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Reduction of Phenyl Trifluoromethyl Ketone with Halomagnesium Alkoxides. An Almost Irreversible Meerwein–Ponndorf–Verley-Type System

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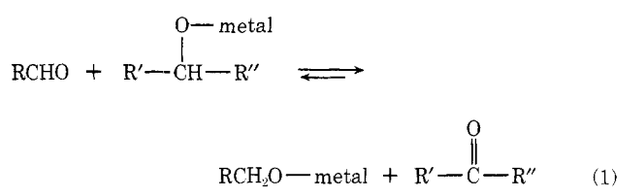
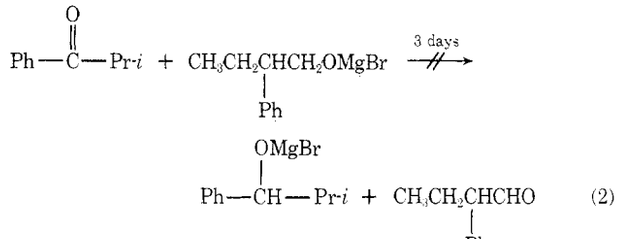
Phenyl trifluoromethyl ketone is reduced rapidly by both primary and secondary bromomagnesium alkoxides to phenyltrifluoromethylcarbinol (as the bromomagnesium salt). Using deuterium-labled alkoxides and chiral alkoxides it was shown that whereas Meerwein–Ponndorf–Verley-type reduction of phenyl trifluoromethyl ketone is facile, the alkoxide produced has little tendency to transfer its hydride to acceptor carbonyl compounds present in the reaction mixture. The electron-withdrawing inductive effect of the trifluoromethyl group is believed to be responsible for this behavior.

Meerwein–Ponndorf–Verley-type reductions (MPV reductions) are equilibrium reactions[1,2] which show a strong preference for the formation of primary alcoholate and ketone in equilibria involving primary and secondary alcoholates[3] (eq 1). A few examples of reductions of ketones by

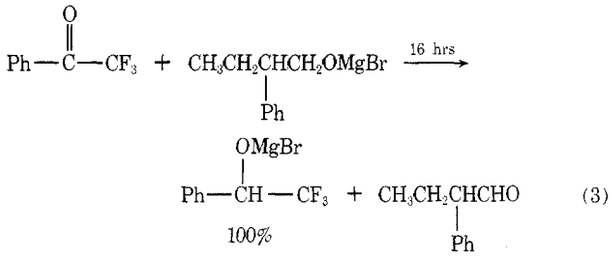


primary alcoholates have been reported[4] but in these cases the reaction was forced to completion by distillation of the aldehyde as it was formed.

In agreement with the above view of the MPV-type reaction we found that treatment of isopropyl phenyl ketone with 2-phenyl-1-butoxymagnesium bromide in ether–benzene at room temperature for 3 days gave no detectable (glpc) amount of isopropylphenylcarbinol after hydrolysis (eq 2). In contrast, we found that phenyl trifluoromethyl



ketone was essentially completely reduced in 16 hr by 2-phenylbutoxymagnesium bromide in ether–benzene at room temperature (eq 3). A similar reaction between 2-



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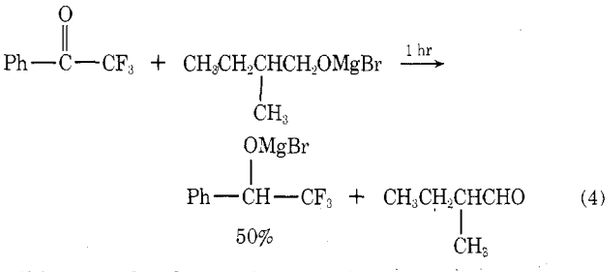
methyl-1-butoxymagnesium bromide and phenyl trifluoromethyl ketone was 50% complete in only 1 hr (eq 4). Also



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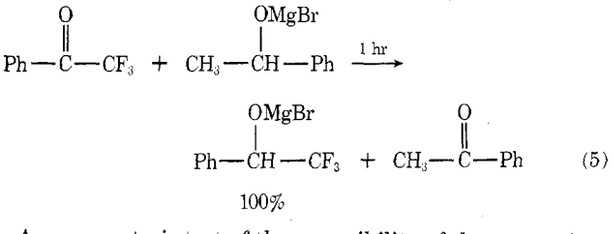
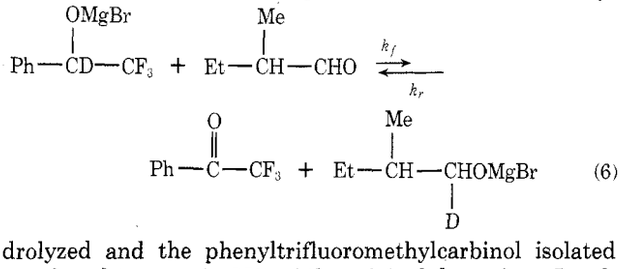
striking was the observation that the bromomagnesium salt of methylphenylcarbinol completely reduced phenyl trifluoromethyl ketone in only 1 hr under the same conditions (eq 5).



(5)

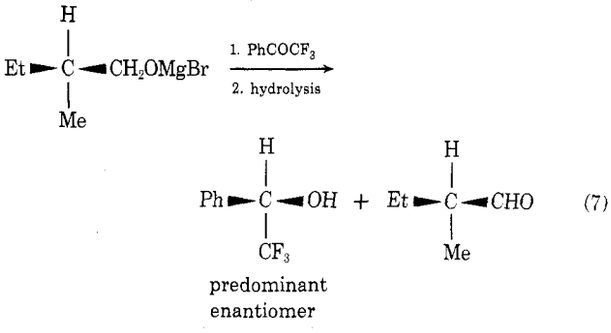
A more esoteric test of the reversibility of the magnesium alkoxide reduction of phenyl trifluoromethyl ketone was also carried out. The bromomagnesium salt of phenyltrifluoromethylcarbinol labeled with deuterium at the carbinol carbon was allowed to stand in ether–benzene solution with 2-methylbutanal for 36 hr (eq 6). The solution was then hy-



(6)

drolyzed and the phenyltrifluoromethylcarbinol isolated was found to contain 95% of the original deuterium. In addition to the driving force toward primary alcoholate the 2-methylbutanal substrate provides a partial "trap" for any deuterium that is transferred from the phenyltrifluoromethylcarbinol salt by virtue of the isotope effect which would favor the loss of hydrogen rather than deuterium from the primary alcoholate in the reverse reaction. Therefore, the very small loss of deuterium implies that there is little tendency for the phenyltrifluorocarbinol salt to transfer its carbinol hydrogen to an aldehyde. Yet, as eq 4 indicates, unlabeled 2-methylbutoxymagnesium bromide reduces phenyl trifluoromethyl ketone rapidly. Thus it is clear that $k_r \gg k_f$; the reduction of phenyl trifluoromethyl ketone by primary or secondary bromomagnesium alkoxides is negligibly reversible at room temperature in ether–benzene solvent for reaction times sufficient to allow appreciable reduction of the ketone. In other words, for all practical purposes such reductions come close to being kinetically controlled.

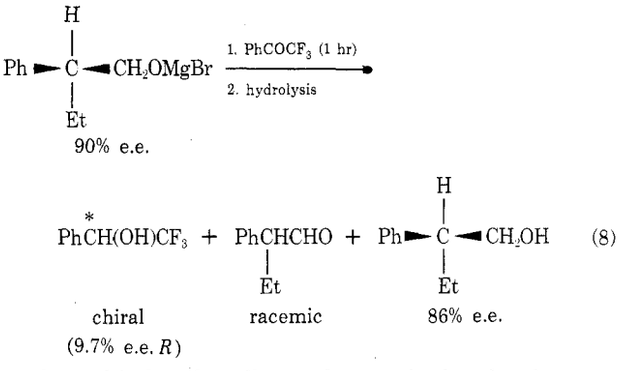
Additional evidence was provided by experiments with salts of optically active alcohols as reducing agents. For example, when phenyl trifluoromethyl ketone was reduced with (*S*)-2-methyl-1-butoxymagnesium bromide (98% optical purity) the phenyltrifluoromethylcarbinol obtained on hydrolysis was enriched in the *R* enantiomer to the extent of 4.9% for a reaction time of 1 hr (eq 7). When the same re-



(7)

duction was allowed to proceed for 26 hr a 5.3% e.e. of the *R* enantiomer was obtained.[5] In other words, there was, within experimental error, no change in per cent enantiomeric excess with an extended reaction time. This is in contrast to most asymmetric MPV-type reductions, which tend toward racemized product as the reaction time is lengthened owing to the equilibrium nature of the reaction (thermodynamic control).[6]

Furthermore, in a study of the reaction of (*S*)-2-phenyl-1-butoxymagnesium bromide (90% e.e.) with phenyltrifluoromethyl ketone (eq 8), it was found that the aldehyde by-



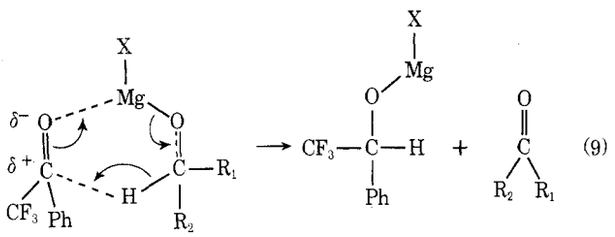
(8)

product, chiral 2-phenylbutanal, racemized under the reaction conditions. However, in an incomplete reaction (ether–benzene solvent, 1 hr reaction time) unreacted alcoholate was hydrolyzed to 86% e.e. (*S*)-2-phenyl-1-butanol. The racemized aldehyde by-product could, in principle, revert to racemic 2-phenyl-1-butoxymagnesium bromide by a MPV-type reaction with the bromomagnesium salt of phenyltrifluoromethylcarbinol or by the same type of reaction with unreacted, chiral 2-phenyl-1-butoxymagnesium bromide. Apparently under the reaction conditions used it undergoes neither of these reactions to a significant extent. Substantial equilibration by either pathway would be reflected in a significantly lower per cent enantiomeric excess for the recovered 2-phenyl-1-butanol from hydrolysis of the 2-phenyl-1-butoxymagnesium bromide. In fact, the enantiomeric purity of recovered 2-phenyl-1-butanol was only 4% lower than that of the starting material.

The results described in this paper are explicable in terms of the mechanism of MPV-type equilibrations and the electronic influence of the trifluoromethyl group. Dis-

parate chemical behavior for carbonyl groups adjacent to perfluoroalkyl groups is a recognized phenomenon.[7]

Compared to the reduction of sterically similar phenyl alkyl ketones the reduction of phenyl trifluoromethyl ketone with a halomagnesium alkoxide should take place more readily, because the strongly electron-withdrawing trifluoromethyl group will make the carbonyl carbon relatively more positive. This will facilitate a hydride-like transfer from the halomagnesium alkoxide, possibly *via* a reduction mode like that represented in eq 9.[8] In order for



(9)

the reverse reaction to occur the halomagnesium salt of phenyltrifluoromethylcarbinol would have to undergo loss of "hydride" from the carbinol carbon. It seems reasonable to expect this process to be impeded by the inductive influence of the trifluoromethyl group. Thus the inductive effect rationalizes both the fact that phenyl trifluoromethyl ketone is rapidly reduced and the fact that once hydrogen is transferred to this ketone it "sticks." Because the MPV-type reduction of phenyl trifluoromethyl ketone is so facile and is an "almost irreversible" reaction a quantitative stereochemical comparison of a wide variety of chiral halomagnesium alkoxide reducing agents under "kinetically controlled" conditions is made feasible. With other ketones meaningful comparisons of the stereochemical results of asymmetric MPV-type reductions with different reducing agents, as well as examples of high asymmetric reduction, are not readily attainable. In many cases the ketone is not readily reduced or partial racemization makes quantitative stereochemical comparisons unwarranted, or both factors conspire to prevent such investigations. We intend to elaborate the stereochemical details of asymmetric MPV-type reductions of phenyl trifluoromethyl ketone in future publications.

The asymmetric reductions reported in this paper (eq 7 and 8) involve competitive transfer of diastereotopic hydrogens from chiral alkoxides to enantiotopic faces of the ketone. In terms of the symmetry arguments that apply to such systems these reductions are similar to certain asymmetric Grignard reductions that have been described previously.[9,10]

Experimental Section

2,2,2-Trifluoro-1-phenylethanol-*1-d*. The deuterium-labeled alcohol was prepared by hydrogenation of trifluoromethyl phenyl ketone (10.4 g, 0.060 mol) with deuterium using ethyl acetate (150 ml) as solvent and predeuterated 5% palladium on carbon as catalyst. Deuterium uptake stopped short of the theoretical amount, but no attempt was made to complete the reaction because the ketone and carbinol are readily separated by distillation. The carbinol was isolated as a clear liquid, bp 73–75° (10 mm) (6.0 g, 58% yield), shown by integration of its nmr spectrum to contain 21% hydrogen at the carbinol position (average of 30 integrations).

(+)-(*S*)-2-Phenylbutanoic Acid. 2-Phenylbutanoic acid was resolved following the procedure of Levine and coworkers.[11] Racemic acid (100 g, 0.61 mol) provided, after four recrystallizations of the cinchonidine salt from 70% ethanol–water, hydrolysis, and distillation, (+)-(*S*)-2-phenylbutanoic acid (60.5 g, 0.37 mol) as a clear liquid: bp 120–122° (1.0 mm); $[\alpha]^{27}D$ +83.9°)neat); 88% e.e. based on a maximum rotation of $[\alpha]^{23}D$ +95.8° (neat).[12]

The mother liquors from several cinchonidine resolutions were combined, evaporated, and hydrolyzed to furnish (−)-(*R*)-2-phenylbutanoic acid: bp 117–118° (0.4 mm); $[\alpha]^{25}D$ −58.4° (neat); 61% e.e.

(+)-(*S*)-2-Phenyl-1-butanol. The *S* alcohol was prepared by the reduction of (+)-(*S*)-2-phenylbutanoic acid, $[\alpha]^{27}D$ +83.9° (neat), 88% e.e. (25.0 g, 0.152 mol), with $LiAlH_4$ (7.0 g, 0.18 mol) in ether (150 ml). After acid hydrolysis, the alcohol (18.4 g, 81%) was isolated as a clear liquid: bp 63–69° (0.4 mm); $[\alpha]^{25}D$ +14.9° (neat); 90% e.e., based on a maximum rotation of $[\alpha]^{25}D$ +16.5° (neat).[13]

Meerwein–Ponndorf–Verley Reductions. A round-bottomed, three-necked flask fitted with a magnetic stirrer, pressure-equalizing addition funnel, reflux-distillation head, septum cap, and nitrogen inlet was flamed dry under a stream of nitrogen. An aliquot of a filtered and standardized solution of *n*-propylmagnesium bromide in ether was injected with a nitrogen-flushed syringe. The alcohol precursor of the magnesium alkoxide was added in benzene *and the solvent composition was adjusted by distillation to a constant boiling point of 55–56°*. The ketone to be reduced was then added in one portion in a small amount of dry benzene to provide clear, homogeneous solutions about 1 *M* in alcoholate. The mixture was stirred at ambient temperatures for the stated reaction time, before being hydrolyzed with ammonium chloride solution. The organic layer was separated, combined with two or three ether extracts of the aqueous layer, dried ($MgSO_4$), and concentrated. Trifluoromethyl phenyl ketone and trifluoromethylphenylcarbinol give very characteristic infrared absorptions at 960 and 1270 cm^{-1}, respectively, which allowed a semiquantitative analysis of the extent of reduction to be carried out on the crude products. The carbinol and ketone were partially separated by distillation and the trifluoromethylphenylcarbinol was purified by preparative glpc on Carbowax 20M (180°) and Apiezon L (175°) columns. Rotation samples of trifluoromethylphenylcarbinol were analyzed by glpc and ir and shown to contain less than 1% of achiral by-products and much less than 1% of any chiral impurities. The ir spectra of purified products were all identical with that of a carefully purified sample of phenyltrifluoromethylcarbinol, and were especially revealing in the region of 2800–3000 cm^{-1} (aliphatic C–H stretch). Most impurities absorb strongly in this region but phenyltrifluoromethylcarbinol gives only a weak absorption.

Reduction of 2-Methylbutanal with 2,2,2-Trifluoro-1-phenylethoxymagnesium Bromide-*1-d* in Ether-Benzene. The alcoholate was prepared from 2,2,2-trifluoro-1-phenylethanol-*1-d* (5.00 g, 0.0284 mol) containing 21% hydrogen at the carbinol position, by reaction with ethereal *n*-propylmagnesium bromide (18 ml, 1.7 *N*, 0.030 mol) in dry benzene. The solvent composition was adjusted by distillation to 55–56°, 2-methy-1-butanal (4.90 g, 0.057 mol) in a small amount of dry benzene was added, and the mixture was stirred for 36 hr. The ir spectrum of the crude product mixture showed that both trifluoromethylphenylcarbinol and 2-methylbutanol were present. The work-up gave 4.3 g of liquid, bp 70–76° (10 mm), which on preparative glpc furnished a sample of trifluoromethylphenylcarbinol shown by integration of its nmr spectrum to contain 25% hydrogen at the carbinol position (average of 30 integrations).

Reduction of Phenyl Trifluoromethyl Ketone. With (*S*)-2-Methyl-1-butoxymagnesium Bromide in Ether–Benzene, 1 Hr. The alcoholate was prepared from an ether solution of *n*-propylmagnesium bromide (30 ml, 1.6 *N*, 0.048 mol) and (−)-(*S*)-2-methyl-1-butanol, $\alpha^{26}D$ −4.70° (neat), 98% e.e. (4.40 g, 0.050 mol), in dry benzene. Solvent composition was adjusted by distillation to 55–56°. Trifluoromethyl phenyl ketone (8.5 g, 0.048 mol) dissolved in a small amount of dry benzene was added, and the mixture was stirred for 1 hr. The ir spectrum of the crude product mixture indicated that about 50% reduction had occurred. After work-up, distillation gave three fractions: 0.5 g, bp 122–130° (1 atm); 2.8 g, bp 30–70° (10 mm); and 3.6 g, bp 73–95° (10 mm). Preparative glpc of fraction 3 gave trifluoromethylphenylcarbinol: $\alpha^{21}D$ −2.03° (neat, l = 1) [lit.[14] $\alpha^{26}D_{max}$ −41.18° (neat, l = 1), $[\alpha]^{26}D$ −31.85°]; 4.9% e.e.

With (*S*)-2-Methyl-1-butoxymagnesium Bromide in Ether–Benzene, 26 Hr. The alcoholate was prepared from an ether solution of *n*-propylmagnesium bromide (28 ml, 1.7 *N*, 0.048 mol) and (−)-(*S*)-2-methyl-1-butanol, $\alpha^{26}D$ −4.70° (neat), 98% e.e. (4.40 g, 0.050 mol), in dry benzene. Solvent composition was adjusted by distillation to 55–56°. Trifluoromethyl phenyl ketone (7.80 g, 0.045 mol) was added in a small amount of dry benzene and the mixture was stirred for 26 hr. Distillation of the products gave 5.4 g of material, bp 73–75° (10 mm), $\alpha^{21}D$ − 2.04° (neat), which on preparative glpc furnished phenyltrifluoromethylcarbinol, $\alpha^{19}D$ −2.20° (neat, l = 1), 5.3% e.e.[14]

With (S)-2-Phenyl-1-butoxymagnesium Bromide in Ether–Benzene, 1 Hr. The alcoholate was prepared from an ether solution of *n*-propylmagnesium bromide (31 ml, 1.6 *N*, 0.050 mol), (+)-(*S*)-2-phenyl-1-butanol, $\alpha^{25}D$ +14.9° (neat), 90% e.e. (8.25 g, 0.055 mol), in dry benzene. Solvent composition was adjusted by distillation to 55–56°. Trifluoromethyl phenyl ketone (8.50 g, 0.048 mol) dissolved in a small amount of dry benzene was added to provide a clear solution which formed a precipitate while the reaction mixture was stirred for 1 hr. Work-up gave four fractions: 2.3 g, bp 32–70° (10 mm); 3.2 g, bp 70–90° (10 mm); 1.2 g, bp 90–105° (10 mm); and 3.9 g, bp 86–90° (1 mm). Preparative glpc of the second fraction provided trifuloromethylphenylcarbinol, $\alpha^{26}D$ −4.0° (neat, l = 1), 9.7% e.e., and a sample of 2-phenylbutanal, $\alpha^{27}D$ 0.000° (neat). Preparative glpc of the fourth fraction provided (+)-(*S*)-2-phenyl-1-butanol, $[\alpha]^{27}D$ +14.25° (neat), 86% e.e.

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Registry No.—(+)-(*S*)-2-Phenylbutanoic acid, 4286-15-1; (−)-(*R*)-2-phenylbutanoic acid, 938-79-4; (+)-(*S*)-2-phenyl-1-butanol, 33442-47-6; trifluoromethyl phenyl ketone, 434-45-7; 2-methylbutanal, 96-17-3; 2,2,2-trifluoro-1-phenyl-ethanol-*1-d*, 2793-54-6; *n*-propyl bromide, 106-94-5; (−)-(*S*)-2-methyl-1-butanol, 1565-80-6; (−)-trifluoromethylphenylcarbinol, 10531-50-7.

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Preparation and Aluminum Chloride Induced Rearrangement of Cyclopropylpyridines

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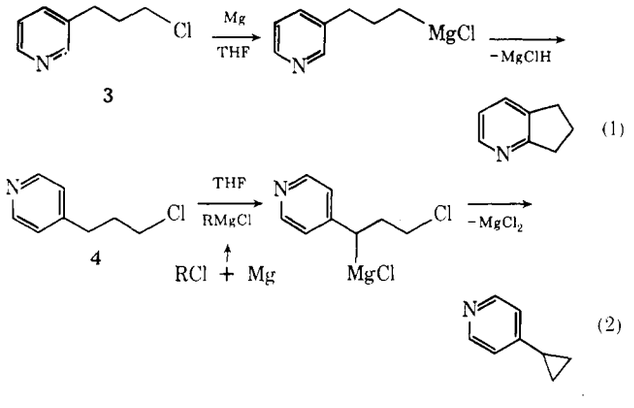
A convenient, two-step preparation of both 2- and 4-cyclopropylpyridines from the corresponding 3-(2- or 4-pyridyl)propanols consists of treatment with thionyl chloride and dehydrohalogenation of the resulting chlorides with potassium *tert*-butoxide. The analogous 3-(3-pyridyl)propanol was converted to *trans*-3-propenylpyridine by a similar procedure. Although the 2- and 4-cyclopropylpyridines were remarkably stable to strong bases, mineral acids, heat, and ultraviolet radiation, they did decompose at *ca.* 400° and were especially reactive toward anhydrous aluminum chloride at 25–45°. Thermally, the 2 isomer yielded 2-picoline, 2-*n*-propylpyridine, ethylene, acetylene, and polymeric material. In the presence of aluminum chloride, both the 2 and 4 isomers gave the corresponding *trans*-propenyl-, isopropenyl-, (2-chloropropyl)-, and (1-chloro-2-propyl)pyridines.

A recent study[1] of the carbocyclization reactions of pyridine derivatives has uncovered two novel reactions of synthetic potential: (1) the first formation of carboannulated pyridine derivatives by intramolecular nucleophilic attack[2] (eq 1); and (2) the detection of 4-cyclopropylpyridine from the reaction of 4-(3-chloropropyl)pyridine with magnesium metal (eq 2). Since the existing syntheses of cyclopropylpyridines are limited in number and in scope, the dechlorometalative closure to the cyclopropane, depicted in eq 2, seemed worth developing as a new synthetic method. Many of the known methods involve more steps or are low yielding.[3] Another approach, namely, the addition of diazoalkanes[4] or sulfonium methylides[5] to vinylpyridines, gives good yields and is convenient, if the appropriate pyridine starting material is available.



The cyclization of 2- and 4-(3-chloropropyl)pyridines by base has proved to be an advantageous route to the respective cyclopropylpyridines, because the conversion of the commercially available propanols to the chloropropanes and thence to the cyclopropanes requires only two steps and gives good overall yields. The enhanced acidity of the methylene groups α to the ring permits a facile formation of the anionic center needed for ring closure (*cf.* eq 2). With the use of 2 equiv of potassium *tert*-butoxide these reactions could be carried out on the isolated, but unpuri-