Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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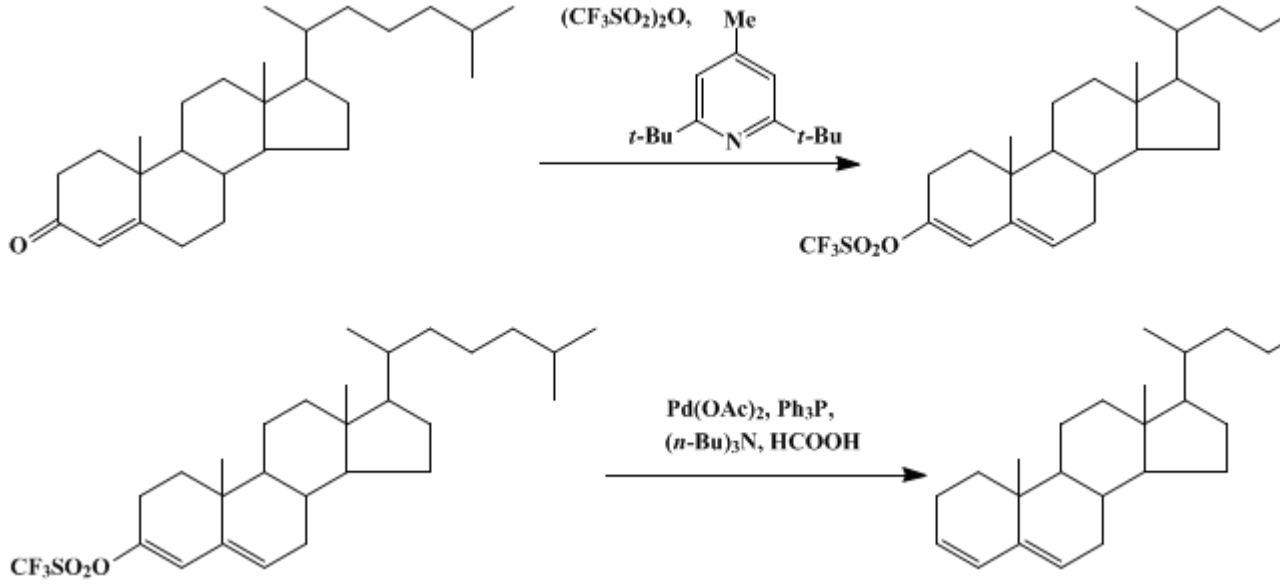
PALLADIUM-CATALYZED REDUCTION OF VINYL TRIFLUOROMETHANESULFONATES TO ALKENES: CHOLESTA-3,5-DIENE



Submitted by Sandro Cacchi[1], Enrico Morera[2], and Giorgio Ortar[2].
Checked by Sean Kerwin, Christopher Schmid, and Clayton H. Heathcock.

1. Procedure

A. *Cholesta-3,5-dien-3-yl trifluoromethanesulfonate.* A dry, 250-mL, two-necked, round-bottomed flask, equipped with a magnetic stirring bar, a rubber septum, and a pressure-equalizing 100-mL dropping funnel fitted with a calcium chloride drying tube, is charged with 4.62 g (22.5 mmol) of 2,6-di-*tert*-butyl-4-methylpyridine (Note 1) and 60 mL of dry dichloromethane (Note 2). Then 3.08 mL (18.75 mmol) of trifluoromethanesulfonic anhydride (Note 3) is added rapidly from a syringe and 5.77 g (15 mmol) of cholest-4-en-3-one (Note 4) diluted 40 mL of dry dichloromethane is added through the dropping funnel, dropwise and with stirring, during 15–20 min. The mixture is stirred for an additional 1 hr at room temperature. During this period the solution turns slightly pink and a white precipitate separates. The solvent is removed with a rotary evaporator and the residue is combined with 100 mL of diethyl ether. The white pyridinium trifluoromethanesulfonate salt is filtered off and washed with additional diethyl ether (3 × 50 mL). The ethereal solution is washed with cold 2 *N* hydrochloric acid (2 × 100 mL) and saturated sodium chloride solution (3 × 100 mL), dried over anhydrous potassium carbonate, and concentrated at reduced pressure. The solid residue (7.21–7.40 g) is recrystallized from hexane to give 6.46–6.72 g (83–87%) of cholesta-3,5-dien-3-yl trifluoromethanesulfonate as white crystals (Note 5), mp 125–126°C (Note 6).

B. *Cholesta-3,5-diene.* A 50-mL, two-necked, round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser with a nitrogen inlet at the top, is charged with 5.00 g (9.68 mmol) of cholesta-3,5-dien-3-yl trifluoromethanesulfonate (1), 6.92 mL (29.03 mmol) of tributylamine (Note 7), 0.043 g (0.19 mmol) of palladium acetate, 0.100 g (0.38 mmol) of triphenylphosphine, and 20.2 mL of *N,N*-dimethylformamide. The mixture is gently flushed with nitrogen for 1–2 min. and capped with a rubber septum. Formic acid, 99%, 0.73 mL (19.42 mmol), is added from a syringe dropwise and with swirling during 2–3 min. The resulting mixture is warmed in an oil bath at 60°C for 1 hr with continuous stirring under nitrogen. During this period the mixture becomes black. The contents of the flask are poured into 50 mL of 2 *N* hydrochloric acid and extracted with two 75-mL portions of ethyl ether. The combined organic phases are then washed with 50 mL of 2 *N* hydrochloric acid, 15 mL of

saturated sodium bicarbonate solution, and two 10-mL portions of saturated sodium chloride solution, and are then dried over anhydrous magnesium sulfate. The drying agent is removed by filtration, the ether is evaporated at reduced pressure, and the solid residue (3.92–4.16 g) is purified by open-column chromatography on 100 g of basic aluminum oxide (Note 8) using hexane as eluent to give 3.12–3.22 g of nearly pure cholesta-3,5-diene, which is recrystallized from acetone to give a first crop (2.92–3.00 g) as white needles (Note 9), mp 81.5–82.5°C (lit.[3] mp 79.5–80°C) (Note 6) and a second crop (0.11–0.15 g, 85–88% overall yield), mp 79.5–80.5°C (Note 6).

2. Notes

1. A commercial sample of 2,6-di-*tert*-butyl-4-methylpyridine from Fluka AG was purified through a short column of silica gel by eluting with hexane. Alternatively, it may be prepared according to the procedure reported in *Organic Syntheses*.[4]
2. Reagent-grade dichloromethane is dried by passing over a column of aluminum oxide (activity I).
3. Trifluoromethanesulfonic anhydride from Fluka AG was stirred over phosphorus pentoxide for 18 hr and distilled. It can also be prepared from trifluoromethanesulfonic acid (Fluka AG) according to the procedure described in *Organic Syntheses*.[5]
4. Cholest-4-en-3-one was purchased from Fluka AG and used without further purification.
5. Spectral data are as follows: ^{1}H NMR (90 MHz, $CDCl_3$) δ: 0.69 (s, 3 H, 13-CH_3), 0.82 (s, 3 H, 10-CH_3), 5.62 (m, 1 H, C-6 H), 6.02 (m, 1 H, C-4 H); MS *m / e*: 516 (M^+).
6. Melting points are uncorrected and were determined with a Köfler hot-stage apparatus.
7. Tributylamine, palladium acetate, triphenylphosphine from Fluka AG and *N,N*-dimethylformamide, and formic acid from Farmitalia Carlo Erba Chemicals were used without further purification.
8. Basic aluminum oxide (activity I) is available from Merck & Company, Inc.
9. This compound has the following physical properties: ^{1}H NMR (90 MHz, $CDCl_3$) δ: 0.69 (s, 3 H, 13-CH_3), 0.82 (s, 3 H, 10-CH_3), 5.4 (m, 1 H, C-6 H), 5.59 (m, 1 H, C-3 H), 5.71 (d, 1 H, J = 10, C-4 H); $[\alpha]_D$ ($CHCl_3$, 1%) −115° (lit.[3] $[\alpha]_D$ −123°).

3. Discussion

The present preparation illustrates a general and convenient method for a two-step deoxygenation of carbonyl compounds to olefins.[6] Related procedures comprise the basic decomposition of *p*-toluenesulfonylhydrazones,[7] the hydride reduction of enol ethers,[8] enol acetates,[9] enamines,[10] the reduction of enol phosphates (and/or enol phosphorodiamidates) by lithium metal in ethylamine (or liquid ammonia),[11] the reduction of enol phosphates by titanium metal under aprotic conditions,[12] the reduction of thioketals by Raney nickel,[13] and the reduction of vinyl sulfides by Raney nickel in the presence of isopropylmagnesium bromide.[14]

Following our first report on the palladium-catalyzed reaction of vinyl triflates with olefins[15] (Heck-type reaction), oxidative insertion of palladium(0) into the carbon–oxygen bond of easily available vinyl and aryl triflates[16] has proved to be a general method for the generation of σ-vinyl and σ-aryl palladium intermediates that can react with a variety of nucleophiles such as olefins,[15 17 18 19] 1-alkynes,[20] disubstituted alkynes,[21] allenes,[22] dialkyl phosphites,[23] triphenylphosphine,[24] silyloxycyclopropanes,[25] cyanide,[26] carbon monoxide in the presence of alcohols,[27] amines,[27] alkynes,[28] and silyloxycyclopropanes.[29]

Palladium-catalyzed cross-coupling of vinyl and aryl triflates with organotion,[30] organozinc,[31] organoboron,[32] organoaluminum,[33] and organosilicon[34] reagents has also been reported.

Reviews dealing with some aspects of the palladium chemistry of vinyl and aryl triflates have been published.[35]

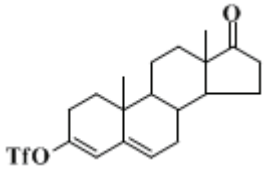
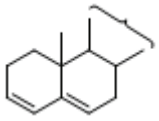
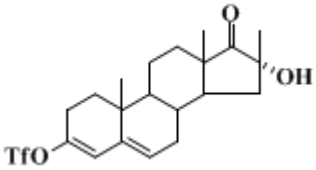
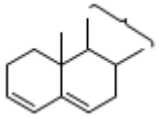
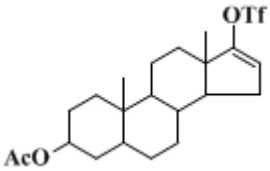
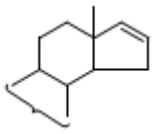
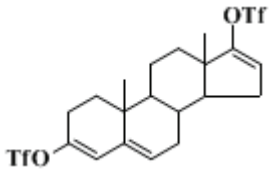
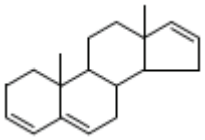
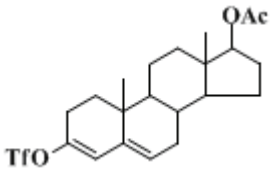
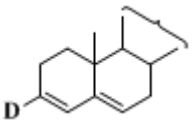
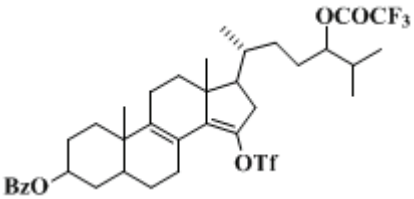
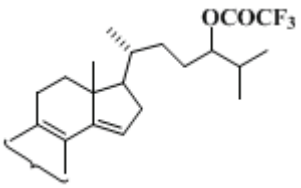
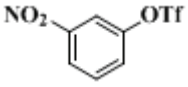
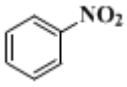
σ-Vinyl palladium triflates are smoothly reduced to alkenes with trialkylammonium formate, usually in high yield. Some advantages of this reduction procedure should be noted. The trialkylammonium formate–palladium reducing system is very simple to use.[36] Clean reduction of vinyl triflates to olefins is observed, and no overreduction is detected. Since vinyl triflates with defined regiochemistry can be easily synthesized,[37] the method is of use in the regioselective synthesis of alkenes and dienes. Ketones, alcohols, ethers, aromatic systems, and presumably a variety of other

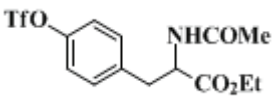
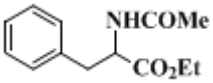
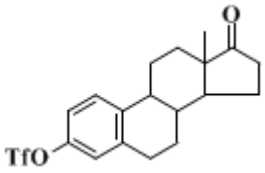
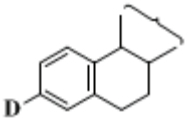
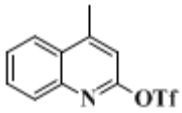
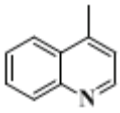
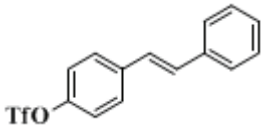
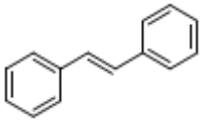
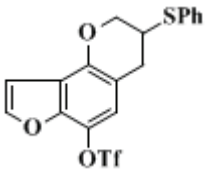
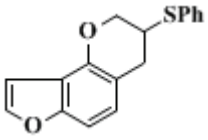
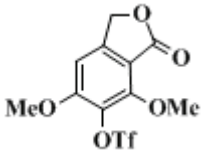
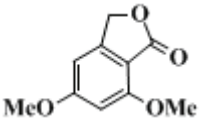
functional groups are unaffected by the reduction conditions. When the reaction is carried out by using DCOOD, this method allows the regioselective and quantitative introduction of a deuterium atom.

The reaction has been successfully extended to the reduction of aryl triflates[38,39,40,41] and fluoroalkanesulfonates[39,42] to arenes.

Some selected examples of palladium-catalyzed reduction of vinyl and aryl triflates are summarized in Table I.

TABLE I
PALLADIUM-CATALYZED REDUCTION OF VINYL AND ARYL TRIFLATES

Substrate	Catalyst	Product	% yield
	$Pd(OAc)_2(PPh_3)_2$		81[6]
	$Pd(OAc)_2(PPh_3)_2$		93[6]
	$Pd(OAc)_2(PPh_3)_2$		85[6]
	$Pd(OAc)_2(PPh_3)_2$		95[6]
	$Pd(OAc)_2(PPh_3)_2$[a]		87[6]
	$Pd(OAc)_2(PPh_3)_2$[a]		95[43]
	$Pd(OAc)_2$/dppf[b]		79[38]
	$Pd(OAc)_2$/dppf[b]		94[38]

			
	$Pd(OAc)_2$/dppf[a]		87[38]
	$Pd(OAc)_2$/dppf		82[38]
	$Pd(OAc)_2(PPh_3)_2$		91[38]
	$Pd(OAc)_2(PPh_3)_2$		90[40]
	$PdCl_2(PPh_3)_2$/dppp[c]		76[41]

[a]DCOOD was used.
[b]DPPF refers to 1, 1'-bis(diphenylphosphino)ferrocene.
[c]DPPP refers to 1,3-bis(diphenylphosphino)propane.

References and Notes

1. Dipartimento di Studi di Chimica e Technologia delle Sostanze Biologicamente Attive, Università degli studi "La Sapienza," P.le A. Moro 5, 00185 Roma, Italy.
2. Dipartimento di Studi Farmaceutici, Università degli Studi "La Sapienza," P.le A. Moro 5, 00185 Roma, Italy.
3. O'Connor, G. L.; Nace, H. R. *J. Am. Chem. Soc.* **1952**, *74*, 5454.
4. Anderson, A. G.; Stang, P. J. *Org. Synth., Coll. Vol. VII* **1990**, 144.
5. Stang, P. J.; Deuber, T. E. *Org. Synth., Coll. Vol. VI* **1988**, 757.
6. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 4821.
7. Shapiro, R. H. *Org. React.* **1976**, *23*, 405, and references cited therein.
8. Larson, G. L.; Hernandez, E.; Alonzo, C.; Nieves, I. *Tetrahedron Lett.* **1975**, 4005; Pino, P.; Lorenzi, G. P. *J. Org. Chem.* **1966**, *31*, 329.
9. Caglioti, L.; Cainelli, G.; Maina, G.; Selva, A. *Gazz. Chim. Ital.* **1962**, *92*, 309; *Chem. Abstr.* **1962**, *57*, 12572*c*.
10. Lewis, J. W.; Lynch, P. P. *Proc. Chem. Soc. London* **1963**, 19; Coulter, J. M.; Lewis, J. W.; Lynch, P. P. *Proc. Chem. Soc. London* **1963**, 19; Coulter, J. M.; Lewis, J. W.; Lynch, P. P. *Tetrahedron* **1968**, *24*, 4489.
11. Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145; Fetizon, M.; Jurion, M.; Anh, N. T. *J.*

Chem. Soc., Chem. Commun. **1969**, 112; Ireland, R. E.; Kowalski, C. J.; Tilley, J. W.; Walba, D. M. *J. Org. Chem.* **1975**, *40*, 990; Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098; Ireland, R. E.; O'Neil, T. H.; Tolman, G. L. *Org. Synth., Coll. Vol. VII* **1990**, 66.

12. Welch, S. C.; Walters, M. E. *J. Org. Chem.* **1978**, *43*, 2715.

13. Ben-Efraim, D. A.; Sondheimer, F. *Tetrahedron* **1969**, *25*, 2823; Fishman, J.; Torigoe, M.; Guzig, H. *J. Org. Chem.* **1963**, *28*, 1443.

14. Trost, B. M.; Ornstein, P. L. *Tetrahedron Lett.* **1981**, *22*, 3463.

15. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 2271;

16. Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283; Hassdenteufel, J. R.; Hanack, M. *Tetrahedron Lett.* **1980**, *21*, 503; Stang, P. J.; Fisk, T. E. *Synthesis* **1979**, 438.

17. Harnisch, W.; Morera, E.; Ortar, G. *J. Org. Chem.* **1985**, *50*, 1990;

18. Scott, W. J.; Pena, M. R.; Swärd, K.; Stoessel, S. J.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 2302;

19. Arcadi, A.; Marinelli, F.; Cacchi, S. *J. Organomet. Chem.* **1986**, *312*, C27; Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1987**, *28*, 3039.

20. Cacchi, S.; Morera, E.; Ortar, G. *Synthesis* **1986**, 320.

21. Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem.* **1992**, *57*, 976.

22. Friess, B.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1988**, *29*, 4089.

23. Petrakis, S. K.; Nagabhushan, T. L. *J. Am. Chem. Soc.* **1987**, *109*, 2831; Holt, D. A.; Erb, J. M. *Tetrahedron Lett.* **1989**, *30*, 5393.

24. Hinkle, R. J.; Stang, P. J.; Kowalski, M. H. *J. Org. Chem.* **1990**, *55*, 5033.

25. Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, *110*, 3296.

26. Piers, E.; Fleming, F. F. *J. Chem. Soc., Chem. Commun.* **1989**, 756; Takagi, K.; Sakakibara, Y. *Chem. Lett.* **1989**, 1957.

27. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109; Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 3931.

28. Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1991**, *32*, 6449.

29. Aoki, S.; Nakamura, E. *Synlett.* **1990**, 741.

30. Stille, J. K.; Tanaka, M. *J. Am. Chem. Soc.* **1987**, *109*, 3785; Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478; Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557.

31. Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955; McCague, R. *Tetrahedron Lett.* **1987**, *28*, 701; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1990**, *31*, 1889; Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. *Synlett.* **1990**, 47.

32. Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett.* **1990**, 221.

33. Saulnier, M. G.; Kadow, J. F.; Tun, M. M.; Langley, D. R.; Vyas, D. M. *J. Am. Chem. Soc.* **1989**, *111*, 8320; Hirota, K.; Isobe, Y.; Maki, Y. *J. Chem. Soc., Perkin Trans.* **1989**, 2513.

34. Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 7075.

35. Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47; Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508; Huang, W.-Y.; Chen, Q.-Y. "The Chemistry of Sulphonic Acids, Esters and Their Derivatives," Patai, S.; Rappoport, Z., Eds.: Wiley: New York, 1991, Chapter 21.

36. Weir, J. R.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 4926; Cacchi, S.; Palmieri, G. *Synthesis* **1984**, 575; Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1986**, *27*, 6397; Tsuji, J.; Sugiura, T.; Minami, I. *Synthesis* **1987**, 603.

37. Crisp, G. T.; Scott, W. J. *Synthesis* **1985**, 335.

38. Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541;

39. Chen, Q.-Y.; He, Y.-B.; Yang, Z.-Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1452;

40. Peterson, G. A.; Kunng, F.-A.; McCallum, J. S.; Wulff, W. D. *Tetrahedron Lett.* **1987**, *28*, 1381.

41. Saa, J. M.; Dopico, M.; Martonell, G.; Garcia-Raso, A. *J. Org. Chem.* **1990**, *55*, 991.

42. Chen, Q.-Y.; He, Y.-B. *Synthesis* **1988**, 896.

43. Dolle, R. E.; Schmidt, S. J.; Erhard, K. F.; Kruse, L. I. *J. Am. Chem. Soc.* **1989**, *111*, 278.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

p-toluenesulfonylhydrazones

vinyl triflates

silyloxycyclopropanes

σ-Vinyl palladium triflates

$Pd(OAc)_2(PPh_3)_2$

$Pd(OAc)_2$/dppf

$PdCl_2(PPh_3)_2$/dppp

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether,
ethyl ether,
diethyl ether (60-29-7)

carbon monoxide (630-08-0)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

formic acid (64-18-6)

nitrogen (7727-37-9)

Raney nickel (7440-02-0)

acetone (67-64-1)

palladium(0) (7440-05-3)

dichloromethane (75-09-2)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

aluminum oxide (1344-28-1)

isopropylmagnesium bromide (920-39-8)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

Cholest-4-en-3-one (601-57-0)

ethylamine (75-04-7)

triphenylphosphine (603-35-0)

tributylamine (102-82-9)

trifluoromethanesulfonic acid (1493-13-6)

Trifluoromethanesulfonic anhydride (358-23-6)

1,3-bis(diphenylphosphino)propane (6737-42-4)

deuterium (7782-39-0)

palladium acetate (3375-31-3)

titanium (7440-32-6)

phosphorus pentoxide (1314-56-3)

Cholesta-3,5-diene (747-90-0)

Cholesta-3,5-dien-3-yl trifluoromethanesulfonate (95667-40-6)

2,6-Di-tert-butyl-4-methylpyridine (38222-83-2)