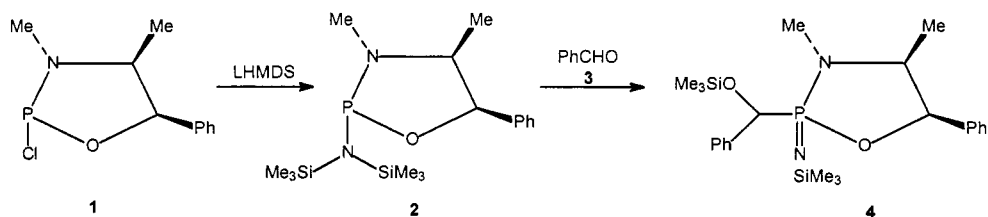


## ABRAMOV Phosphonylation

Stereoselective phosphonylation of aldehydes by means of phosphordiamidates



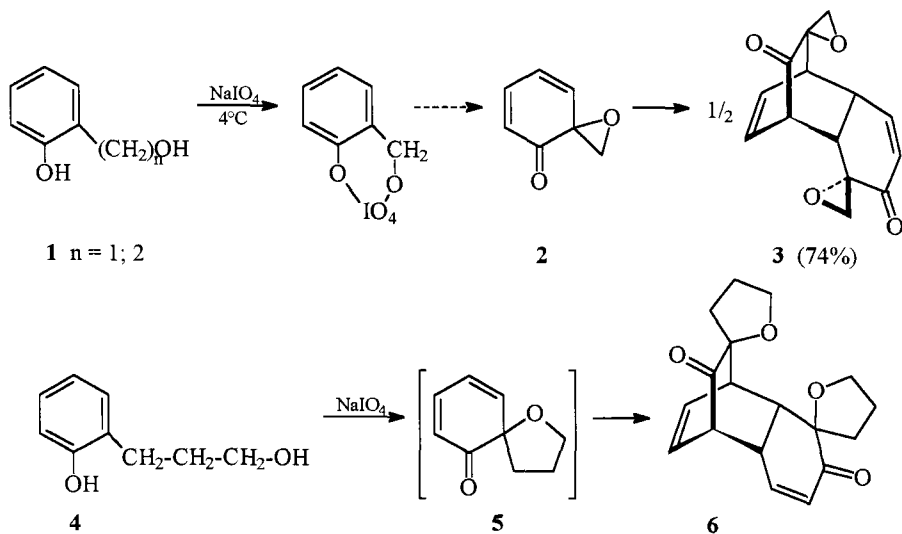
1	Abramov, V. S.	<i>Dokl. Akad. NaukSSSR</i>	<b>1954</b>	95	991
2	Kee, T. P.	<i>J. Chem. Soc. Perkin 1</i>	<b>1994</b>		3183
3	Evans, D. A.	<i>J. Am. Chem. Soc.</i>	<b>1978</b>	100	3467
4	Devitt, P. G.	<i>J. Chem. Soc. Perkin 1</i>	<b>1993</b>		2701

**(1R, 2S)-O, N-Ephedrine P-N (SiMe<sub>3</sub>)<sub>2</sub> (2).**<sup>2</sup> To a stirred solution of (1R, 2S)-O, N-ephedrine PCl 1 (240 mg, 1.07 mmol) in THF (20 mL) at  $-78^{\circ}\text{C}$  was added a solution of LiN (SiMe<sub>3</sub>)<sub>2</sub> in THF (1.07 mL of 1 M, 1.07 mmol). After allowing the mixture to warm to  $20^{\circ}\text{C}$ , it was stirred for another hour. The solvent was removed under vacuum and the residue was extracted with pentane. Evaporation of the pentane under reduced pressure gave 290 mg of 2 (83%) of 96-98% epimeric purity. Flash filtration of the pentane solution through basic alumina improved the epimeric purity to 98%.

**(1R, 2S)-O, N-Ephedrine P(NSiMe<sub>3</sub>)CHPh(OSiMe<sub>3</sub>) (4).** To a solution of 2 (410 mg, 1.15 mmol) in pentane (15 mL) was added at  $20^{\circ}\text{C}$  a solution of benzaldehyde 3 (120 mg, 1.15 mmol) under stirring. After 3 h the solution was filtered and the volatile components were removed in vacuum, to afford 440 mg of 4 (83%), 92% diastereoselectivity.

## ADLER Phenol Oxidation

Oxidation of *o*-alkoxyphenols with sodium metaperiodate to afford 6,6-spiro-2,4-cyclohexadienones which dimerize spontaneously to a Diels-Alder adduct.

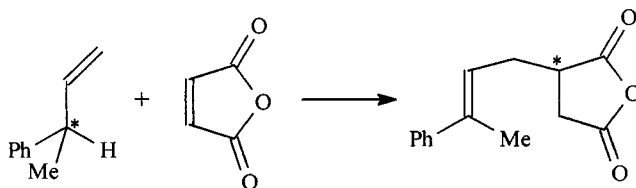
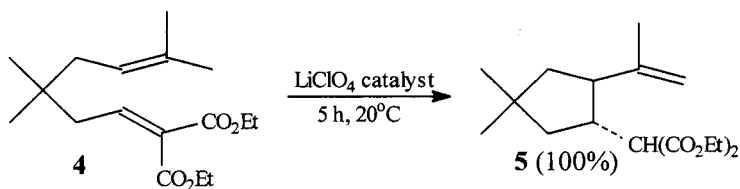
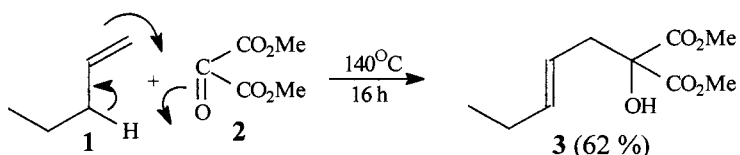


1	Adler, E.	<i>Acta Chem. Scand.</i>	1959	13	1959
2	Adler, E.	<i>Acta Chem. Scand.</i>	1960	14	1261; 1580
3	Adler, E.	<i>Acta Chem. Scand.</i>	1962	16	529
4	Adler, E.	<i>Acta Chem. Scand.</i>	1971	25	2055

**Spirooxirane 3.**<sup>4</sup> NaIO<sub>4</sub> (47 g; 0.22 mol) in water (1000 mL) was added to a stirred solution of 2-hydroxybenzyl alcohol **1** (24.83 g; 0.2 mol) in water (1500 mL). After 10 min, colorless crystals appear. The mixture was kept for 24 h at 4°C in the dark. The crystalline product was filtered, washed (water) and dried in vacuum over P<sub>2</sub>O<sub>5</sub> to afford 18.05 g of **3** (74%), mp 194-195°C.

## ALDER (Ene) Reaction

Thermal or catalytic sigmatropic rearrangement with H-transfer and C-C bond formation either inter or intramolecular and with chiral induction (see 1st edition).



1	Alder, K.	<i>Chem. Ber</i>	<b>1943</b>	76	27
2	Usieli, V.	<i>J. Org. Chem.</i>	<b>1973</b>	38	1703
3	Achmatowicz, O.	<i>J. Org. Chem.</i>	<b>1980</b>	45	1228
4	Snider, B. B.	<i>J. Org. Chem.</i>	<b>1982</b>	47	745
5	Hill, R.	<i>J. Am. Chem. Soc.</i>	<b>1964</b>	86	965
6	Oppolzer, W.	<i>Angew. Chem. Int. Ed.</i>	<b>1978</b>	17	476
7	Sarkar, T.K.	<i>Synlett.</i>	<b>1996</b>		97

**Methyl 2-hydroxy-2-carbomethoxy-4-heptenoate 3.**<sup>3</sup> A solution of dimethyl mesoxalate **2** (1.46 g, 10 mmol) and 1-pentene **1** (0.7 g, 10 mmol) in  $\text{CH}_2\text{Cl}_2$  was heated at 140°C for 16 h. The solvent was removed and the residue distilled under reduced pressure. The fraction collected between 90 and 105°C (0.5 torr) was diluted with  $\text{Et}_2\text{O}$  (20 mL), washed with water and dried. The residue after evaporation of the solvent, gave on distillation 1.55 g of **3** (62%), bp 89-90°C (0.2 torr).

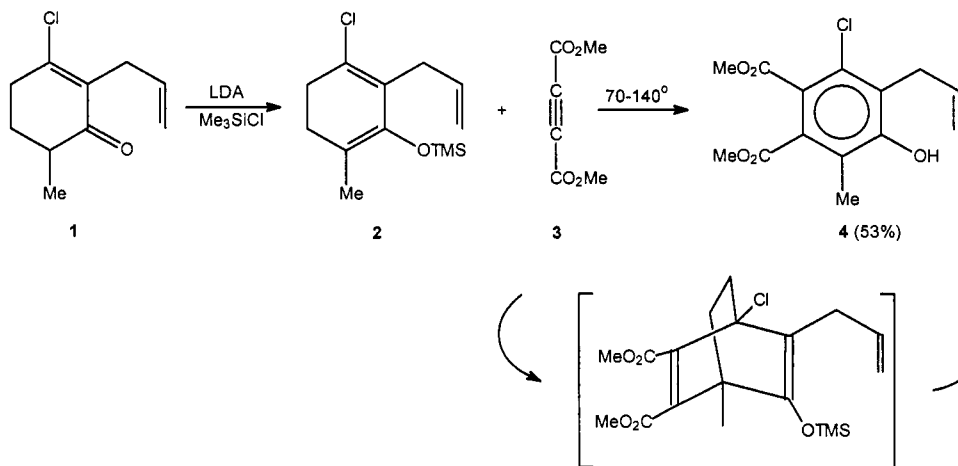
**Diethyl (2-isopropenyl-4,4-dimethyl cyclopentyl)-1-malonate 5.**<sup>7</sup>

The catalyst:  $\text{LiClO}_4$  (2.0 g) in  $\text{Et}_2\text{O}$  (10 mL) was stirred with silica gel for 30 min. After evaporation of the solvent in vacuum the catalyst was dried for 24 h at 150°C and 0.1 torr.

The catalyst (50 mg) and **4** (298 mg, 1 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was stirred at 20°C for 5 h under Ar. After removal of the catalyst and evaporation of the solvent, **5** was obtained in quantitative yield.

## ALDER-RICKERT Cycloaddition

Synthesis of polysubstituted benzenes by a Diels-Alder reaction of cyclohexadienes with acetylenes, via bicyclooctadienes.



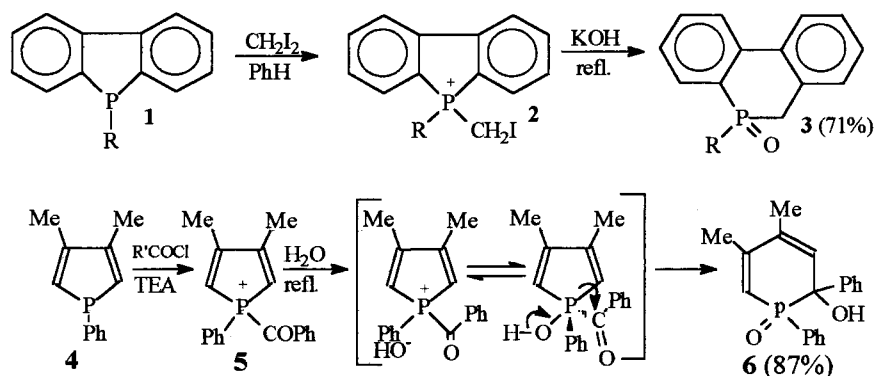
1	Alder, K., Richert, H. F.	<i>Liebigs Ann.</i>	<b>1936</b>	524	180
2	Birch, A. J.	<i>Aust. J. Chem.</i>	<b>1969</b>	22	2635
3	Danishefsky, S.	<i>J. Am. Chem. Soc.</i>	<b>1974</b>	96	7807
4	Patterson, J. W.	<i>J. Org. Chem.</i>	<b>1995</b>	60	560

**1-Chloro-4-methyl-2-(2-propenyl)-3-(trimethylsilyloxy)-1,3-cyclohexadiene (2).**<sup>4</sup> A solution of LDA was prepared by adding n-BuLi (40.6 mL of 1.6 N hexane solution) to  $i\text{Pr}_2\text{NH}$  (9.1 mL, 65 mmol) in THF (110 mL) at  $-40^\circ\text{C}$ . After cooling to  $-70^\circ\text{C}$ , the reaction mixture was treated with TMS-Cl (12 mL) added over 10 min, followed by 3-chloro-6-methyl-2-(2-propenyl)cyclohex-2-enone **1** (11 g, 59 mmol). After 30 min stirring at  $-70^\circ\text{C}$ ,  $\text{Et}_3\text{N}$  (20 mL) was added and the mixture was poured into ice water and hexane. The organic layer was washed, dried ( $\text{K}_2\text{CO}_3$ ) and distilled (Kugelrohr) to afford 12.02 g of **2** (79%), bp  $80^\circ\text{C}/0.2\text{ mm}$ .

**Dimethyl 3-chloro-5-hydroxy-6-methyl-4-(2-propenyl)-phthalate (4).** A solution of **2** (12 g, 47 mol) and DMAD (dimethyl acetylenedicarboxylate) (9 mL, 73 mmol) in xylene (45 mL) was heated at  $70^\circ\text{C}$  for 2 h and then at  $145^\circ\text{C}$  for 4 h. Evaporation of the solvent in vacuum followed by routine work up and chromatography (silica gel, ethyl acetate: hexane) afforded 9.48 g of **4** (53%) as an oil.

## ALLEN - MILLAR - TRIPPETT Phosphonium Rearrangement

Ring enlargement via hydrolysis of cyclic phosphonium salts obtained by alkylation (acylation) of cyclic phosphines.



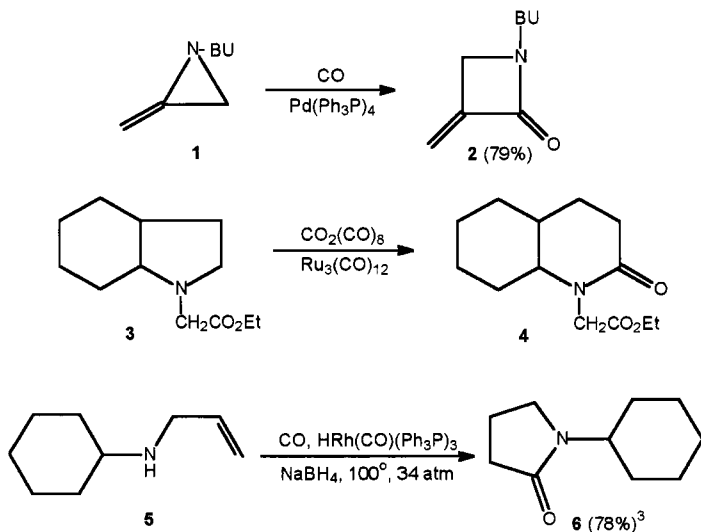
1	Allen, D.W., Millar, I.T.	<i>Chem.Ind.</i>	1967	2178
2	Allen, D.W., Millar, I.T.	<i>J.Chem.Soc. C</i>	1969	252
3	Trippett, S.	<i>Chem.Comm.</i>	1967	1113
4	Tebby, J.C.	<i>J.Chem.Soc. C</i>	1971	1064
5	Mathey, F.	<i>Tetrahedron</i>	1972	28 4171
6	Mathey, F.	<i>Tetrahedron</i>	1973	29 707
7	Allen, D.W.	<i>J.Chem.Soc. Perkin 1</i>	1976	2050
8	Markl, G.	<i>Angew.Chem.Int.Ed.</i>	1987	26 1134
9	Keglevich, Gy.	<i>J.Org.Chem.</i>	1990	55 6361
10	Keglevich, Gy.	<i>Synthesis</i>	1993	931

**9-Methyl-9,10-dihydro-9-phosphaphenanthrene-9-oxide (3).**<sup>1</sup> The phosphonium salt **2** (R = Me) (0.7 g, 1.5 mmol) in aqueous acetone containing KOH solution was heated to reflux for 2 h. Extraction of the cold mixture with  $\text{CHCl}_3$ , evaporation of the solvent and chromatography (silica gel, EtOAc : EtOH 7:3) afforded 0.24 g of **3** (71%). Purification by preparative TLC with EtOAc.

**2-Hydroxy-1,2-dihydroxyphosphinine oxide 6.**<sup>6</sup> Benzoyl chloride (10 g, 71.1 mmol) was added to **4** (7.52 g, 40 mmol) and  $\text{Et}_3\text{N}$  (20 mL) in  $\text{Et}_2\text{O}$  (300 mL). After 3 h stirring under reflux **5** was hydrolyzed with water (150 mL) (reflux 2 h). The next day the precipitate was removed by filtration and the filtrate dried ( $\text{MgSO}_4$ ). Evaporation of the solvent and recrystallization from PhMe afforded 10.8 g of **6** (87%).

## ALPER Carbonylation

Carbonylation of cyclic amines, hydroformylation (CO-H<sub>2</sub>) of amino olefins catalyzed by metal (Pd, Ru, Rh) complexes (see 1st edition).



1	Alper, H.	<i>J. Chem. Soc. Chem. Commun.</i>	1983	102	1270
2	Alper, H.	<i>Tetrahedron, Lett.</i>	1987	28	3237
3	Alper, H.	<i>J. Org. Chem.</i>	1992	57	3328
4	Alper, H.	<i>J. Am. Chem. Soc.</i>	1990	112	2803
5	Alper, H.	<i>Aldrichimica Acta</i>	1991	24	3
6	Alper, H.	<i>J. Am. Chem. Soc.</i>	1992	114	7018

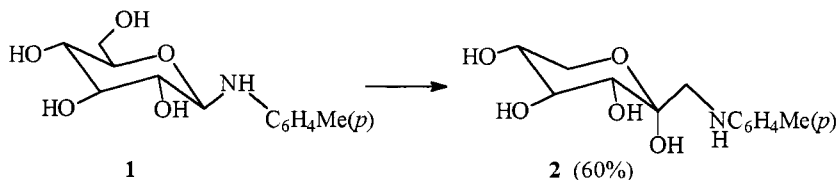
**N-(n-Butyl)- $\alpha$ -methylene- $\beta$ -lactam (2).**<sup>2</sup> CO was bubbled through Pd(OAc)<sub>2</sub> or Pd(Ph<sub>3</sub>P)<sub>4</sub> (0.136 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL). After 2 min Ph<sub>3</sub>P (0.54 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added followed by aziridine 1 in CH<sub>2</sub>Cl<sub>2</sub>. After 40 h evaporation and preparative TLC (silica gel hexane :EtOAc 8:1) yielded 2 (79%).

**Perhydroquinolinone (4).**<sup>6</sup> Perhydroindole 3 (311 mg, 1.32 mmol), a mixture of CO<sub>2</sub>(CO)<sub>8</sub> and Ru<sub>3</sub>(CO)<sub>12</sub> in PhH (10 mL) in a glass lined autoclave purged and pressurized with 54 atm of CO was heated to 200-220 °C for 3 days. Work up and preparative TLC gave 249 mg of 4 (79%).

**N-Cyclohexyl-2-pyrrolidone (6).**<sup>3</sup> 5 (278 mg, 2 mmol), NaBH<sub>4</sub> (75 mg, 2.25 mmol) and HRh(CO)(Ph<sub>3</sub>P)<sub>3</sub> (18.36 mg, 0.02 mmol) in i-PrOH (0.5 mL) and CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was treated with CO at 34.5 atm, with heating and stirring for 30 h at 100 °C. Work up and chromatography afforded 260 mg of 6 (78%).

## A M A D O R I Glucosamine Rearrangement

Rearrangement of N-glucosides of aldoses to glucosides of ketoses (see 1st edition).

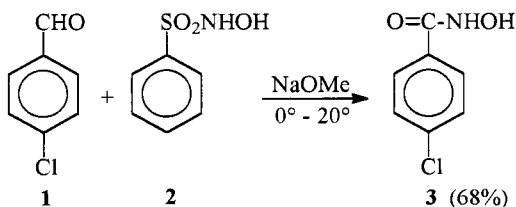


1	Amadori, M.	<i>Atti. Accad. Lincei</i>	<b>1925</b>	2	337 (6)
2	Weygand, F.	<i>Chem. Ber.</i>	<b>1940</b>	73	1259
3	Hixon, R.M.	<i>J. Am. Chem. Soc.</i>	<b>1944</b>	66	483
4	Ames, G.R.	<i>J. Org. Chem.</i>	<b>1962</b>	27	390
5	Gomez-Sanchez, A.	<i>Carbohydrate Res.</i>	<b>1992</b>	229	302
6	Winckel, D.	<i>Rec. Trav. Chim.</i>	<b>1995</b>	114	321
7	Horvat, S.	<i>J. Chem. Soc. Perkin 1</i>	<b>1998</b>		909

**1-Deoxy-1-*p*-tolylamino-D-fructose 2.**<sup>3</sup> A mixture of  $\alpha$ -D-glucose **1** (100 g; 555 mmol), *p*-toluidine (80 g; 533 mmol), water (25 mL) and 2N AcOH (5 mL) was heated to 100°C for 30 min. To the cooled mixture was added anh. EtOH (100 mL) and after 24 h the precipitate was filtered, washed with EtOH:Et<sub>2</sub>O (2:3), to give 94 g of **2** (60%), m.p. 152-153°C.

## A N G E L I - R I M I N I Hydroxamic Acid Synthesis

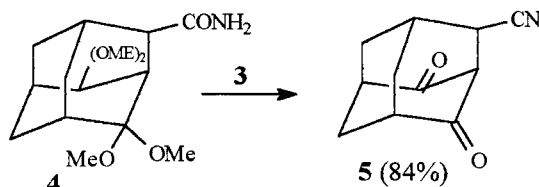
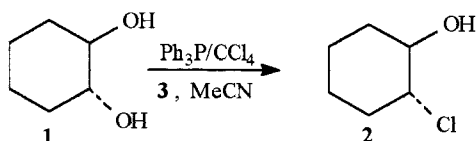
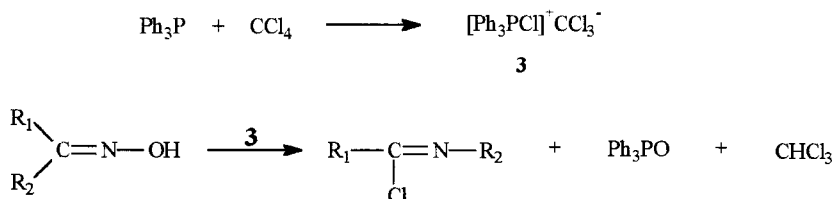
Synthesis of hydroxamic acids from aldehydes and N-sulfonylhydroxylamine; also used as a color test for aldehydes (see 1st edition).



1	Angeli, A.	<i>Gazz. Chim. Ital.</i>	<b>1896</b>	26	17 (II)
2	Rimini, E.	<i>Gazz. Chim. Ital.</i>	<b>1901</b>	31	84 (I)
3	Hassner, A.	<i>J. Org. Chem.</i>	<b>1970</b>	35	1952
4	Lwowsky, W.	<i>Angew. Chem. Int. Ed.</i>	<b>1967</b>	6	897

## APPEL Halogenation Reagent

Triphenyl phosphine and carbon tetrachloride (or tetrabromide), a reagent for chlorine (bromine) substitution, dehydration.



1	Rabinowitz, R. Marcus, R.	<i>J. Am. Chem. Soc.</i>	<b>1962</b>	84	1312
2	Appel, R.	<i>Chem. Ber</i>	<b>1971</b>	104	1030
3	Appel, R.	<i>Chem. Ber</i>	<b>1975</b>	108	2680
4	Evans, S.A. Jr.	<i>J. Org. Chem.</i>	<b>1981</b>	46	3361
5	Appel, R.	<i>Angew. Chem. Int. Ed.</i>	<b>1975</b>	14	801
6	Brinkman, H.R.	<i>Synthesis</i>	<b>1992</b>		1093

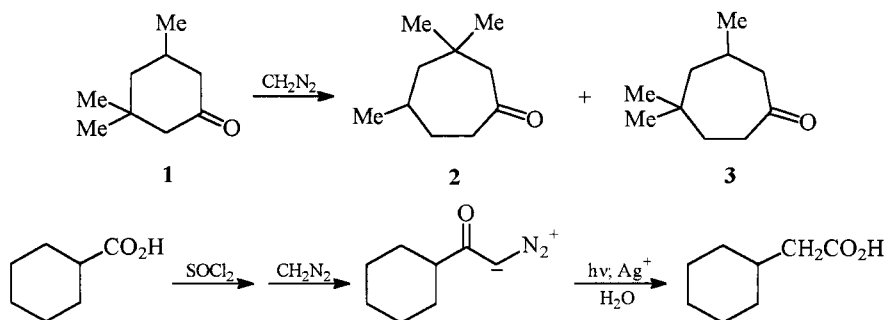
**Trans-2-chlorocyclohexanol (2).**<sup>4</sup> Trans-1,2-cyclohexanediol **1** (1.91 g, 16.5 mmol) was added to a solution of **3** (triphenylphosphine 4.93 g, 16.5 mmol in anh.  $\text{CCl}_4$  30 mL) and MeCN (10 mL). After 24 h reflux and work up, there was obtained 1.95 g of **2** (88%).

**2-Cyano-adamantan-4,8-dione (5).**<sup>2</sup> To 4,4,8,8-tetramethoxy-2-carboxamido-adamantane **4** (300 mg, 1.0 mmol),  $\text{Ph}_3\text{P}$  (393 mg, 1.5 mmol) and  $\text{Et}_3\text{N}$  anh. (101 mg, 1 mmol) in anh.  $\text{CH}_2\text{Cl}_2$  (30 mL), was added  $\text{CCl}_4$  (154 mg, 1 mmol). After 15 h reflux, the solvent was removed by distillation and the residue chromatographed (silica gel, petroleum ether /  $\text{Me}_2\text{CO}$ ). The product in water :  $\text{Me}_2\text{CO}$  (1:1, 40 mL) and conc  $\text{H}_2\text{SO}_4$  (5 drops) was refluxed for 3 h. Evaporation of the solvent and recrystallization from petroleum ether afforded 168 mg of **5** (89%), mp 255-257°C.



## ARNDT-EISSERT Homologation

Homologation of carboxylic acids or ketones via diazocompounds (see 1st edition).

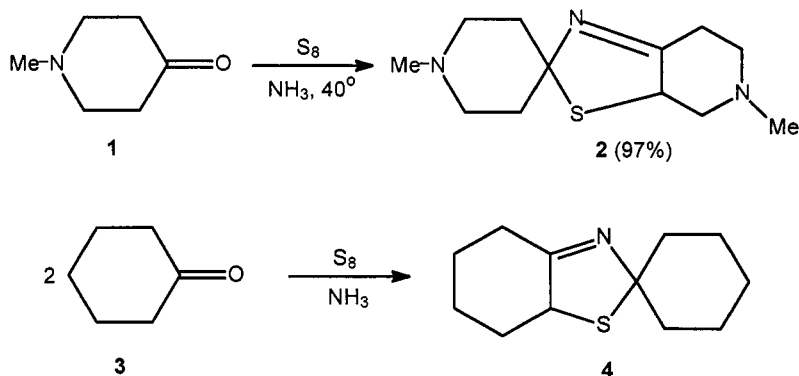


1	Eistert, B.; Arndt, F.	<i>Chem. Ber.</i>	1927	60	1364
2	Barbier, F.	<i>Helv. Chim. Acta</i>	1940	23	523
3	Gokel, G.	<i>Synthesis</i>	1976		181
4	Aryama, T.	<i>Chem. Pharm. Bull.</i>	1981	29	3249
5	Smith, A.B.	<i>J. Am. Chem. Soc.</i>	1986	108	3110
6	Weigand, F.	<i>Angew. Chem.</i>	1960	72	535
7	Bachmann, W.E.	<i>Org. React.</i>	1942	1	38

**Ketones 2 and 3.**<sup>2</sup> To cooled **1** (100 g; 0.71 mol) in MeOH (225 mL) and 50% KOH was added slowly nitrosomethylurea (74 g; 0.68 mol) at 0°C so that the solution became colorless before the next portion was added. After several hours filtration neutralization with AcOH and distillation afforded a mixture of **2** and **3**, bp 70-95°C/11 mm, see also ref 4.

## ASINGER Thiazoline Synthesis

Synthesis of thiazolines from ketones, sulfur and  $\text{NH}_3$  with the possibility to obtain thioketones.



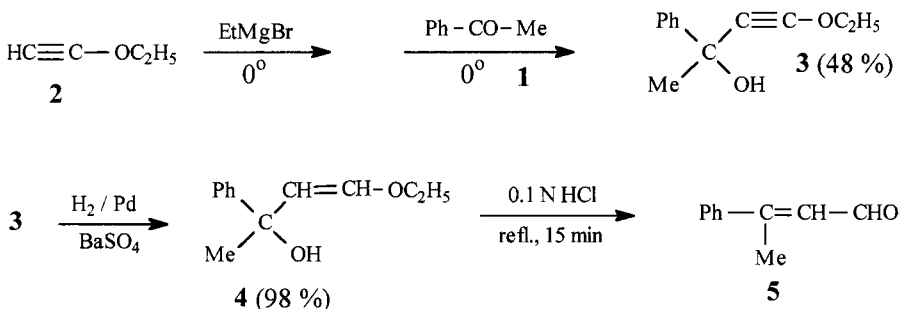
1	Asinger, F.	<i>Liebigs Ann.</i>	<b>1957</b>	602	37
2	Asinger, F.	<i>Liebigs Ann.</i>	<b>1957</b>	606	67
3	Asinger, F.	<i>Liebigs Ann.</i>	<b>1964</b>	674	57
4	Asinger, F.	<i>Angew. Chem.</i>	<b>1958</b>	70	372
5	Lyle, E. R.	<i>J. org. Chem.</i>	<b>1965</b>	30	293
6	Domling, A.	<i>Tetrahedron</i>	<b>1995</b>	51	755

**1, 6-Dimethyl-2',4',5',6',7',7'-a-hexahydrospiro piperidine-4,2-thiazolo [5,4-c]pyridine. 2HCl (2).**<sup>5</sup> A stirred and ice cooled suspension of sulfur (6.0 g, 187 mmol) in 1-methyl-4-piperidone **1** (40 g, 354 mmol) was treated with a flow of  $\text{NH}_3$  maintaining the temperature between 40-50 °C. The bubbling of  $\text{NH}_3$  was continued until all traces of sulfur disappeared (ca 2). The excess of  $\text{NH}_3$  was removed in vacuum, the mixture was diluted with 50%  $\text{K}_2\text{CO}_3$  solution (200 mL) and extracted with  $\text{Et}_2\text{O}$  (5×100 mL). The dried solution ( $\text{K}_2\text{CO}_3$  anh) was treated with dry HCl. The solid was filtered, washed ( $\text{Et}_2\text{O}$ ) and dried (vacuum) to give 53.5 g of **2. HCl** (97.8%), mp 200-205 °C. After recrystallization, mp 240-241 °C( $\text{EtOH}:\text{iPrOH}$ ).

**2,2-Pentamethylene-4,5-tetramethylene-3-thiazoline (4).**<sup>2</sup> Into a mixture of sulfur (32 g, 1 mol) in cyclohexanone **3** (196 g, 2 mol) was bubbled a stream of  $\text{NH}_3$  at 40-50 °C for 1-2 h. After another 30 min bubbling of  $\text{NH}_3$  under gentle heating at the same temperature, usual work up and vacuum distillation afforded 170 g of **4** (80%), mp 81.5-82 °C, bp 156-157 °C/11 mm.

**ARENS – VAN DORP** Cinnamaldehyde Synthesis

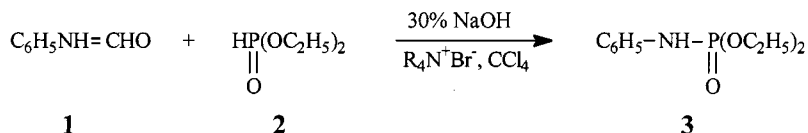
Synthesis of cinnamaldehydes from aryl ketones, and ethoxyacetylene (see 1st edition).



- |   |                            |                          |             |     |      |
|---|----------------------------|--------------------------|-------------|-----|------|
| 1 | Arens, J.F., v. Dorp, A.D. | <i>Nature</i>            | <b>1947</b> | 160 | 189  |
| 2 | Isler, O.                  | <i>Helv. Chim. Acta</i>  | <b>1956</b> | 39  | 259  |
| 3 | Kell, P.S.                 | <i>J. Am. Chem. Soc.</i> | <b>1959</b> | 81  | 4117 |

**ATHERTON – TODD** Phosphoramidate Synthesis

Synthesis phosphoramidates from formamides and dialkyl phosphite (see 1st edition).

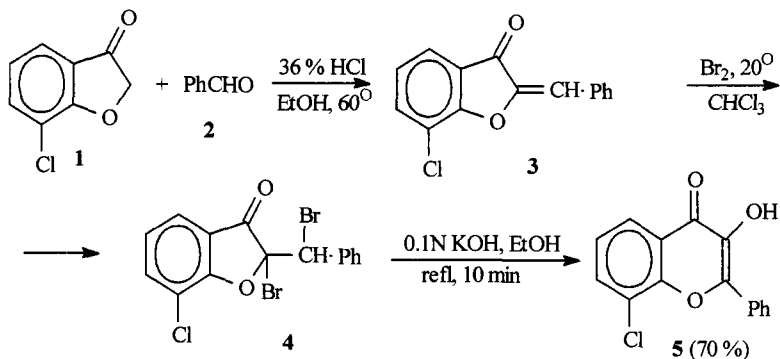


- |   |                            |                                |             |         |
|---|----------------------------|--------------------------------|-------------|---------|
| 1 | Atherton, F.R., Todd, A.R. | <i>J. Chem. Soc.</i>           | <b>1945</b> | 660     |
| 2 | Wadsworth, W.S.            | <i>J. Am. Chem. Soc.</i>       | <b>1962</b> | 84 1316 |
| 3 | Zwierzak, A.               | <i>Synthesis</i>               | <b>1982</b> | 922     |
| 4 | Lukanow, L.K.              | <i>Synthesis</i>               | <b>1985</b> | 671     |
| 5 | Hovalla, D.                | <i>Tetrahedron Lett.</i>       | <b>1992</b> | 33 2817 |
| 6 | Garrigue, B.               | <i>Synth. Commun.</i>          | <b>1995</b> | 25 871  |
| 7 | Liu, L.Z.                  | <i>Org. Prep. Proced. Int.</i> | <b>1996</b> | 28 490  |

**Diethyl N-phenylphosphoramidate (3).**<sup>4</sup> To an ice cooled stirred suspension of formylanilide **1** (605 mg, 5mmol) in  $\text{CHCl}_4$  (25 mL) was added 30 % NaOH (10 mL) and benzyltriethylammonium bromide (0.2 g). Diethyl phosphite **2** (828 mg, 6 mmol) in  $\text{CCl}_4$  (5 mL) was added dropwise. After 1 h at  $0^\circ$  and 4 h at  $20^\circ\text{C}$ , the organic layer gave **3**, after crystallization, 0.687 g (60 %), mp  $96\text{--}97^\circ\text{C}$ .

**AUWERS Flavone Synthesis**

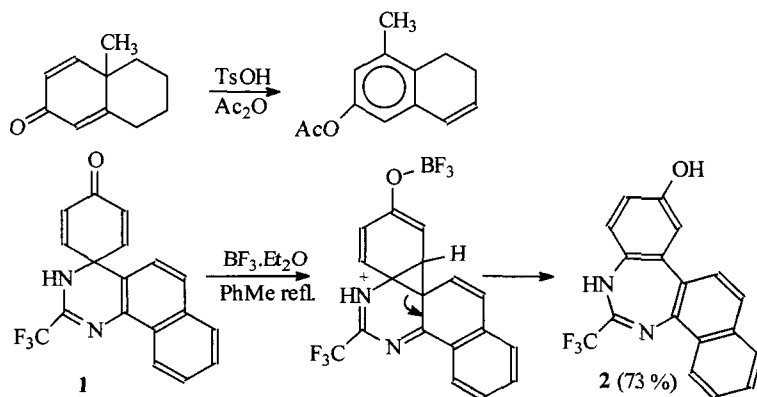
Synthesis of benzopyran-4-ones (flavones) from o-hydroxychalcones or from benzofuran-3-ones (see 1st edition).



1	Auwers, K.	<i>Chem. Ber.</i>	<b>1908</b>	41	4233
2	Minton, T. H.	<i>J. Chem. Soc.</i>	<b>1922</b>	121	1598
3	Ingham, B. H.	<i>J. Chem. Soc.</i>	<b>1931</b>		895
4	Acharya, B. C.	<i>J. Chem. Soc.</i>	<b>1940</b>		817

**AUWERS – INHOFFEN Dienone–Phenol Rearrangement**

Rearrangement of dienones to phenols catalyzed by acids.



1	Auwers, K.	<i>Liebigs Ann.</i>	<b>1921</b>	425	217
2	Inhoffen, C.	<i>Angew. Chem.</i>	<b>1940</b>	53	473
3	Djerassi, C.	<i>J. Am. Chem. Soc.</i>	<b>1951</b>	73	990
4	Winstein, S.	<i>J. Am. Chem. Soc.</i>	<b>1957</b>	79	3109
5	Eneyama, K.	<i>J. Org. Chem.</i>	<b>1995</b>	60	6402