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of Reliable Methods
for the Preparation
of Organic Compounds

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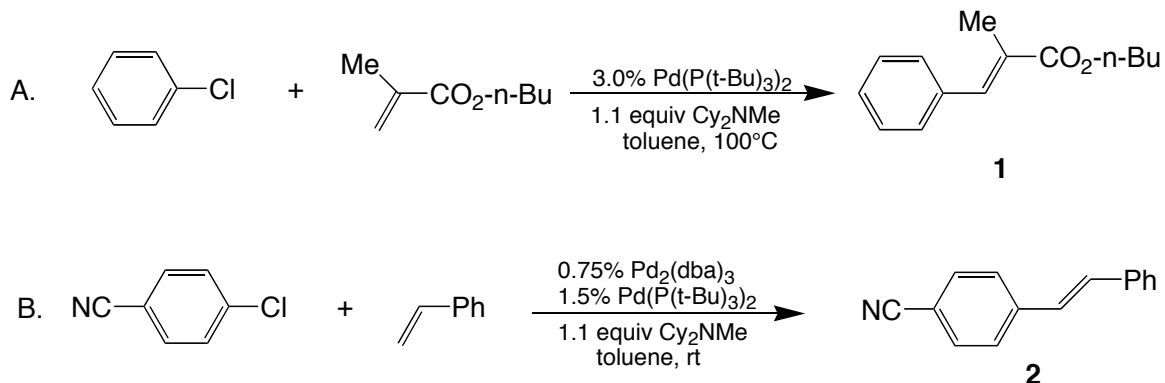
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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**HECK REACTIONS OF ARYL CHLORIDES CATALYZED BY
PALLADIUM/TRI-*tert*-BUTYLPHOSPHINE:
(*E*)-2-METHYL-3-PHENYLACRYLIC ACID BUTYL ESTER AND
(*E*)-4-(2-PHENYLETHENYL)BENZONITRILE
[2-Propenoic acid, 2-methyl-3-phenyl-, butyl ester
and Benzonitrile, 4-[(1*E*)-2-phenylethenyl]]**



Submitted by Adam F. Littke and Gregory C. Fu.¹

Checked by Michael H. Ober and Scott E. Denmark.

1. Procedure

A. (*E*)-2-Methyl-3-phenylacrylic acid butyl ester (**1**). An oven-dried, 250-mL, three-necked, round-bottomed flask equipped with a reflux condenser (fitted with an argon inlet adapter), rubber septum, glass stopper, and a teflon-coated magnetic stir bar is cooled to room temperature under a flow of argon. The flask is charged with bis(tri-*tert*-butylphosphine)palladium ($\text{Pd}(\text{P}(t\text{-Bu})_3)_2$) (0.482 g, 0.943 mmol, 3.0 mol% Pd) (Notes 1, 2) and again purged with argon. Toluene (32 mL) (Notes 9, 10) is added, and the mixture is stirred at room temperature, resulting in a homogeneous brown-orange solution. Chlorobenzene (3.20 mL, 31.5 mmol) (Note 11), *N*-methyldicyclohexylamine (Cy_2NMe) (7.50 mL, 35.0 mmol) (Note 12), and butyl methacrylate (5.50 mL, 34.6 mmol) (Note 12) are then added successively via syringe. The resulting mixture is allowed to stir at room temperature for 5 min, resulting in a homogeneous light-orange solution. The rubber septum is then replaced with a glass stopper, and the

flask is heated in a 100 °C oil bath under a positive pressure of argon for 22 hr (Note 13). Upon heating, the solution becomes bright canary-yellow in color, and within 10-15 min the formation of a white precipitate (the amine hydrochloride salt) is observed. Upon completion of the reaction, shiny deposits of palladium metal form on the sides of the flask, and a large quantity of white precipitate is present. The reaction mixture is allowed to cool to room temperature and then diluted with 100 mL of diethyl ether. The resulting solution is washed with 100 mL of H₂O, and the aqueous layer is extracted with three 50-mL portions of diethyl ether. The combined organic phases are washed with 100 mL of brine and then concentrated by rotary evaporation. Any residual solvent is removed at 0.5 mm. The crude product, a dark-brown oil, is then purified by flash column chromatography (Note 14) to afford 6.67 - 6.72 g (95%) of **1** as a pale red-orange liquid. This liquid appears to be pure by ¹H and ¹³C NMR spectroscopy; however, if desired, the discoloration can be removed by filtering the product through a small column of silica gel (3 cm diameter x 10 cm height), which furnishes 6.49-6.62 g (95-96%) of **1** as a clear, colorless liquid (Notes 15 and 16).

B. (E)-4-(2-Phenylethenyl)benzonitrile (2). An oven-dried, 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, glass stopper, and a teflon-coated magnetic stir bar is cooled to room temperature under a flow of argon. The flask is charged successively with bis(tri-*tert*-butylphosphine)palladium [(Pd(P(*t*-Bu)₃)₂)] (0.238 g, 0.466 mmol, 1.5 mol% Pd) (Notes 1, 2), tris(dibenzylideneacetone)dipalladium(0) (Pd₂(dba)₃) (0.213 g, 0.233 mmol, 1.5 mol% Pd) (Note 3), and 4-chlorobenzonitrile (4.25 g, 30.9 mmol) (Note 17). The flask is purged with argon, and 62 mL of toluene is added (Notes 9, 10, 18). The resulting mixture is stirred at room temperature, resulting in a dark, red-purple solution. *N*-Methyldicyclohexylamine (7.5 mL, 35.0 mmol) (Note 12) and styrene (3.8 mL, 33.2 mmol) (Note 19) are then added via syringe. The reaction mixture is allowed to stir at room temperature under a positive pressure of argon for 72 hr (Note 13). Within the first 1-2 hr, the color changes from deep red-purple to dark brown, and a precipitate (the amine hydrochloride salt) begins to form. Upon completion of the reaction, 100 mL of ethyl acetate is added, and the resulting solution is washed with 100 mL of water. The aqueous layer is separated and extracted with three 50-mL portions of diethyl ether, and the combined organic phases

are concentrated by rotary evaporation. Any residual solvent is removed at 0.5 mm. The crude product, a yellow solid, is purified via flash column chromatography (Note 20) to afford 5.30-5.34 g (83-84%) of **2** as white crystalline spheres (Notes 21, 22, 23).

2. Notes

1. Pd(P(*t*-Bu)₃)₂ was prepared according to the following procedure. In a nitrogen-filled Vacuum Atmospheres glovebox, a 100-mL, one-neck, round-bottomed flask equipped with a teflon-coated magnetic stir bar is charged with tris(dibenzylideneacetone)dipalladium(0) (Pd₂(dba)₃) (2.98 g, 3.25 mmol) (Note 3). A solution of tri-*tert*-butylphosphine (P(*t*-Bu)₃) (2.88 g, 14.2 mmol) (Note 4) in 43 mL of *N,N*-dimethylformamide (DMF) (Note 5) is then added to the reaction flask via a glass pipette, and the resulting dark green-brown solution is stirred at room temperature for 23 hr. The reaction mixture is then filtered through a 30-mL medium-porosity glass frit to collect the unpurified product, Pd(P(*t*-Bu)₃)₂, as a gray solid. The reaction flask is rinsed with three 6-mL portions of DMF and 5 mL of methanol (Note 6), which are passed through the glass frit (the final rinses should be colorless). The reaction product is then dissolved in 100 mL of toluene (Note 7), and the resulting solution is filtered through a 3-cm diameter 0.45 μm Gelman acrodisc (to remove some insoluble black material) into a 250-mL Schlenk tube, affording a homogeneous orange-yellow solution. The Schlenk tube is removed from the glovebox, and the toluene solution is concentrated under high vacuum (0.5mm) to a volume of approximately 25 mL, at which point a white crystalline solid begins to precipitate. The Schlenk tube is taken into the glovebox, and the toluene solution and crystalline solid are transferred to a 250-mL Erlenmeyer flask via a glass pipette. MeOH (100 mL) is then added slowly via pipette over 10 min, resulting in the precipitation of additional white crystalline solid. The solution is allowed to stand for one hour, and then the mother liquor is separated from the solid via pipette. The solid is washed with two 10-mL portions of MeOH, transferred to a tared 20-mL glass vial, and dried under high vacuum, affording 2.41 g (72%) of Pd(P(*t*-Bu)₃)₂ as a white, crystalline

solid (Note 8). The $\text{Pd}(\text{P}(t\text{-Bu})_3)_2$ can be stored indefinitely under nitrogen in a Vacuum Atmospheres glovebox. Although $\text{Pd}[\text{P}(t\text{-Bu})_3]_2$ has been reported to be "stable in air in the solid state,"² if a glovebox is not available, it is recommended that $\text{Pd}[\text{P}(t\text{-Bu})_3]_2$ be stored in a tightly capped vial in a desiccator, preferably under argon or nitrogen. **Alternative workup and crystallization:** After the reaction mixture has stirred for 23 hours, the resulting precipitate is collected by filtration, washed thoroughly with DMF, and then dissolved in hexane. The hexane solution is filtered and concentrated, yielding $\text{Pd}(\text{P}(t\text{-Bu})_3)_2$ as white crystals.

2. Alternatively, $\text{Pd}[\text{P}(t\text{-Bu})_3]_2$ may be purchased from Strem Chemicals.

3. $\text{Pd}_2(\text{dba})_3$ was purchased from the Aldrich Chemical Company and used as received.

4. $\text{P}(t\text{-Bu})_3$ (99%) was purchased from Strem Chemicals and used as received.

5. DMF (anhydrous, DriSolv) was purchased from EM Science and degassed under high vacuum for 10-15 min prior to use.

6. Methanol (certified A.C.S., purchased from Fisher Scientific) was distilled from $\text{Mg}(\text{OMe})_2$ and was degassed by three freeze-pump-thaw cycles prior to use.

7. Toluene (J. T. Baker; CYCLE-TRAINER solvent delivery kegs) was vigorously purged with argon for 2 h and then passed through two packed columns of neutral alumina and copper(II) oxide under argon pressure.³

8. $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 202 MHz): δ 85.3; ^1H NMR (C_6D_6 , 500 MHz): δ 1.51 (t, $J = 5.4$ Hz). The NMR sample must be prepared under inert atmosphere to avoid aerobic oxidation of the catalyst as evidenced by free $\text{P}(t\text{-Bu})_3$ at δ 1.27 ppm in the ^1H NMR spectrum. Even with these precautions, ca. 1% of $\text{P}(t\text{-Bu})_3$ is observed.

9. Toluene (anhydrous, 99.8%, Sure/SealTM bottle) was purchased from the Aldrich Chemical Company and used as received.

10. 1,4-Dioxane is an equally suitable solvent for these Heck couplings (and is the solvent used in the published procedures); however, due to the lower cost and the lower toxicity of toluene, it was chosen as the solvent for these reactions.

11. Chlorobenzene (anhydrous, 99.8%, Sure/Seal™ bottle) was purchased from the Aldrich Chemical Company and used as received.

12. *N*-Methyldicyclohexylamine (97%) and butyl methacrylate (99%) were purchased from the Aldrich Chemical Company and gently sparged with argon for 5-10 min prior to use.

13. The progress of the reaction was monitored by GC.

14. Flash column chromatography was performed using silica gel (6 cm diameter x 35 cm height), eluting with 19/1 hexane/diethyl ether.

15. Compound **1** has the following properties: bp 111 °C (1 mm) ¹H NMR (CDCl₃, 500 MHz) δ: 0.98 (t, *J* = 7.5, 3H), 1.45 (sext, *J* = 1.0, 2H), 1.71 (qn, *J* = 1.0, 2H), 2.12 (d, *J* = 1.5, 3H), 4.22 (t, *J* = 6.6, 2H), 7.33 (m, 1H), 7.39 (m, 4H), 7.68 (apparent d, *J* = 1.5, 1H); ¹³C NMR (CDCl₃, 126 MHz): δ 13.7, 14.0, 19.3, 30.7, 64.8, 128.2, 128.4, 128.7, 129.6, 136.0, 138.8, 168.8; IR (neat, cm⁻¹): 3059, 3026, 2960, 2933, 2873, 1709, 1635, 1492, 1448, 1388, 1356, 1254, 1201, 1115, 1074, 1003, 931, 766, 704; Anal. Calcd for C₁₄H₁₈O₂: C, 77.03; H, 8.31. Found: C, 77.02; H, 8.30.

16. The checkers found that the product could be further purified by distillation (110 °C/1 mm).

17. 4-Chlorobenzonitrile (99%) was purchased from Aldrich Chemical Company and used as received.

18. To allow more efficient stirring, it was beneficial to run this reaction at half of the concentration (2 mL solvent per mmol of aryl chloride) of the original published procedure (1 mL solvent per mmol of aryl chloride).

19. Styrene (99+%) was purchased from Aldrich Chemical Company and gently sparged with argon for 5-10 min prior to use.

20. Flash column chromatography was performed using silica gel (10 cm diameter x 27 cm height), eluting with 4/1 toluene/hexane. A small amount of aryl chloride that remained unreacted after 72 hr was recovered mixed with a small quantity (<5%) of the desired product.

21. Compound **2** has the following properties: mp (corr.) 115-117 °C (lit.⁴ mp 115 °C); ¹H NMR (CDCl₃, 500 MHz): δ 7.09 (d, *J* = 16.5, 1H), 7.22 (d, *J* = 16.5, 1H), 7.33 (d, *J* = 7.1, 1H), 7.40 (t, *J* = 7.1, 2H), 7.54 (d, *J* = 7.5, 2H), 7.59 (d, *J* = 8.3, 2H), 7.64 (d, *J* = 8.4, 2H); ¹³C NMR (CDCl₃, 126 MHz): δ 110.8, 119.3, 126.9, 127.0, 127.1, 128.9, 129.1, 132.6, 132.7, 136.5, 142.1; IR (neat, cm⁻¹): 3029, 2964, 2225, 1648, 1604, 1531, 1450, 1278,

1226, 1174, 1095, 966, 821, 769; Anal. Calcd for C₁₅H₁₁N: C, 87.78; H, 5.40; N, 6.82. Found: C, 87.43; H, 5.26; N, 6.86.

22. The checkers found that the product could be further purified by sublimation (127 °C/0.5 mm).

23. The submitters obtained the product in 89% yield.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Since its discovery in the early 1970's, the palladium-catalyzed arylation of olefins (Heck reaction; eq 1 and Figure 1)^{5,6} has been applied to a diverse array of fields, ranging from natural products synthesis^{7,8} to materials science⁹ to bioorganic chemistry.¹⁰ This powerful carbon-carbon bond-forming process has been practiced on an industrial scale for the production of compounds such as naproxen¹¹ and octyl methoxycinnamate.¹² The Heck reaction is typically performed in the presence of a palladium/tertiary phosphine catalyst and a stoichiometric amount of an inorganic or organic base. High functional-group tolerance and the ready availability and low cost of simple olefins contribute to the exceptional utility of the Heck arylation.

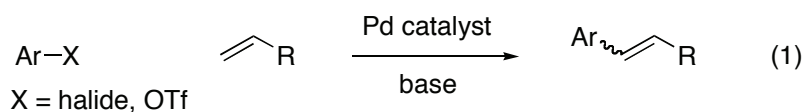
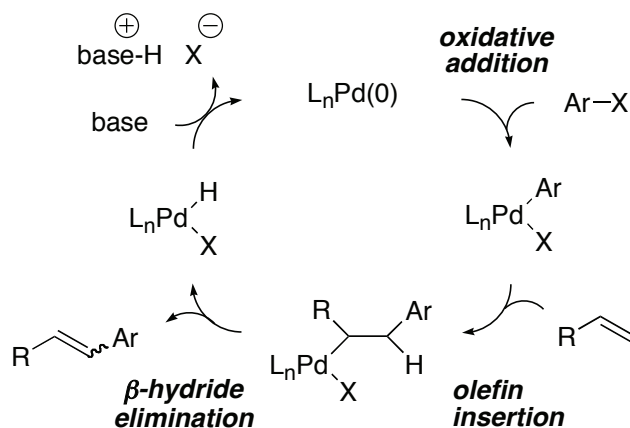


Figure 1
Outline of the Catalytic Cycle for the Heck Coupling Reaction



Until recently, one important unsolved problem for the Heck reaction was the poor reactivity of aryl chlorides, which are arguably the most attractive class of aryl halides, due to their lower price and greater availability as compared with the corresponding bromides and iodides.^{13,14} For the few catalyst systems that have displayed activity for Heck couplings of aryl chlorides (e.g., those of Milstein (bulky, electron-rich chelating bisphosphines),¹⁵ Herrmann (palladacycles, *N*-heterocyclic carbenes),¹⁶ Reetz (tetraphenylphosphonium salts),¹⁷ and Beller (phosphites),^{18,19,20} the scope of the reactions has been quite narrow and the reaction temperatures have been rather high (≥ 120 °C). This need for elevated temperatures can be problematic for a variety of reasons, including decomposition of thermally unstable substrates and decreased regio- and stereoselectivities.

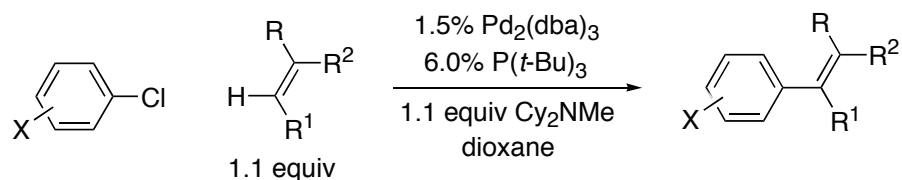
$\text{Pd}/\text{P}(t\text{-Bu})_3$, in the presence of Cy_2NMe , is an unusually mild and versatile catalyst for Heck reactions of aryl chlorides (Tables 1 and 2) (as well as for room-temperature reactions of aryl bromides).^{21,22,23} Example A, the coupling of chlorobenzene with butyl methacrylate, illustrates the application of this method to the stereoselective synthesis of a trisubstituted olefin; α -methylcinnamic acid derivatives are an important family of compounds that possess biological activity (e.g., hypolipidemic²⁴ and antibiotic²⁵) and serve as intermediates in the synthesis of pharmaceuticals (e.g., Sulindac, a non-steroidal anti-inflammatory drug²⁶). Example B, the coupling of 4-chlorobenzonitrile with styrene, demonstrates that $\text{Pd}/\text{P}(t\text{-Bu})_3$

can catalyze the Heck reaction of activated aryl chlorides *at room temperature*.

From a practical point of view, it is worth noting that Heck reactions catalyzed by Pd/P(*t*-Bu)₃ do not typically require rigorously purified reagents or solvents. In addition, the palladium and phosphine sources, Pd[P(*t*-Bu)₃]₂ and Pd₂(dba)₃, are commercially available and can be handled in air.

Thus, in terms of scope, mildness, and convenience, Pd/P(*t*-Bu)₃ provides an attractive method for achieving Heck couplings of aryl chlorides.

Table 1.
Heck Couplings of Aryl Chlorides at Elevated Temperature



Entry	Aryl Chloride	Olefin	Temperature	Product	Yield ^{a,b}
1 ^c			70 °C		67% ^d
2			120 °C		72%
3			120 °C		80%
4			100 °C		76%
5			120 °C		72%

^aIsolated yield, average of two runs. ^bE:Z ratio is >20:1, as determined by ¹H NMR.

^c3.6% P(*t*-Bu)₃ was used. ^dProduct includes 2.5% P(*t*-Bu)₃/OP(*t*-Bu)₃.

Table 2.
Heck Couplings of Activated Aryl Chlorides at Room Temperature

Entry	Aryl Chloride	Olefin	Product	Yield ^{a,b}
1			 6:1 E:Z	70%
2			 5:1 E:Z 	10 : 1 87% ^c
3				90%
4				79%
5 ^d				87%
6 ^e				57% ^f

^aIsolated yield, average of two runs. ^bUnless otherwise indicated, the E:Z ratio is >20:1, as determined by ¹H NMR. ^cProduct includes 5% 4'-chloroacetophenone. ^d3 equiv. of olefin was used. ^e2 equiv. of olefin was used. ^fProduct includes 2% P(*t*-Bu)₃/OP(*t*-Bu)₃.

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22. See also: Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, 121, 2123-2132.
23. Generally, for Pd/P(*t*-Bu)₃-catalyzed Heck couplings that proceed at elevated temperature, a 1:2 Pd:phosphine ratio is preferred. For reactions that occur at room temperature, a 1:1 Pd:phosphine ratio is usually desirable (2:1 mixture of Pd(P(*t*-Bu)₃)₂:Pd₂(dba)₃).
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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

(*E*)-2-Methyl-3-phenylacrylic acid butyl ester: 2-Propenoic acid, 2-methyl-3-phenyl-, butyl ester, (2*E*)-; (21511-00-5).

Bis (tri-*tert*-butylphosphine)palladium: Palladium, bis[tris(1,1-dimethylethyl)phosphine]- ; (53199-31-8).

N-Methyldicyclohexylamine: Cyclohexanamine, *N*-cyclohexyl-*N*-methyl- ; (7560-83-0)

Chlorobenzene: Benzene, chloro-; (108-90-7)

Butyl methacrylate: 1-Propenoic acid, 2-methyl-, butyl ester ; (97-88-1)

(*E*)-4-(2-Phenylethenyl)benzotrile: Benzotrile, 4-[(1*E*)-2-phenylethenyl]- ; (13041-79-7)

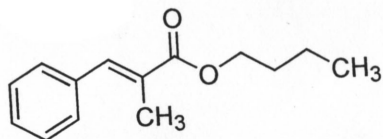
Tris(dibenzylideneacetone)dipalladium: Palladium, tris[μ -[(1,2- η :4,5- η)-(1*E*,4*E*)-1,5,-diphenyl-1,4-pentadien-3-one]]di- ; (51364-51-3)

4-Chlorobenzotrile: Benzotrile, 4-chloro- ; (623-03-0)

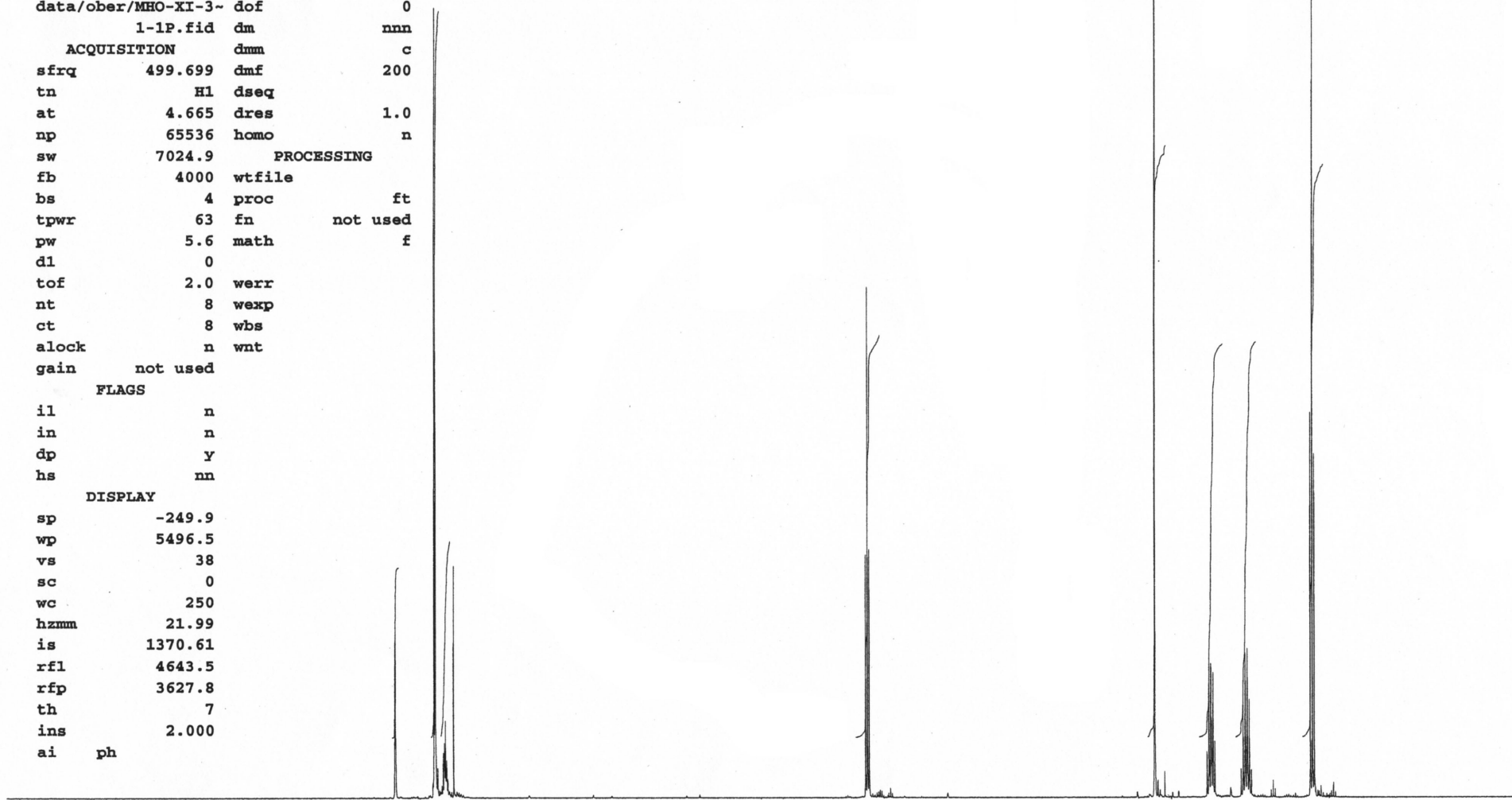
Tri-*tert*-butylphosphine: Phosphine, tris(1,1-dimethylethyl)- ; (13716-12-6)

MHO-XI-31-1P

exp2 s2pul



SAMPLE DEC. & VT
date Jan 31 2003 dfrq 499.699
solvent CDC13 dn H1
file /export/home/~ dpwr 20
data/ober/MHO-XI-3~ dof 0
1-1P.fid dm nnn
ACQUISITION dmm c
sfrq 499.699 dmf 200
tn H1 dseq
at 4.665 dres 1.0
np 65536 homo n
sw 7024.9 PROCESSING
fb 4000 wtfile
bs 4 proc ft
tpwr 63 fn not used
pw 5.6 math f
d1 0
tof 2.0 werr
nt 8 wexp
ct 8 wbs
alock n wnt
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -249.9
wp 5496.5
vs 38
sc 0
wc 250
hzmm 21.99
is 1370.61
rfl 4643.5
rfp 3627.8
th 7
ins 2.000
ai ph



10

9

8

7

6

5

4

3

2

1

ppm

0.84 0.98
3.60

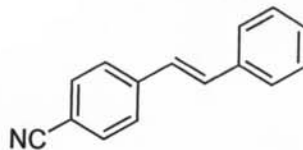
2.00

2.94 1.96

1.95 2.84

MHO-XI-32-1P

exp2 s2pul



```
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solvent  CDC13    dn        H1
file  /export/home/~ dpwr      20
data/ober/MHO-XI-3~ dof        0
          2-1P.fid  dm        nnn
ACQUISITION    dmm          c
sfrq      499.699  dmf      200
tn         H1     dseq
at         4.665  dres      1.0
np        65536  homo      n
sw        7024.9          PROCESSING
fb         4000  wtfile
bs         4     proc      ft
tpwr       63    fn      not used
pw         5.6   math      f
dl         0
tof        2.0  werr
nt         8    wexp
ct         8    wbs
alock      n     wnt
gain      not used
          FLAGS
il         n
in         n
dp         y
hs         nn
          DISPLAY
sp        -249.9
wp        5496.5
vs         50
sc         0
wc         250
hzmm      21.99
is        1000.00
rfl       4643.3
rfp       3627.8
th         7
ins       2.000
ai      ph
```

