Table III

compd[a]	mp, °C	yield, %	recryst solvt	formula (MW)	anal.[b] % calcd/found C	H	N
8a	195-7	88	ethanol	$C_{17}H_{12}N_4O_2$ (304.31)	67.10	3.97	18.41
					67.30	4.10	18.20
8b	248-9	85	acetic acid	$C_{20}H_{16}N_4O_3$ (360.38)	66.66	4.48	15.55
					66.90	4.30	15.30
8c	227-9	85	acetic acid	$C_{19}H_{13}N_4O_2Cl$ (364.79)	62.56	3.59	15.36
					62.30	3.60	15.20
10a	183-5	93	acetic acid	$C_{17}H_{14}N_4O_3$ (322.33)	63.35	4.38	17.38
					63.50	4.30	17.50
10b	220-2	95	acetic acid	$C_{20}H_{18}N_4O_4$ (378.39)	63.49	4.79	18.81
					63.30	4.90	14.60
10c	215-7	93	acetic acid	$C_{19}H_{15}N_4O_3Cl$ (382.81)	59.62	3.95	14.64
					59.40	4.20	14.40

[a] **8a**, UV λ_{max} (log ϵ) = 216 (4.99), 315 (4.30) nm; IR 1690, 1650 (C=O) cm^{-1}; ^1H NMR δ 3.78 (s, 3 H, NMe), 7.40-8.40 (m, 9 H, ArH). [b] **8c**: Cl, calcd 9.72, found 10.00. **10c**: Cl, calcd 9.26, found 9.50.

acid (0.01 mol) in water (20 mL) for 15 min, during which time a crystalline precipitate began to separate. After cooling, the product was collected, dried and purified by dissolving in aqueous 5% NaOH solution, filtered, and reprecipitated with concentrated hydrochloric acid as yellow precipitates of **2a-d** in almost quantitative yield (Table I).

5-Amino-1,6-dioxo-5,6-dihydro-1*H*-*as*-triazino[4,3-*a*]-quinazolines 3a-d. Each of compounds **2a-d** (0.01 mol) was heated under reflux in glacial acetic acid (20 mL) for 3-5 h. The product obtained upon cooling was collected and crystallized from acetic acid as yellow crystals of **3a-d** (Table I).

5-(Arylideneamino)triazinoquinazolines 5a-g. General Procedure. The following exemplifies the procedure. Compound **3b** (0.01 mol) was heated under reflux in glacial acetic acid (15 mL) with benzaldehyde (0.01 mol) and fused sodium acetate (2 g) for 1-2 h, during which time a crystalline precipitate began to separate. After cooling, the product was collected, dried, and crystallized from acetic acid as yellow crystals of **5a** (Table II).

Action of Nitrous Acid on 3a-d. To a suspension of each of **3a-d** (0.5 g) in 6 N HCl (10 mL) was added dropwise while cooling and stirring sodium nitrite solution (0.5 g in 15 mL of water). The reaction mixture was left at room temperature for 15 min. The solid obtained was collected, washed with water, and crystallized from DMF as yellow crystals of **6a-d** (Table II).

Thermal Deamination of Compounds 3b,d. A mixture of each of **3b** and **3d** (0.01 mol) was heated at 180-200 °C in an oil bath with benzaldehyde (0.011 mol) for 2 h, during which time benzonitrile was noticeably evolved (and identified by IR and GC after extraction with chloroform from the reaction vessels). After cooling, the residue was triturated with ethanol. The obtained products were then crystallized from DMF as yellow crystals and were proved to be **6b** and **6d**, respectively.

Pyrolysis of Compound 5a. Compound **5a** (0.5 g) was heated at 250 °C (metal bath) for 30 min during which time benzonitrile was noticeably evolved. The solid remained was crystallized from DMF into compound **6b**.

Action of Diazomethane on 6b. An ethereal solution of diazomethane (prepared from 3 g of *N*-methyl-*N*-nitrosourea and 50 mL of ether) was added to 1 g of compound **6b**. After standing overnight in the refrigerator, the solution was evaporated at room temperature. The remaining solid was crystallized from ethanol into yellow crystals of **7**, mp 199 °C, yield 88%. Anal. Calcd. for $C_{17}H_{12}N_4O_2$ (304.31): C, 67.10; H, 3.97; N, 19.41. Found: C, 66.90; H, 3.80; N, 18.20. UV λ_{max} = 218, 270 nm; IR (KBr) 1720, 1695 (C=O) cm^{-1}; ^1H NMR δ 3.68 (s, 3 H, NMe), 7.35-8.35 (m, 9 H, Ar H).

Preparation of α-Keto Acid Hydrazones 10a-c. Compound **9**[8] (0.01 mol) was heated under reflux with the appropriate α-keto acid (0.01 mol) in ethanol (20 mL) for 15 min, during which time a crystalline precipitate began to separate. After cooling, the product was collected, dried, and crystallized from acetic acid as yellow crystals of **10a-c** (Table III).

Preparation of Compound 11. (a) A solution of compound **10b** (0.5 g) in DMF (10 mL) was heated under reflux for 2 h, cooled, and then diluted with water. The precipitate was collected and recrystallized from ethanol into yellow crystals of **11**, mp 158 °C, yield 72%. Anal. Calcd for $C_{16}H_{14}N_4O$ (278.32): C, 69.05; H, 5.07; N, 20.13. Found: C, 69.10; H, 4.80; N, 20.20.

(b) A solution of compound **9** (0.01 mol) and benzaldehyde (0.01 mol) in ethanol (15 mL) was heated under reflux for 10 min. The solid obtained upon cooling was crystallized from ethanol and proved to be **11** (mixed mp), yield 92%; ^1H NMR δ 3.56 (s, 3 H, NMe), 7.06-8.26 (m, 9 H, Ar H), 8.56 (s, 1 H, benzal CH), 9.36 (s, 1 H, NH).

Registry No. **1**, 19062-39-6; **2a**, 123565-87-7; **2b**, 123565-88-8; **2c**, 123593-02-2; **2d**, 123565-89-9; **3a**, 123565-90-2; **3b**, 123565-91-3; **3c**, 123565-92-4; **3d**, 123565-93-5; **5a**, 123565-94-6; **5b**, 123565-95-7; **5c**, 123565-96-8; **5d**, 123565-97-9; **5e**, 123565-98-0; **5f**, 123565-99-1; **5g**, 123566-00-7; **6a**, 123566-01-8; **6b**, 123566-02-9; **6c**, 123566-03-0; **6d**, 123566-04-1; **7**, 123566-05-2; **8a**, 123566-06-3; **8b**, 123566-07-4; **8c**, 123566-08-5; **9**, 61507-80-0; **10a**, 123593-03-3; **10b**, 123566-09-6; **10c**, 123566-10-9; **11**, 123566-11-0; *p*-ClC_6H_4CH=$CHCOCO_2H$, 33185-97-6; PhCHO, 100-52-7; *p*-$MeOC_6H_4CHO$, 123-11-5; P-ClC_6H_4CHO, 104-88-1; pyruvic acid, 127-17-3; phenylglyoxylic acid, 611-73-4; benzylidinepyruvic acid, 17451-19-3; *p*-methoxybenzylidenepyruvic acid, 17451-21-7; benzonitrile, 100-47-0.

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Microbiological Transformations. 13. A Direct Synthesis of Both *S* and *R* Enantiomers of 5-Hexadecanolide via an Enantioselective Microbiological Baeyer-Villiger Reaction

Véronique Alphand, Alain Archelas, and Roland Furstoss*

Laboratoire de Chimie Organique et Bioorganique, Faculté des Sciences de Luminy, 70, route Léon Lachamp, case 901, 13288 Marseille Cedex 9, France

Received January 23, 1989

The conversion of ketones to esters or lactones, i.e., the Baeyer-Villiger reaction,[1] is obviously one of the very important reactions in organic synthesis. However, the corresponding asymmetric Baeyer-Villiger reaction seems, up to now, to be unknown in the chemical literature. On the other hand, various studies have shown that "biological Baeyer-Villiger" reactions are involved in the oxidative degradation of a wide variety of organic compounds,[2] e.g.,

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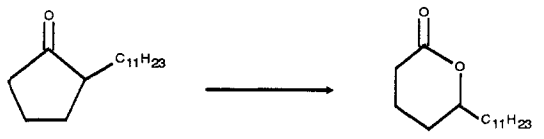
Table I. Microbiological Oxidation of Ketone 1 by *A. calcoaceticus* NCIB 9871 in the Presence of TEPP (0.8 mM)

	recovered ketone 1			lactone 2		
time,[a] h	yield,[b] %	$[\alpha]^{25}_D$ (Et_2O)	optical purity,[c] %	yield,[b] %	$[\alpha]^{25}_D$ (THF)	optical purity[d] (ee),[d] %
1	65	−29.2° (c = 0.8)	36	25	−29.8° (c = 0.7)	74 (73)
3	40	−57.9° (c = 1.0)	71	40	−25.2° (c = 0.9)	63 (60)
4.5	30	−77.0° (c = 1.5)	95	40	−13.0° (c = 0.9)	32 (33)

[a] After addition of ketone 1. [b] Yields estimated by GC analysis and based on racemic starting material. [c] (*S*)-(+)-2-Undecylcyclopentanone: $[\alpha]^{24}_D$ +81.0° (*c* 1.04, ether).[14e] [d] (*S*)-(−)-5-Hexadecanolide: $[\alpha]^{21.5}_D$ −40.2° (*c* 1.66, THF).[14f] [e] Enantiomeric excess values determined by following the method of Saucy et al.[24]

Scheme I. Bioconversion of 2-Undecylcyclopentanone (1) by *Acinetobacter* strains



1 2

acyclic[3] and cyclic ketones[4-6] or diketones[7] like camphor,[8] fenchone,[9] and steroids.[10] However, only a few examples have been described showing that such enzymatic reactions may lead to optically active lactones.[4a,7,11,12] In the course of our work on the biological oxidation of various substrates,[13] we decided to explore the possibilities of asymmetric synthesis offered by this type of enzyme. The pioneering work of Trudgill et al.[5] and Walsh et al.[2,6] has shown that *Acinetobacter* strains are able to perform "biological Baeyer–Villiger" reactions using a protein monooxygenase (cyclohexanone oxygenase EC 1.14.13.–) which has been isolated and characterized. Very recently, Taschner et al. also described some very interesting results on prochiral substrates using this purified enzyme and a NADPH recycling system. However, no indication about the scale of the reaction is given in this paper.[12] We here describe the use of these enzymes in order to perform a preparative enantioselective synthesis from racemic material which allows direct access to both (*S*)- and (*R*)-5-hexadecanolide, a pheromone isolated from the oriental hornet *Vespa orientalis*.[14,15]

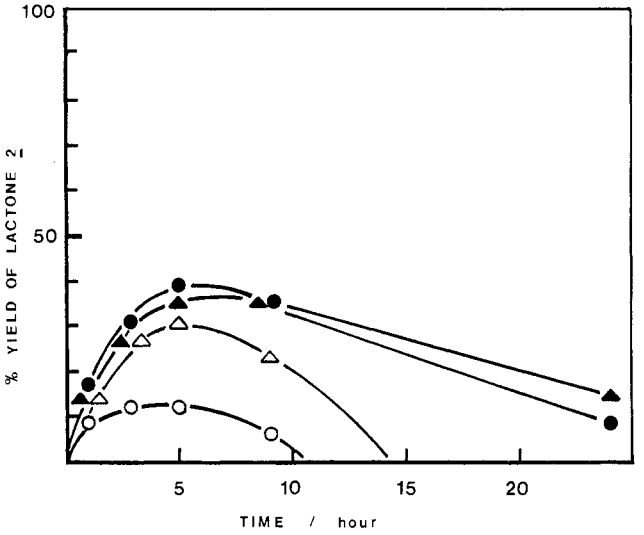


Figure 1. Effect of TEPP adjunction on the yield of lactone **2** formed: ○, without inhibitor (TEPP); △, 0.08 mM TEPP; ●, 0.8 mM TEPP; ▲, 1.6 mM TEPP.

Results

Because of the difficulties inherent in the large-scale purification of enzymes, we decided to conduct our studies using whole-cell processes.

The strain *Acinetobacter calcoaceticus* NCIB 9871 has been grown on cyclohexanol as the only carbon source.[5] After 15 h of growth, racemic 2-undecylcyclopentanone (**1**)[16] was added to the fermentation medium (1 g/L) and its disappearance was followed by gas chromatography. Ketone **1** was metabolized in about 20 h, and the corresponding 5-hexadecanolide (**2**) was formed as expected (Scheme I). The yield reached a maximum of about 10% after 5 h, but lactone **2** disappeared completely after about 10 h. Presumably, either lactone **2** is rapidly hydrolyzed by a lactone hydrolase, as previously proposed,[5] or ketone **1** is consumed by some other metabolic pathway (e.g., an enzymatic hydroxylation[17]).

The presence of such a lactone hydrolase, although not proven, is consistent with the stability of this lactone under the reaction conditions (pH 7.1) in the absence of the microorganism. Also, attempts to recover lactone by acidic

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Table II. Microbiological Oxidation of Ketone 1 by *Acinetobacter* TD 63

	recovered ketone 1			lactone 2		
time,[a] h	yield,[b] %	$[\alpha]^{25}_D$ (Et_2O)	optical purity,[c] %	yield,[b] %	$[\alpha]^{25}_D$ (THF)	optical purity[d] (ee),[e] %
1.5	65	−20.5° (c = 0.6)	25	25	−18.5° (c = 1.1)	46 (44)
2.5	50	−38.0° (c = 1.0)	47	45	−18.4° (c = 0.8)	45 (44)
4	35	−61.0° (c = 1.3)	75	55	−15.3° (c = 0.8)	38 (36)
5.5	25	−74.4° (c = 0.8)	92	65	−15.5° (c = 0.7)	38 (31)

[a] After addition of ketone 1. [b] Yields estimated by GC analysis and based on racemic starting material. [c] (*S*)-(+)-2-Undecylcyclopentanone: $[\alpha]^{24}_D$ +81.0° (*c* 1.04, ether).[14e] [d] (*S*)-(−)-5-Hexadecanolid: $[\alpha]^{21.5}_D$ −40.2° (*c* 1.66, THF).[14f] [e] Enantiomeric excess values determined by following the method of Saucy et al.[24]

treatment of the medium were unsuccessful.

Therefore, in an attempt to prevent lactone hydrolysis, we performed experiments in the presence of possible hydrolase inhibitors, i.e., phenylmethanesulfonyl fluoride (PMSF),[18] *p*-tosyl-L-phenylalanine chloromethyl ketone (TPCK),[19] benzamidine, α-lipoic acid,[20] isatoic anhydride,[21] EDTA, *p*-(chloromercurio)benzoate (PCMB),[22] and tetraethyl pyrophosphate (TEPP).[3a,23] These experiments, conducted by using δ-valerolactone and crude cell extracts,[5] showed that PMSF, isatoic anhydride, and TEPP are all efficient inhibitors of the lactone hydrolase. However, when these inhibitors were added to the whole-cell culture before addition of 1, only TEPP allowed accumulation of the desired lactone 2. Thus, when the incubation was conducted in the presence of 0.8 mM TEPP, the yield of lactone reached a maximum of 40% after about 5 h. Interestingly, this yield appears to be relatively independent of the initial inhibitor concentration, although at high concentration of TEPP the yield dropped to 15% after 24 h (Figure 1).

The yields and optical purities of the lactone and recovered ketone are shown in Table I. Thus lactone 2 of the 2*S* configuration is produced with an *optical purity of 74%* and is isolated in 25% yield. The recovered ketone of the 2*R* configuration can also be obtained, *with a 95% optical purity* (30% yield), thus allowing direct access to the (*R*)-(+)-5-hexadecanolide by a chemical Baeyer–Villiger reaction, which has been shown recently to be the sole bioactive enantiomer.[25]

Another way to avoid lactone degradation would be to use a strain lacking the hydrolase activity. An *Acinetobacter* species (*Acinetobacter* TD 63), unable to grow on cyclohexanol but able to metabolize 1,2-cyclohexanediol, has been isolated by Trudgill et al.[26] Since these authors have postulated that this strain was devoid of lactone hydrolase, we decided to use this microorganism. The results (Table II) show that lactone 2 was formed rapidly from 1, but that the optical purity obtained was at best 46%. However, the recovered ketone 1 was obtained with 92% optical purity.

Examination of our various results also indicates that, whereas the overall yield of products obtained by using *A. calcoaceticus* decreases over time (some substrate and/or product is metabolized further), this is not the case with *Acinetobacter* TD 63. With the two *Acinetobacter* strains, a second metabolite is formed (about 10% yield) if the incubation is carried out for more than 24 h (Scheme I). Its structure is tentatively assigned as 2-undecylvalerolactone on the basis of GC/MS analysis. This indicates that either the reaction is not totally regiospecific or a second enzymatic system is involved.

In conclusion, this work describes the preparative asymmetric synthesis of 5-hexadecanolide (2) using a biological Baeyer–Villiger reaction achieved by two strains of *Acinetobacter*. This allows the three-step synthesis of (*S*)-(−)-5-hexadecanolide as well as direct access to (*R*)-(+)-2-undecylcyclopentanone, a precursor for chemical synthesis of (*R*)-(+)-5-hexadecanolide. These products were obtained with optical purities of 74 and 95%, respectively. We consider the possibility of asymmetric microbiological Baeyer–Villiger reaction to be very useful in organic synthesis, since such chiral lactones are valuable synthons for further transformations to biologically active natural products.[27] We are currently studying the scope and limitations of this process.

Experimental Section

General Procedures and Materials. ^1H and ^{13}C NMR spectra were recorded (at 80 and 200 MHz) in $CDCl_3$. GC/MS measurements were performed by using a HP 1 column. FID gas chromatography analyses were performed by using a capillary column (OV-1701 25 m).

All chemicals were purchased from Fluka, Prolabo, or Janssen. Racemic 5-hexadecanolide (2) was prepared by chemical Baeyer–Villiger transformation of 1 using *m*-chloroperbenzoic acid (MCPBA).[28] Tetraethyl pyrophosphate was obtained from diethyl phosphorochloridate.[23]

Bacterial Strains. *A. calcoaceticus* NCIB 9871 and *Acinetobacter* TD 63 were gifts from Profs. C. T. Walsh and P. W. Trudgill, respectively. Stock cultures were grown on nutrient agar at 30 °C, stored at 4 °C, and subcultured at monthly intervals.

Typical Bioconversion of 2-Undecylcyclopentanone (1). The cultures are achieved by using the medium described by Walsh et al.[6] *A. calcoaceticus* NCIB 9871 grows on cyclohexanol (1 g/L) and *Acinetobacter* TD 63 on 1,2-cyclohexanediol (1.5 g/L). Fifty milliliters of culture medium in a 500-mL Erlenmeyer flask is inoculated from nutrient agar slope. After 24 h of growth at 30 °C (shaking at 150 rpm), 10-mL portions of this preculture are used to inoculate 500 mL of medium placed in a 3-L baffled flask. After 15 h of growth, under the same experimental conditions, 0.5 g of ketone 1 in 2.5 mL of ethanol is added to the 500-mL culture (i.e., 1 g/L) in the case of *A. calcoaceticus* NCIB 9871, and 0.25 g of ketone 1 (i.e., 0.5 g/L) in the case of *Acinetobacter* TD 63. The reaction is followed by periodic removal of 1-mL aliquots, which are extracted with 1 mL of ethyl acetate and analyzed by capillary GC using dibutyl phthalate as an internal standard. After completion of the reaction, the whole

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culture is extracted similarly by using ethyl acetate or, alternatively, by performing continuous extraction with methylene chloride for 24 h. The obtained products are purified by flash chromatography (silica gel, Merck 60H, hexane/ether, 4/3) and bulb-to-bulb distillation. When used, the inhibitors are added to the culture 45 min before substrate 1 addition. The concentration of TEPP for preparative-scale experiments is 0.8 mM (200 μL/L of culture).

6-Undecyltetrahydro-2*H*-pyran-2-one (5-hexadecanolide) (2) was identified by IR, ^1H NMR, and ^{13}C NMR spectroscopy and by comparison with an authentic sample. Mass spectrometry: [M^+] 254; *m/z* 99 (100), 114 (16).

3-Undecyltetrahydro-2*H*-pyran-2-one was characterized by GC/MS of a mixture consisting of 95% of this compound and 5% **2**. Retention times: **3**, 4.4 min; **2**, 4.5 min (OV-1701 column, 230 °C, He flow, 1 bar). GC/MS: [M^+] 254; *m/z* 113 (60), 100 (100), 95 (7), 55 (15), 43 (9), 41 (15).

Selection of Lactone Hydrolase Inhibitors. *A. calcoaceticus* cells were grown, harvested by centrifugation, and disrupted as previously described.[5] A 200-μL (6 mg of P) aliquot was added in 1 mL of phosphate buffer (pH 7.1) at 30 °C containing 1 or 5 mM of the selected potential inhibitor. After 10 min of stirring, 10 μL (11 mg) of δ-valerolactone was added. The medium was extracted 1 h later with 3-mL of ethyl acetate, and the remaining lactone amount was checked by GC analysis using dodecane as internal standard.

Acknowledgment. This work has been supported in part by the "Groupement Scientifique Arômes" and the CNRS. One of us (V.A.) is the very grateful recipient of a studentship from these organizations. We also thank very much Profs. P. W. Trudgill, C. T. Walsh, and J. Chen for their generous gifts of *Acinetobacter* TD 63 and *A. calcoaceticus* NCIB 9871 slants.

Registry No. (±)-1, 83019-13-0; (*S*)-2, 59812-97-4.

Palladium-Catalyzed Reduction of Aryl Sulfonates. Reduction versus Hydrolysis and Selectivity Control

Walter Cabri,* Silvia De Bernardinis, Franco Francalanci, and Sergio Penco

Farmitalia-Carlo Erba S.r.l. (Erbamont Group), R&D, via Dei Gracchi, 35-20146 Milano, Italy

Roberto Santi*

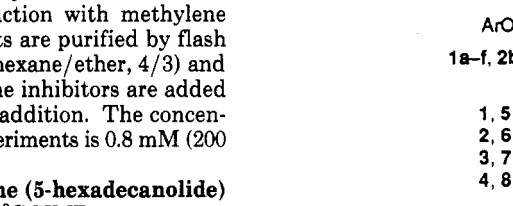
Istituto Guido Donegani, via Fauser, 4-28100 Novara, Italy

Received May 25, 1989

Introduction

Deoxygenation of phenols appears to be an important tool in the field of organic synthesis;[1] palladium-catalyzed reduction of perfluoroalkane sulfonates has arisen in the last few years as an important method with mild reaction conditions and concomitant high chemoselectivity.[2] However, the synthesis of perfluoroalkane sulfonates from the corresponding phenols can sometimes be a major problem[3] in terms of selectivity, stability, and cost. In spite of these drawbacks, to the best of our knowledge, no effort has been carried out to extend the scope of this and related reactions to the more accessible and stable mesylates, tosylates, etc.[4] In this paper we report our results on the palladium-catalyzed reduction of sulfonates **1a–f**, **2b**, **3b**, and **4a–f** to the corresponding arenes **5–8** (Scheme I).[5] We have focused our attention on the study of effects of solvent, reaction conditions, and, mostly, the nature of palladium ligands on the course of reaction.

Scheme I



Results and Discussion

Palladium-catalyzed reductions were performed with a catalyst, generated "in situ", from $Pd(AcO)_2$ and the appropriate ligand. Among the several hydride sources reported in the literature,[6] triethylammonium formate was chosen because of its compatibility with all of our substrates.

Reduction of 1-naphthyl triflate **1a** was reported by Wulff and co-workers to proceed in high yield at 60 °C by using $Pd(PPh_3)_4$ (2 mol %) as catalyst and DMF as solvent.[2c] Under the same experimental conditions, we found that 1-naphthyl sulfonates **1b–f** failed to react; even at 90 °C only a very small amount of naphthalene **5** was formed after 48 h. Concomitant decomposition of the catalyst was observed, suggesting that oxidative addition was too slow. The substitution of PPh_3, with the more electron donating PCH_3Ph_2 and $P(CH_3)_2Ph$ ligands,[7] which in principle should give rise to faster oxidative addition, led only to trace amounts of naphthalene due to complete decomposition of formate.[8] In searching for a more efficient system, we used a 1,3-bis(diphenylphosphino)propane (DPPP) containing catalyst that is very active in alkoxycarbonylation reactions.[9] This complex proved to be a better catalyst for triflate reduction than the one based on PPh_3 (Table I, entries 1–3); its use actually allowed us to carry out reduction of sulfonates **1b–f** in high yields provided that the temperature was 90 °C (entries 4–8). The nature of substituents on the aryl sulfonate moiety affects the reduction, the order of reactivity being *p*-F > H ≫ *p*-Me > *p*-OMe; mesylate **1f** turned out to be as reactive as *p*-methoxybenzenesulfonate **1e**. Substrates **2b** and **3b**, bearing potentially reducible groups such as nitrile and acetyl on the phenyl ring, were completely converted to benzonitrile **6** and acetophenone **7**, respectively (entries

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