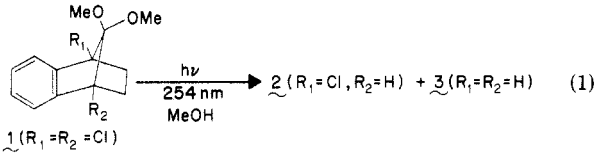
procedures.[7] The presence of the methoxy groups is a matter of synthetic convenience and there is no spectral evidence for interaction with the benzene ring. Photolysis of a 0.02 M solution of **1** in methanol, using a low-pressure mercury source (254 nm), led to the formation of two major products observable by GLC (eq 1). At 72% loss of **1**, the



(1)

ratio of **2**/**3** was 2.6; there is no evidence of the bridgehead ethers one might expect from heterolytic cleavage.[2,8] At higher conversion (84%) the ratio of **2**/**3** diminished to 1.7, indicating that **2** was fragmenting to **3**. This was confirmed by photolysis of the monochloro photoproduct wherein clean reduction to **3** was observed.[9]

The quantum efficiency (ϕ) for photofragmentation of **2** to **3** was determined using the photosolvolysis of *exo*-2-chlorobenzonorbornene in methanol (ϕ = 0.55)[6] as a secondary actinometer. The measured value of 0.024 may be compared with ϕ's reported for (unconstrained) benzyl chloride (0.26–1.0, depending on the solvent)[10] and to the 0.55 observed for the homobenzylic 2-position (see above).

Experimental Section

^{1}H NMR were obtained with a Perkin Elmer R-32 (90 MHz), a Varian XL-200 (200 MHz), or a Nicolet NT-470 (470 MHz) spectrometer. ^{13}C NMR spectra were recorded on the Varian XL-200 spectrometer at 50 MHz. Mass spectra were obtained with a Finnigan automated gas chromatography EI/CI mass spectrometer. Vapor-phase chromatography utilized Varian Model 90-P, A-90-P, and A-700 chromatographs for preparative work and Model 1200 or 1400 FID chromatographs with a Hewlett-Packard 3380 or 3380-A digital integrator for quantitative studies. Photochemical studies mainly employed a rotating turntable with quartz tubes and a Hanovia Model 68814-45 low-pressure mercury arc lamp.

Photolysis of 1,4-Dichloro-7,7-dimethoxybenzonorbornene (1).[7] In a typical procedure, 500 mg (1.8 mmol) of **1** was dissolved in 100 mL of methanol (Burdick and Jackson Spectroquality, sparged with argon for 30 min, and irradiated for 440 min, with constant argon bubbling, using the 254-nm lamp. After addition of some solid Na_2CO_3 to reduce acidity, the methanol was removed on a rotary evaporator and the residue taken up in dichloromethane. Analysis by a 20 ft × $^1/_4$ in. 10% FFAP on 60/80 mesh Chromosorb W (AW-DMCS) column at 210 °C (90 mL of He/min) showed compounds **2** (t_r 25 min) and **3** (t_r 12.4 min)[7] plus ethylene glycol (t_r 4.8 min) and traces of an unidentified product (t_r 19 min).

1-Chloro-7,7-dimethoxybenzonorbornene (**2**) has hitherto been reported and was isolated by preparative VPC: ^{1}H NMR ($CDCl_3$, 470 MHz) δ 7.20–7.40 (m, 4 H, Ar), 3.51 (s, 3 H, anti OCH_3), 3.30 (d, 1 H, bridgehead H), 3.20 (s, 3 H, syn OCH_3), 2.35 (dd, 2 H, CH exo), 1.45 (dd, 2 H, CH endo); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.89 (C-3), 34.84 (C-2), 45.22 (C-4), 50.63, 51.96 (OCH_3), 74.76 (C-1), 115.32 (C-7), 119.87, 120.97, 126.59, 127.19, 141.50 (Ar); mass spectrum (70 eV) 238, 240 ($M^{\bullet+}$), 163, 165 (base peak + isotope peak, M − $CH(OCH_3)_2$).

Anal. Calcd for $C_{13}H_{15}ClO_2$: C, 65.40; H, 6.33; Cl, 14.85. Found: C, 65.81; H, 6.35; Cl, 14.44.

Quantum Efficiency for Conversion of 2 to 3. Compound **2** was made up as a 8.04 × 10^{-3} M solution in methanol and charged (5.0 mL) into two matched quartz tubes. Two other matched tubes were charged with 5.0 mL of 1.00 × 10^{-2} M *exo*-benzobicyclo[2.2.1]hepten-2-yl chloride (**4**) in methanol. The five tubes were degassed with argon for 30 min and the three solutions of **2** irradiated for 181 min. One of the solutions of **4** was irradiated for the intial 10.3 min (lamp prewarmed for 50 min) and the other for the final 10.3 min. Analysis of **4** was by a 10 ft × $^1/_8$ in. 10% Carbowax 20 M column at 130 °C by comparison with unirradiated solution. Analysis of **3** was on the same column using bibenzyl as an internal standard; both tubes gave the same ϕ_3 = 0.024.

Acknowledgment. We thank the National Science Foundation (Grant CHE-8318825) for support of this research. The carbon-13 NMR data were obtained on an instrument provided by NSF Grant CHE 8004246, the 470-MHz data were obtaiend through the Purdue University Biological Magnetic Resonance Laboratory (Grant NIH-RR01077), and the GC–Ms data were obtained on an instrument provided by NSF Grant CHE-8010832.

Registry No. 1, 34201-94-0; 2, 103620-91-3; 3, 29370-70-5.

(7) Wilt, J. W.; Vasiliauskas, E. *J. Org. Chem.* **1972**, *37*, 1467.

(8) The lack of ionic product from the chloride is consistent with and extends other studies[2a] showing that photolysis of 1-iodonorbornane in methanol gives 89% ether whereas 1-bromonorbornane only gives 30% ether.

(9) Earlier studies[6] have shown that, for example, *exo*-2-chlorononorbornane, is not susceptible to *inter*molecular aryl sensitization.

(10) Cristol, S. J.; Bindel, T. H. *J. Org. Chem.* **1980**, *45*, 951. Ivanov, V. B.; Ivanov, V. L.; Kuz'min, M. G. *J. Org. Chem. USSR (Engl. Transl.)* **1973**, *9*, 345.

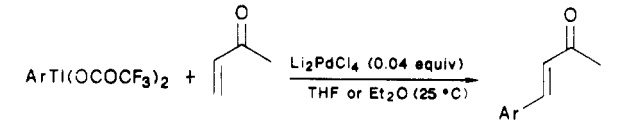
Ketovinylation of Arylthallium Compounds Catalyzed by Lithium Tetrachloropalladate

Richard A. Kjonaas

Department of Chemistry, Indiana State University, Terre Haute, Indiana 47809

Received March 14, 1986

We report here the results of our study in which methyl vinyl ketone is β-arylated by a Li_2PdCl_4-catalyzed reaction with various thallated aromatic compounds.



The palladium(II)-catalyzed olefinatioin of arylthallium compounds was first reported by Spencer and Thorpe in 1975.[1] Since then, numerous examples and variations of this reaction have been reported.[2] Except for one isolated case,[3] however, none of those examples have involved the use of a vinyl ketone as the olefin.[4] That one isolated case was the Pd(II)-catalyzed reaction of methyl vinyl ketone with a thallated indole. It involved the use of a high

(1) Spencer, T.; Thorpe, F. G. *J. Organomet. Chem.* **1975**, *99*, C8–C10.

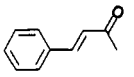
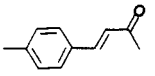
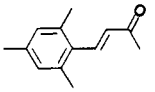
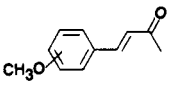
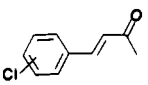
(2) (a) Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274–5284. (b) Uemura, S.; Miyoshi, H.; Wakasugi, M.; Okano, M.; Itoh, O.; Isumi, T.; Ichikawa, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 553–554. (c) Larock, R. C.; Liu, C.-L.; Lau, H. H.; Varaprath, S. *Tetrahedron Lett.* **1984**, *25*, 4459–4462.

(3) Somei, M.; Hasegawa, T.; Kaneko, C. *Heterocycles* **1983**, *20*, 1983–1985.

(4) Methyl vinyl ketone has been used in Heck-type reactions involving substrates other than arylthallium compounds; see the following for examples. (a) Diphenylmercury: Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518–5526. (b) Vinylic iodides: Ziegler, F. E.; Chakraborty, U. R.; Weisenfeld, R. B. *Tetrahedron* **1981**, *37*, 4035–4040. (c) Aryl halides (very low yields): Zebovitz, T. C.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3907–3909. (d) Aryl halides under phase-transfer conditions: Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287–1289. (e) Alkylpalladium complexes: Holton, R. A.; Kjonaas, R. A. *J. Organomet. Chem.* **1977**, *133*, C5–C9. (f) Arylmercury compounds under conditions giving protonation rather than elimination: Cacchi, S.; Misiti, D. *J. Org. Chem.* **1982**, *47*, 2995–2999.

0022-3263/86/1951-3708$01.50/0

Table I. Li_2PdCl_4-Catalyzed Reaction of $ArTl(OCOCF_3)_2$ with CH_2=$CHCOCH_3$

Ar	product	solvent	equiv[a] of CH_2=$CHCOCH_3$	time,[b] h	yield,[c] %
phenyl		THF	1.1	5	94
		THF	5.0	1.5	98
		ether	1.1	1.5	86
		ether	5.0	1	93
p-tolyl		THF	1.1	6	97
		THF	5.0	0.5	99
		ether	1.1	3.5	81
		ether	5.0	0.5	94
mesityl		THF	1.1	5	96
		THF	5.0	1	98
		ether	1.1	48	85
		ether	5.0	1	91
o/*p*-anisyl	 1:10 mixture of *o* and *p* isomers	THF	1.1	15	72
		THF	5.0	7	80
		ether	1.1	4	76
		ether	5.0	1	92
o/*p*-chlorophenyl	 1:3 mixture of *o* and *p* isomers	THF	1.1	48	25
		THF	5.0	12	47
		ether	1.1	48	24
		ether	5.0	12	46

[a] The number of mmol of methyl vinyl ketone per mmol of aryllithium bis(trifluoroacetate) and 0.04 mmol of Li_2PdCl_4. [b] The reactions were allowed to run until a black precipitate and/or silver mirror appeared. [c] All yields were determined by quantitative GC.

temperature (120 °C) and a very inconvenient solvent (*N*,*N*-dimethylformamide).

The reactions reported herein are carried out at 25 °C in tetrahydrofuran (THF) or diethyl ether. As shown in Table I, the yields are generally quite high, even when the final product has three contiguously substituted carbons. The reaction is not affected by the presence of moisture or air. The formation of biaryls as unwanted side products is essentially undetectable except when the thallated aromatic compound and Li_2PdCl_4 are allowed to react with each other prior to the introduction of methyl vinyl ketone to the reaction mixture. Thus, the order of addition of reagents to the reaction vessel is of some importance except when biaryl formation is stericly prohibited.[5]

The 1:10 and 1:3 ratios of ortho and para products in the last two examples in Table I are no doubt due to the fact that the thallated aromatics themselves were mixtures of ortho and para isomers. It has been reported that under suitable conditions, the thallation of anisole and chlorobenzene produces ortho:para ratios of 7:93 and 23:77, respectively.[6,7]

Presumably, the reaction preceeds by way of the transmetalation/insertion/reductive elimination pathway that has been proposed for similar reactions.[1,8] The resulting Pd(0) is apparently reoxidized by Tl(III) and then recycled.

The high cost and extreme toxicity of thallium reagents is an obvious disadvantage for the use of thallated aromatics in any reaction. These compounds, however, offer an attractive feature—a large variety of them can be prepared in high yield, and in many cases, it is possible to select the position of thallation by varying the reaction conditions.[6,7] Because of this, the vinylation reaction reported here is complementary to other Heck-type reactions which involve aryl moieties and vinyl ketones.[4a,d]

Experimental Section

Materials. The arylthallium bis(trifluoroacetates) were prepared by established procedures.[6,7] *Thallium and thallium compounds are extremely toxic and should be handled with utmost care.*[9,10] Thallic trifluoroacetate (94%) was obtained from Aldrich Chemical Co. and was used without further purification. THF was stored under reflux with sodium metal and benzophenone in a recycling solvent still. Fisher reagent grade anhydrous diethyl ether with BHT as a preservative was used without distillation. Li_2PdCl_4 was prepared by dissolving $PdCl_2$ and LiCl in water (heating is required), evaporating the water, and heating in vacuo at 100 °C until a red-purple solid was obtained.

Identification of Products. All seven of the α,β-unsaturated ketones reported in the table were identified by comparing the ^1H NMR (Varian T-60), TLC, and GC retention times (coinjection on a 6-ft. 10% OV-1 WHP 80/100 column) with those of authentic samples. The seven authentic samples were prepared by aldol condensation of acetone with the corresponding aromatic aldehyde and were purified by vacuum distillation.

General Procedure. To a stirring solution of 1.00 mmol of thallated aromatic compound and 1.10 mmol or 5.00 mmol of methyl vinyl ketone in 2.5 mL of THF or diethyl ether at 25 °C was added 0.04 mmol of Li_2PdCl_4 (either 10 mg of solid Li_2PdCl_4 or 0.10 mL of a solution made by dissolving 262 mg in 2.5 mL of THF). The flask was stoppered and the reaction mixture was allowed to stir until it turned black. This mixture was then treated in one of the following ways: (A) an internal standard was added and the mixture was analyzed by GC to obtain the yield or (B) 3 mL of ether and 3 mL of water were added and the organic phase was dried and evaporated to give the crude product.

Acknowledgment. Financial support from the Indiana State University Research Committee and Sigma Xi, The Scientific Research Society, is gratefully acknowledged.

Registry No. I (R_1 = R_2 = R_3 = H), 23586-54-1; I (R_1 = R_3 = H, R_2 = CH_3), 23586-55-2; I (R_1 = R_2 = R_3 = CH_3), 23586-57-4; I (R_1 = CH_3O, R_2 = R_3 = H), 28688-21-3; I (R_1 = R_3 = H, R_2 =

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(6) Taylor, E. C.; Kienzle, F.; Robey, R. L.; McKillop, A.; Hunt, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 4845–4850.
(7) McKillop, A.; Hunt, J. D.; Zelesko, M. J.; Fowler, J. S.; Taylor, E. C.; McGillivray, G.; Kienzle, F. *J. Am. Chem. Soc.* **1971**, *93*, 4841–4844.
(8) Heck, R. F. *Org. React.* (*N.Y.*) **1982**, *27*, 345–390.
(9) For a discussion of the toxicity of thallium and recommended laboratory procedures, see: Taylor, E. C.; McKillop, A. *Acc. Chem. Res.* **1970**, *3*, 338–346.
(10) For information on the use of ferric cyanoferrate(II) ("Prussian Blue") as an antidote in thallium poisoning, see: Heydlauf, H. *Eur. J. Pharmacol.* **1969**, *6*, 340–344.

CH_3O), 28688-23-5; I (R_1 = Cl, R_2 = R_3 = H), 28688-27-9; I (R_1 = R_3 = H, R_2 = Cl), 23586-58-5; II (R_1 = R_2 = R_3 = H), 122-57-6; II (R_1 = R_3 = H, R_2 = CH_3), 3160-38-1; II (R_1 = R_2 = R_3 = CH_3), 53389-56-3; II (R_1 = CH_3O, R_2 = R_3 = H), 10542-87-7; II (R_1 = R_3 = H, R_2 = CH_3O), 943-88-4; II (R_1 = Cl, R_2 = R_3 = H), 20766-37-4; II (R_1 = R_3 = H, R_2 = Cl), 3160-40-5; H_2C=CHCO-CH_3, 78-94-4; Li_2PdCl_4, 15525-45-8.

Asymmetric Epoxidation of Allyl Alcohol: Efficient Routes to Homochiral β-Adrenergic Blocking Agents

Janice M. Klunder, Soo Y. Ko, and K. Barry Sharpless*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

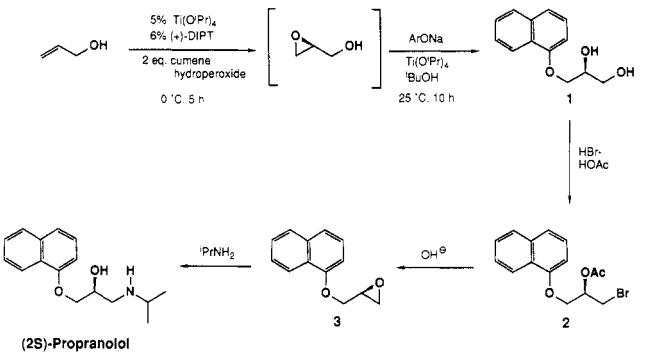
Received April 15, 1986

Since the discovery of the titanium-catalyzed asymmetric epoxidation of allylic alcohols in 1980,[1] ongoing efforts in these laboratories have been directed toward expanding the scope and synthetic utility of the reaction. A serious limitation of the original procedure has been its failure when applied to substrates with a strong propensity for undergoing ring-opening reactions. Of the many reaction modifications which have been explored, the recent development of an effective catalytic procedure[2] has offered the most general solution to this important problem and has allowed even allyl alcohol to be included for the first time on the roster of successful substrates. Although a full description of this new development will be reported shortly, the practical importance of homochiral glycidol in the synthesis of β-adrenergic blocking agents (β-blockers) prompts us to disclose here two very efficient routes to (2*S*)-propranolol, each utilizing the asymmetric epoxidation of allyl alcohol.[3-5]

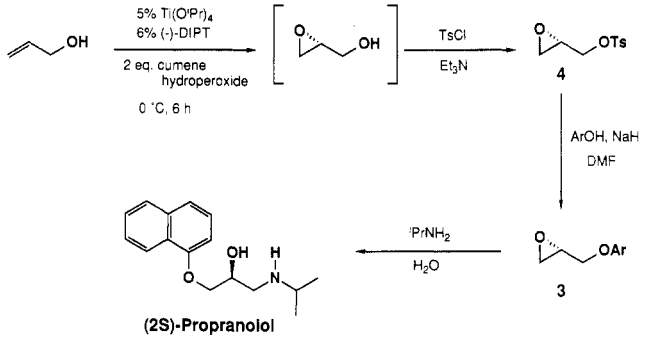
A common strategy used in the two procedures is the in situ derivatization of glycidol: after completion of the asymmetric epoxidation reaction, the unstable glycidol is derivatized rather than isolated directly from the reaction mixture. These derivatives are not only easier to handle, but are also more advanced synthetic intermediates than is the parent glycidol.

In the first procedure, glycidol is opened in situ by 1-naphthoxide (Scheme I). Thus, after asymmetric epoxidation is complete, the excess hydroperoxide is reduced with trimethyl phosphite, and the reaction mixture is treated with sodium 1-naphthoxide in *tert*-butyl alcohol in the presence of 1 equiv $Ti(O\text{-}i\text{-}Pr)_4$.[6] The opening

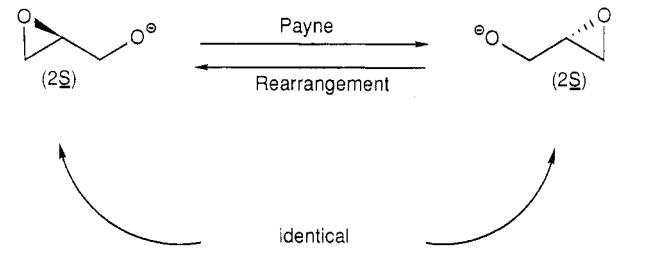
Scheme I



Scheme II



Scheme III



product, diol **1**, is then converted to the epoxide **3** by a known procedure.[7] Ring opening of **3** with isopropylamine gives (2*S*)-propranolol. Recrystallization of the hydrochloride salt yields enantiomerically pure (2*S*)-(−)-propranolol hydrochloride in 48% overall yield from allyl alcohol.

In the alternative procedure (Scheme II), catalytic asymmetric epoxidation of allyl alcohol is followed, again after reduction of excess hydroperoxide with trimethyl phosphite, by in situ tosylation of the intermediate glycidol. The isolated glycidyl tosylate (**4**) is crystalline, of high (≥90%) enantiomeric purity, and indefinitely stable to handling and storage at room temperature. A convenient, one-pot procedure is then employed to convert (2*S*)-glycidyl tosylate into the β-blocker (2*S*)-propranolol. Thus, treatment of **4** with sodium 1-naphthoxide in DMF results in selective displacement of the tosylate moiety to afford epoxy ether **3**. Epoxide opening is effected by refluxing the entire reaction mixture with isopropylamine and water to give (2*S*)-propranolol. Recrystallization of the hydrochloride salt as above provides (2*S*)-(−)-propranolol hydrochloride in 70% yield from **4**.

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