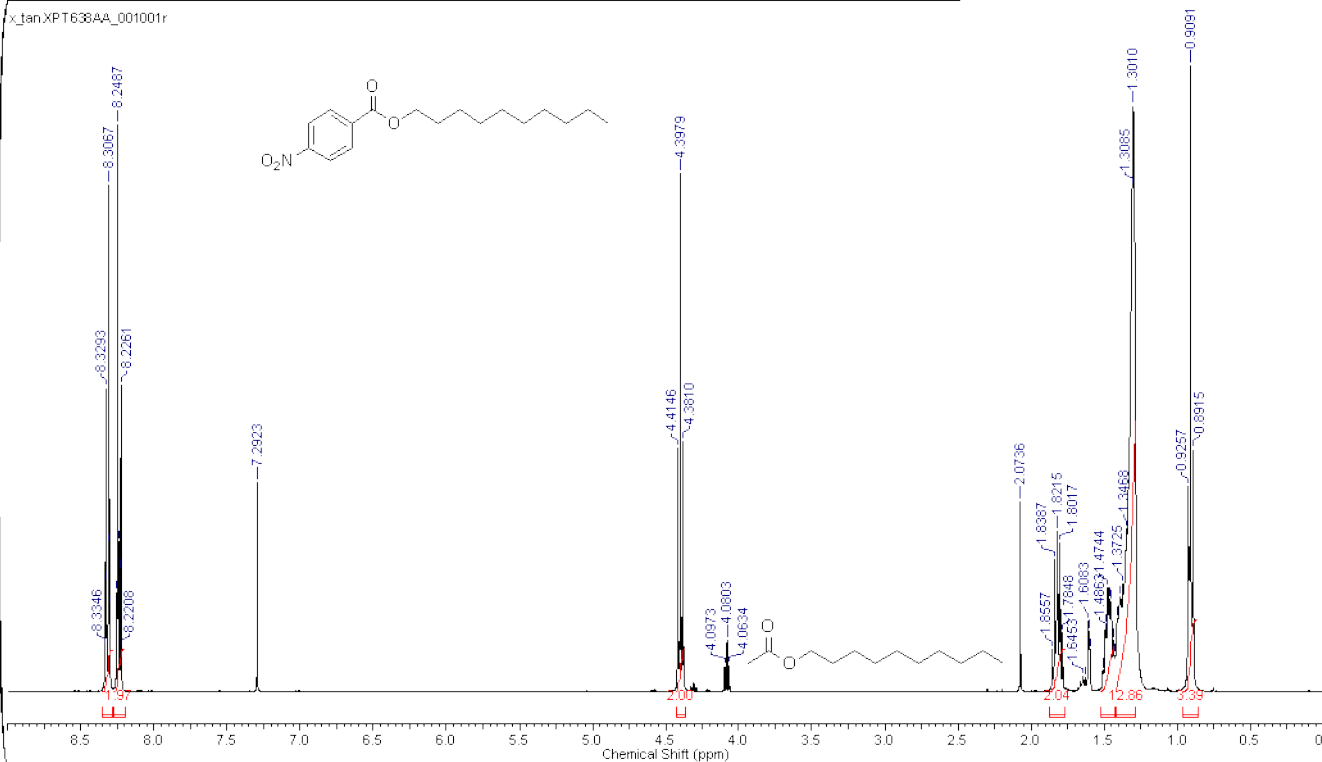
Decyl 4-nitrobenzoate **6h**¹¹

1-Decanol (0.19 mg, 1.0 mmol) and 4-nitrobenzoic acid (334 mg, 2.00 mmol) were combined with phosphorane **3a** according to the general procedure. The product was obtained as colourless oil after purification (220 mg, 72% yield).

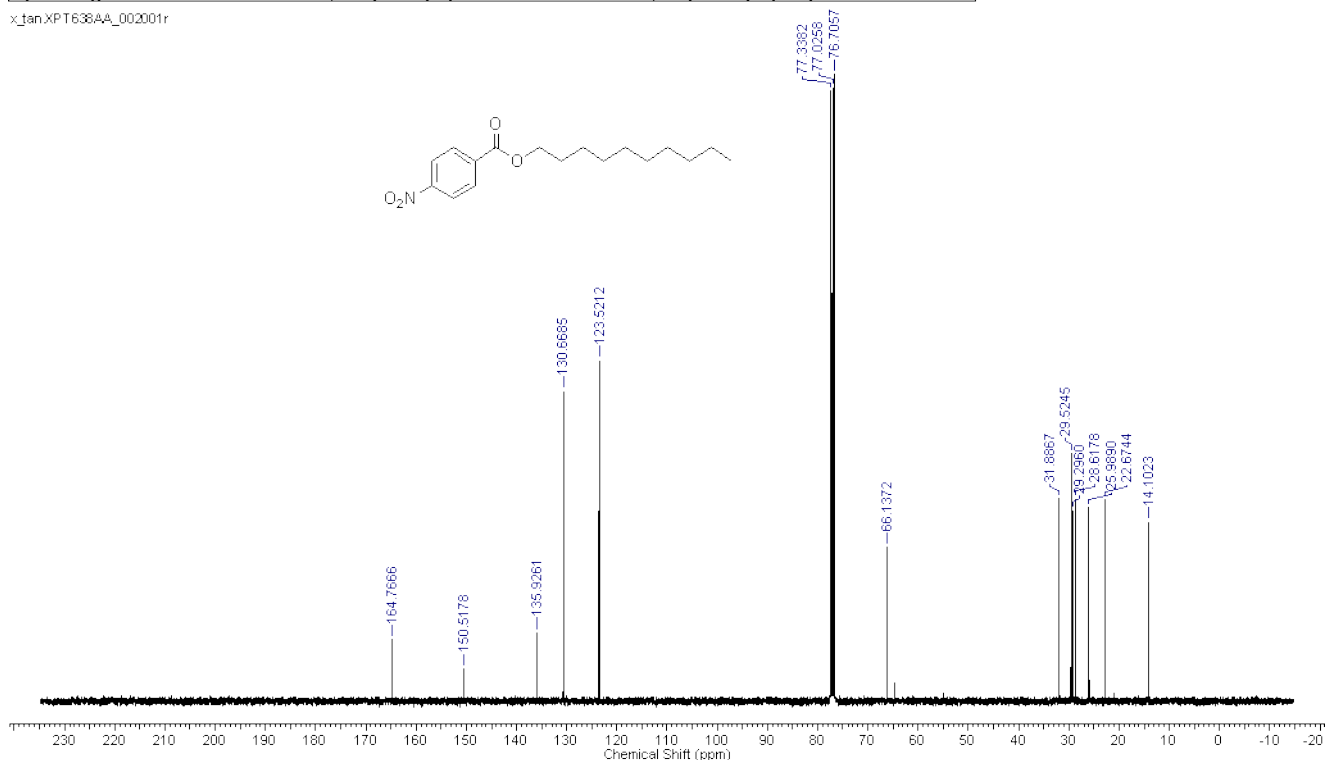
¹H NMR (400 MHz, CDCl₃) δ 8.32 (2 H, d, *J* = 9.0 Hz, ArH), 8.23 (2 H, d, *J* = 9.0 Hz, ArH), 4.40 (2 H, t, *J* = 6.8 Hz, CH₂), 1.82 (2 H, quint., *J* = 6.8 Hz, CH₂), 1.44 - 1.51 (2 H, m, CH₂), 1.28 - 1.42 (12 H, m, 6x CH₂), 0.90 (3 H, t, *J* = 6.8 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm 164.8, 150.5, 135.9, 130.7, 123.5, 66.1, 31.9, 29.5, 29.3, 29.3, 28.61, 26.0, 22.7, 14.1.

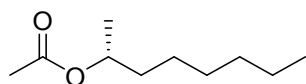
¹¹ Z. Wu, R. J. Ono, Z. Chen and C. W. Bielawski, *J. Am. Chem. Soc.*, 2010, **132**, 14000-14001.

Acquisition Time (sec)	3.9846	Comment	Slot No. 11 Sample ID:XPT638AA SupervisorID:rdent Lab Phone No. 13540 UserID: x_tan		
Date	31 Oct 2012 18:10:08	Date Stamp	31 Oct 2012 18:10:08		
File Name	C:\Documents and Settings\Denton\My Documents\X@\Personal folders\X.TANG\NMR\NMR (Denton)\601-700\X_tan\XPT638AA\pdata\11r				
Frequency (MHz)	400.20	Nucleus	¹ H	Number of Transients	16
Original Points Count	32768	Owner	nmtuser	Points Count	65536
Receiver Gain	256.00	SW(cyclical) (Hz)	8223.68	Solvent	CHLOROFORM-d
Spectrum Type	STANDARD	Sweep Width (Hz)	8223.56	Temperature (degree C)	25.000
				Origin	dpq400
				Pulse Sequence	zqc30
				Spectrum Offset (Hz)	2471.2361



Acquisition Time (sec)	0.6521	Comment	Slot No. 11 Sample ID:XPT638AA SupervisorID:rdent Lab Phone No. 13540 UserID: x_tan		
Date	01 Nov 2012 05:20:00	Date Stamp	01 Nov 2012 05:20:00		
File Name	C:\Documents and Settings\Denton\My Documents\X@\Personal folders\X.TANG\NMR\NMR (Denton)\601-700\X_tan\XPT638AA\pdata\11r				
Frequency (MHz)	100.63	Nucleus	¹³ C	Number of Transients	2048
Original Points Count	16384	Owner	nmtuser	Points Count	32768
Receiver Gain	16384.00	SW(cyclical) (Hz)	25125.63	Solvent	CHLOROFORM-d
Spectrum Type	STANDARD	Sweep Width (Hz)	25124.86	Temperature (degree C)	25.000
				Origin	dpq400
				Pulse Sequence	zqcq30
				Spectrum Offset (Hz)	11069.3428





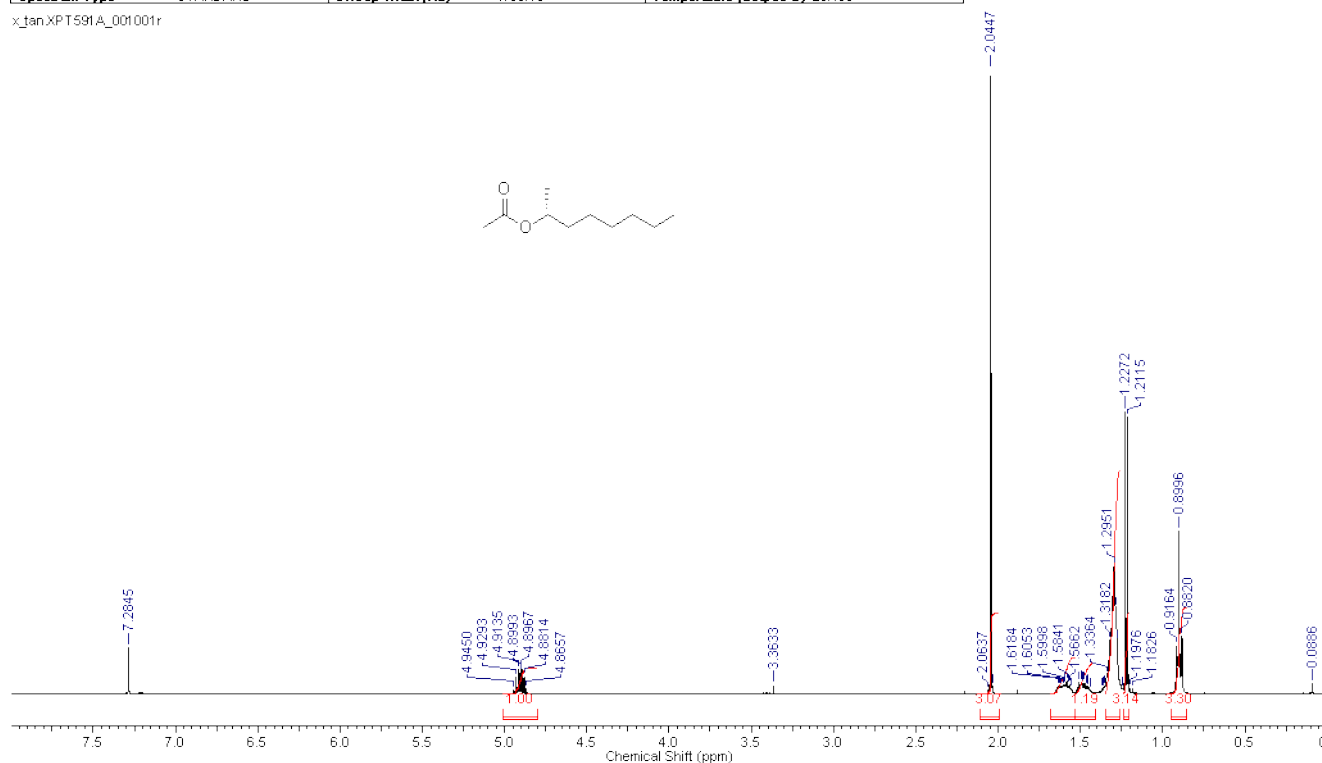
(*R*)-Octan-2-yl acetate **6i**¹²

(*S*)-2-Octanol (0.16 mL, 1.0 mmol) and acetic acid (0.11 mL, 2.0 mmol) were combined with phosphorane **3a** according to the general procedure. The product was obtained as colourless oil after purification (86 mg, 50% yield).

¹H NMR (400 MHz, CDCl₃) δ 4.91 (1 H, sept., *J* = 6.3 Hz, CH), 2.04 (3 H, s, CH₃), 1.55 - 1.64 (1 H, m, CH₂), 1.44 - 1.52 (1 H, m, CH₂), 1.26 - 1.36 (8 H, m, 4xCH₂), 1.21 (3 H, d, *J* = 6.3 Hz, CH₃), 0.89 (3 H, t, *J* = 6.7 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm 170.8, 71.1, 35.9, 31.7, 29.1, 25.4, 22.6, 21.4, 20.0, 14.1.

Acquisition Time (sec)	3.4210	Comment	UserID: x_tan SampleID: XPT591A SupervisorID: rderik LabPhone No. 000 Slot Number 52
Date	23 Aug 2012 01:29:52	Date Stamp	23 Aug 2012 01:29:52
File Name	C:\Documents and Settings\Denton\My Documents\@Personal folders\X.TANG\@NMR\NMR (Denton)\601-600\%_tan.XPT591A\1\data\1\1		
Frequency (MHz)	400.13	Nucleus	¹ H
Original Points Count	16384	Owner	nmruser
Receiver Gain	90.50	SW (cycles) (Hz)	4789.27
Spectrum Type	STANDARD	Sweep Width (Hz)	4789.13
		Number of Transients	16
		Points Count	32768
		Solvent	CHLOROFORM-d
		Temperature (degree C)	25.160
		Origin	ay400
		Pulse Sequence	zg30
		Spectrum Offset (Hz)	2200.7131

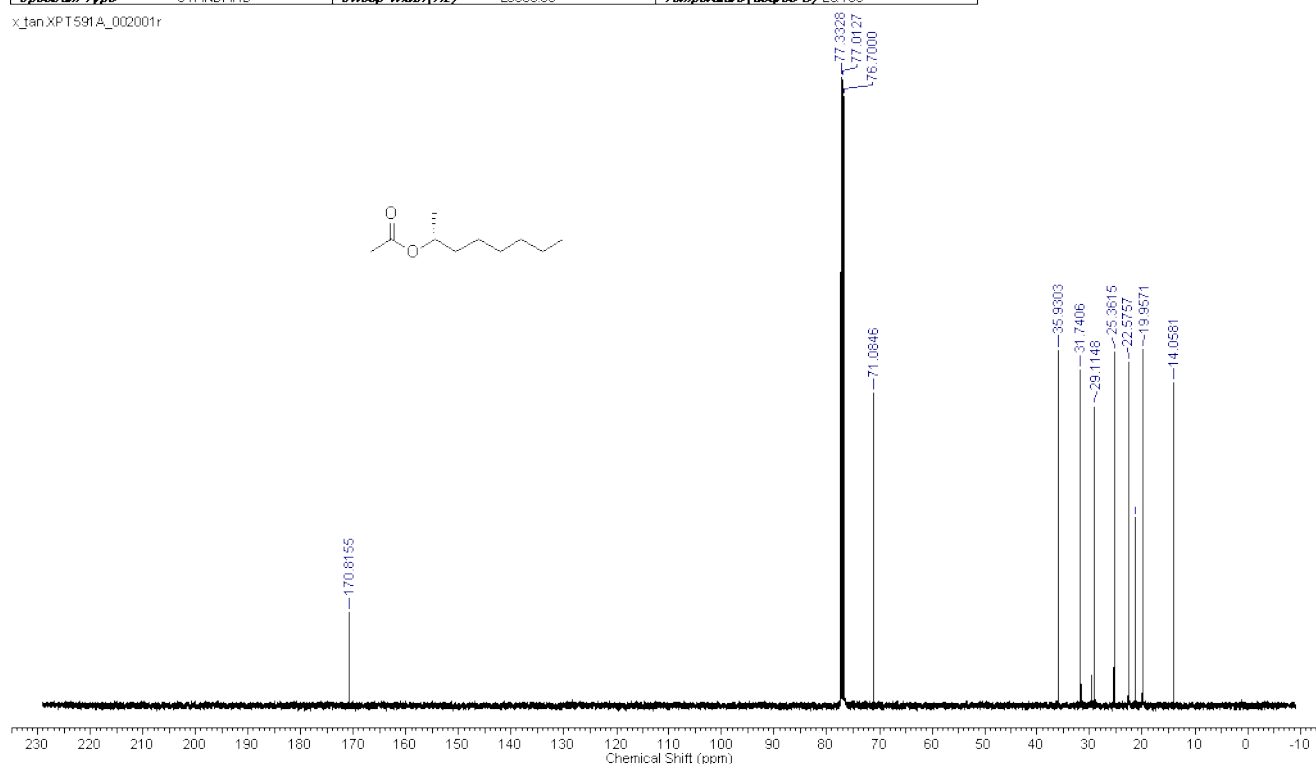
x_tan.XPT591A_001001r



¹² M. Paivio, D. Mavrynsky, R. Leino and L. T. Kanerva, *Eur. J. Org. Chem.*, **2011**, 1452-1457.

Acquisition Time (sec)	0.6832	Comment	UserID: x_tan_SampleID: XPT591A_SupervisorID: rderit_Lab Phone No: 000_Slot Number: 52
Date	23 Aug 2012 02:31:44	Date Stamp	23 Aug 2012 02:31:44
File Name	C:\Documents and Settings\Denton\My Documents\X\Personal folders\X.TANG\NMR\NMR (Denton)\501-600\X_tan.XPT591A\2\data\1\1r		
Frequency (MHz)	100.61	Nucleus	¹³ C
Original Points Count	16384	Owner	mmuser
Receiver Gain	20642.50	SW (cycles) (Hz)	23980.81
Spectrum Type	STANDARD	Sweep Width (Hz)	23980.08
		Solvent	CHLOROFORM-d
		Temperature (degree C)	25.160
		Origin	av400
		Points Count	32768
		Pulse Sequence	zgpg30
		Spectrum Offset (Hz)	11065.5117

x_tan.XPT591A_002001r

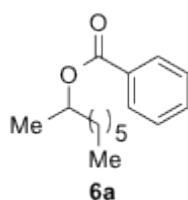


2.2 Stereochemical analyses

The samples were diluted to 1mg/mL.

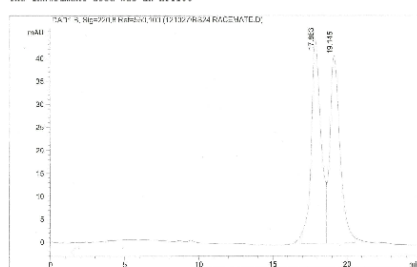
The column used was a Chiralpak AD-RH 4.6x250mm, 5µm, the eluent was water/acetonitrile in a 40:60 ratio. The run was isocratic at 1mL/min over 25 minutes.

Racemic 6a



Sequence Name
 Method Name
 Data File

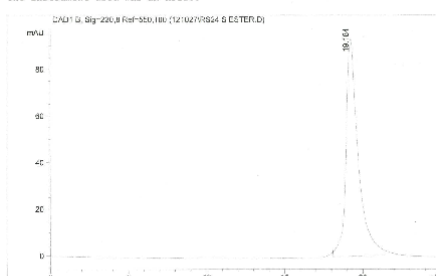
The instrument used was an RP1100



Signal	Peak	Area	Height	Width	Asymmetry	Area %	Area S
1	17.860	44.680	0.674	0.764	0.709e3	51.422	
2	19.145	42.701	0.709	0.672	1.942e3	48.572	

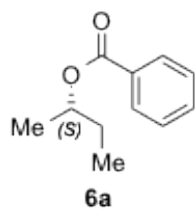
Sequence Name
 Method Name
 Data File

The instrument used was an RP1100

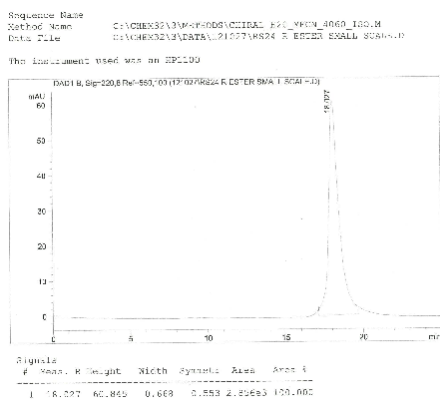
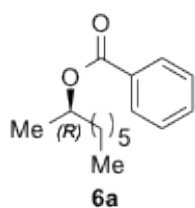


Signal	Peak	Area	Height	Width	Asymmetry	Area %	Area S
1	19.01	33.175	0.780	0.511	5.073e3	100.000	

(S)-6a



(R)-6a

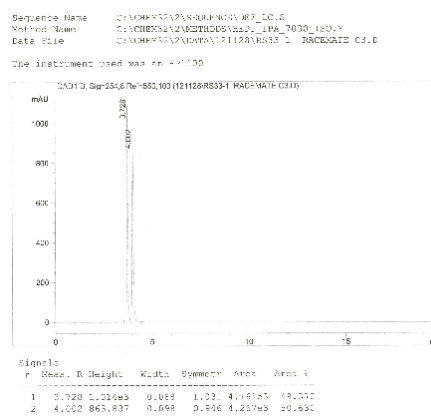
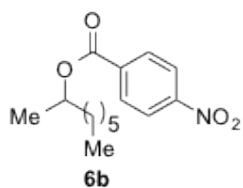


Prepared according to general procedure for Mitsunobu couplings using from (*S*)-2-octanolbenzoic and phosphorane **3a**.

$[\alpha]_D^{23} - 37.4$ (c 1.73 CHCl₃)

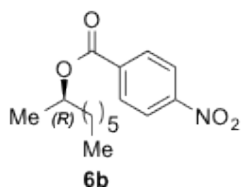
literature comparison: $[\alpha]_D^{23} - 33.6$ (c 0.14 CH₂Cl₂).¹³

Racemic 6b



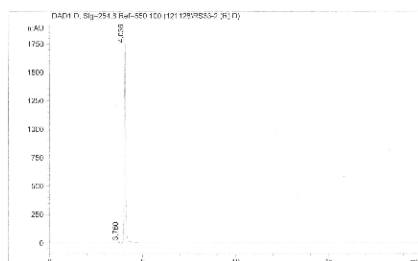
(R)-6b

¹³ T.M. Konrad, P. Schmitz, W. Leitner and G. Franciò *Chem. Eur. J.* **2013**, *19*, 13299-13303.



Sequence Name C:\NMR\2\2\500\NCT\001_02_05
 Method Name C:\NMR\2\2\500\NCT\001_02_05_150.M
 Data File C:\NMR\2\2\500\NCT\001_02_05_150.D

The instrument used was an HPLC

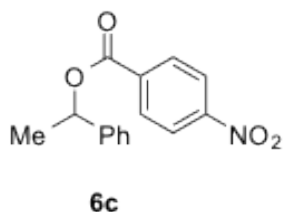


Signal	Peak	RetTime	Width	Symmetry	Area	Area %
1	1	7.056	0.059	0.716	25.028	0.271
2	2	7.056	0.059	0.717	1.085e4	11.729

Prepared according to general procedure for Mitsunobu couplings using from (*S*)-2-octanol, 4-nitrobenzoic and phosphorane **3a**.

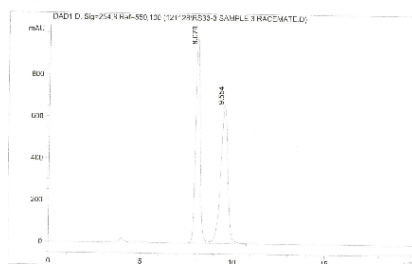
$[\alpha]_D^{23} - 34.2$ (c 2.21 CHCl₃)

Racemic **6c**



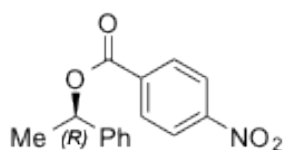
Sequence Name C:\NMR\2\2\500\NCT\001_02_05
 Method Name C:\NMR\2\2\500\NCT\001_02_05_150.M
 Data File C:\NMR\2\2\500\NCT\001_02_05_150.D

The instrument used was an HPLC



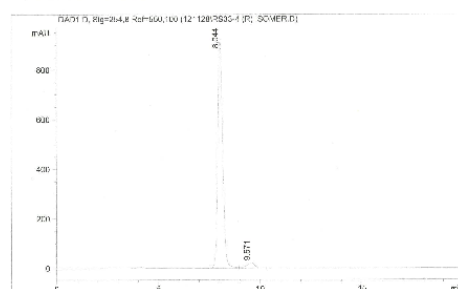
Signal	Peak	RetTime	Width	Symmetry	Area	Area %
1	1	8.075	0.272	0.735	1.715e4	49.575
2	2	9.514	0.416	1.133	1.758e4	50.422

(*R*)-**6c**



Sequence Name C:\NMR\2\2\500\NCT\001_02_05
 Method Name C:\NMR\2\2\500\NCT\001_02_05_150.M
 Data File C:\NMR\2\2\500\NCT\001_02_05_150.D

The instrument used was an HPLC



Signal	Peak	RetTime	Width	Symmetry	Area	Area %
1	1	8.264	0.196	0.777	2.416e4	96.482
2	2	9.577	0.416	1.297	36.138	1.550

Prepared according to general procedure for Mitsunobu couplings using from (*S*)-1-phenylethanol, 4-nitrobenzoic and phosphorane **3a**.

$[\alpha]_D^{23} - 50.5$ (c 1.29, CHCl₃)

literature comparison: $[\alpha]_D^{23} - 51.4$ (c 1.00 CH₂Cl₂).¹⁴

¹⁴ T. Yuen, S. But and P. Toy, *J. Am. Chem. Soc.* **2006**, *128*, 9636.