From the foregoing, it is apparent that treatment of a complex, substituted hydrocarbon substrate with either elemental fluorine or a fluoroxy reagent (with radical inhibitor) comprises an effective, predictable, and regioselective process for substitution at saturated carbon.[12]

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(5) Fluorinations were carried out as in ref 4, solvents used were mixtures of $CFCl_3$ and $CHCl_3$ or CH_2Cl_2. All reactions were carried out under aerobic conditions in the presence of excess sodium trifluoroacetate and/or anhydrous sodium fluoride to prevent HF catalyzed elimination of HF.

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(9) The 14α-fluoro-17-keto compounds **3b** and **7** differed from the 14α-H parents by $\Delta M_D \sim -20°$. The 14α-fluoro-17β-acetyl compounds **4b** and **8** differ from the 14α-H parents by $\Delta M_D \sim +30°$. In the case of analogous 14-hydroxylated compounds the 14β-series has $\Delta M_D \sim -180$ to $-200°$ (S. H. Eppstein, P. D. Meister, D. H. Peterson, H. C. Murray, H. M. L. Osborn, A. Weintraub, L. M. Reineke, and R. C. Meeks, *J. Am. Chem. Soc.*, **80**, 3382 (1958), and F. Sondheimer, S. Burstein, and R. Mechoulam, *ibid.*, **82**, 3209 (1960)) while ΔM_D for 14α-hydroxylation is -40 to $-60°$ for the ketone and $\sim+40°$ for the 17β-acetyl side chain (Eppstein et al., *ibid.*). Again on the basis of substituent effects on the 19CH_3 resonances and the approximately equal effects of OH and F, one would expect the CH_3 resonance of a 14β-fluoro-17β-acetyl isomer of **4b** or **8** to occur at $\sim\delta$ 0.9 ppm while that of a 14α-epimer should occur at $\sim$0.73 ppm. The observed value for **4b** and **8** is 0.77 ppm (N. S. Bhacca and D. H. Williams "Applications of NMR spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964). Under conditions which readily epimerize 14β,17β-acetyl compounds the 14α-fluoro-17β-acetyl compounds described here were stable. This supports the configurations assigned.

(10) The location and configuration of the fluorine in compounds **9b** and **9d** follow clearly from NMR spectral data. We have observed the 9α-fluorine to resonate at 179–180 and the 14α-fluorine to resonate at 160–162. In each case the resonance appears as a broad multiplet. In the case of **9d** and **9b** the fluorine resonance occurs at 170 and is in each case a quartet, J = 31 Hz, indicative of equivalent coupling to three hydrogens (16α, 16β, and 20). This pattern is inconsistent with fluorine in any position save 17.

(11) The compound clearly bears a 17α-fluorine (^{19}F NMR: 170 ppm, quartet, J = 31 Hz). The second fluorine which resonates at 135.5 ppm ($W/2$ = 45 Hz) is clearly tertiary and is not located at C_5, 9, or 14. The ^{1}H resonance of the hydrogens at C-26 and C-27 has been shifted downfield by 0.48 ppm with respect to cholesterol and these hydrogens resonate as a doublet (J = 20 Hz), parameters consistent with the presence of a 25-fluorine substituent.

(12) All new compounds had the correct composition established by microanalysis. Optical rotations were measured in $CHCl_3$ on ca. 1% solution, ^{1}H NMR spectra were measured in $CDCl_3$ and reported as shifts downfield from internal Me_4Si (δ). ^{19}F NMR spectra were measured in $CHCl_3$ and reported as shifts upfield from internal $CFCl_3$ (ϕ^*). Complete ^{13}C NMR spectra were obtained for representatives 9α-, 14α-, and 17α-fluorinated steroids. In each case the spectra supported the assigned structures and stereochemistry. We thank Drs. L. Phillips and R. B. Jones (Imperial College, London), for these measurements which (with interpretation) will be published by them elsewhere.

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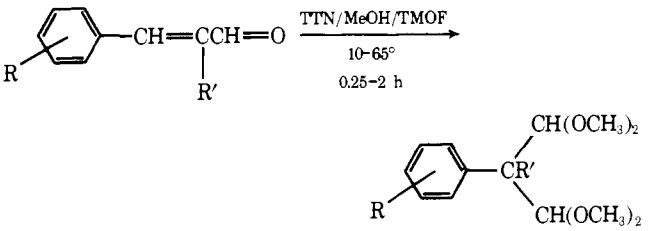
Novel Oxidative Rearrangements with Thallium(III) Nitrate (TTN) in Trimethyl Orthoformate (TMOF)[1]

Sir:

Thallium(III) nitrate (TTN), since its introduction several years ago as a conveniently prepared, highly specific, and often unique oxidant,[2] has been used to effect a wide variety of organic transformations.[3-12] The commonly employed solvents for these reactions have been dilute nitric acid, acidic methanol, or aqueous glyme containing perchloric acid. There have been reports, however, of disappointing failures with these reagent/solvent combinations. For example, α,β-unsaturated aldehydes, ketones, and esters react very slowly to give complex mixtures of products; *seven* products are obtained upon attempted oxidation of cinnamaldehyde in dilute nitric acid, four of which were identified as phenylacetaldehyde, phenylglyoxal, phenylglyoxylic acid, and benzaldehyde.[12]

Scheme I. Conversion of Cinnamaldehydes to Arylmalondialdehyde Tetramethylacetals



(a) R = R' = H, 79%
(b) R = 4-CH_3O, R' = H, 84%
(c) R = 4-O_2N, R' = H, 63%
(d) R = H, R' = CH_3, 83%
(e) R = 3-O_2N, R' = CH_3, 50%

We wish to report the remarkable effectiveness of methanol/trimethyl orthoformate (MeOH/TMOF) (1:1) or of TMOF alone as solvents for certain TTN-mediated oxidations. Reactions such as the above, which fail in the usual solvents, proceed rapidly and cleanly in MeOH/TMOF; in addition, strikingly different products are obtained with some substrates in MeOH/TMOF rather than MeOH itself. These results are summarized below.

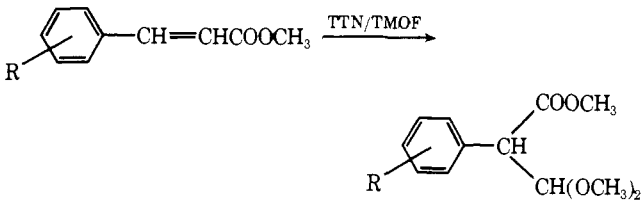
We have found that cinnamaldehydes rearrange cleanly with TTN/MeOH/TMOF to give arylmalondialdehyde tetramethylacetals. It is remarkable that this conversion proceeds in good yield even when the migrating group is *p*-nitrophenyl (see Scheme I). This transformation proceeds by an initial TTN-catalyzed conversion of the cinnamaldehyde to its dimethylacetal;[13] the oxidative rearrangement which then follows methoxythallation is analogous to the TTN-mediated rearrangement of styrene to phenylacetaldehyde.[9]

The above arylmalondialdehyde synthesis from cinnamaldehydes constitutes a potentially general synthetic method for the conversion of an aryl CHO into a *tert*-butyl substituent. Thus, benzaldehyde was converted into α-methylcinnamaldehyde by aldol condensation with propionaldehyde. Oxidative rearrangement with TTN/MeOH/TMOF then gave methylphenylmalondialdehyde tetramethylacetal. Acid-catalyzed exchange with ethanedithiol, followed by reduction under Wolff–Kischner conditions, gave *tert*-butylbenzene. This conversion can obviously be readily adapted to the synthesis of *gem*-dimethyl derivatives of the type $ArC(CH_3)_2R$, a substitution pattern laborious to introduce by classical methods.

Although cinnamic esters have been reported to react slowly or not at all with TTN/MeOH,[12] we have found that these substrates, in analogous fashion to cinnamaldehydes, are smoothly rearranged with TTN/MeOH/TMOF or TTN/TMOF to methyl α-(dimethoxymethyl)arylacetates. Some typical conversions are reported in Scheme II.

Acetophenone rearranges smoothly to methyl phenylacetate on treatment with 1 equiv of TTN in MeOH.[10] With MeOH/TMOF as solvent, however, *2* mol of TTN are consumed, and the product is methyl α-methoxyphenylacetate. Methyl phenylacetate itself is not an intermediate in this conversion, since it is recovered unchanged under the reaction conditions. We have been able to show that α-methoxystyrene (from TTN-catalyzed loss of methanol from acetophenone dimethylketal) and the trimethyl orthoester of phenylacetic acid are both intermediates in this conversion, which therefore

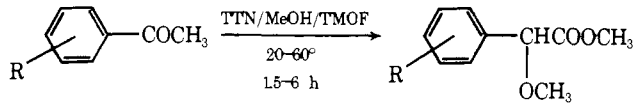
Scheme II. Conversion of Methyl Cinnamates to Methyl α-(Dimethoxymethyl)arylacetates



(a) R = H, 96%[a]
(b) R = 4-CH_3, 96%[a]
(c) R = 4-CH_3O, 90%[b]
(d) R = 2-F, 83%[a]
(e) R = 4-Cl, 96%[a]

[a] Reaction run under reflux. [b] Reaction run at 20°.

Scheme III. Conversion of Acetophenones to Methyl α-Methoxyarylacetates



(a) R = H, 70%
(b) R = 4-CH_3O, 81%
(c) R = 4-O_2N, 87%
(d) R = 3-C_6H_5O, 97%

involves two successive methoxythallation reactions. The first utilizes α-methoxystyrene as substrate, and involves an aryl migration; the second utilizes phenylketene dimethylketal as substrate, and terminates with oxidative displacement of thallium by methanol. This synthesis of methyl α-methoxyarylacetates is general; some representative conversions are summarized in Scheme III.

We have observed α-methoxylation of other carbonyl compounds under the same reaction conditions. For example, cyclohexanone and cyclopentanone are converted to their respective α-methoxyketals, phenylacetaldehyde is converted to α-methoxyphenylacetaldehyde dimethylacetal, and methoxyacetophenone is converted to phenylglyoxal dimethylacetal dimethylketal.

Although propiophenone was reported to rearrange to methyl α-methylphenylacetate in very low yield with TTN/MeOH,[10] we have now found that the rearrangement is essentially quantitative in MeOH/TMOF. In an analogous oxidative rearrangement, butyrophenone is converted to methyl α-ethylphenylacetate (93%). No α-methoxylation is observed in the latter two cases, apparently for steric reasons.

The full role of TMOF in the above oxidations is not yet clear. With some carbonyl compounds, initial conversion to acetals, ketals, or vinyl ethers (catalyzed by TTN, and more rapid with TMOF than with MeOH alone) occurs prior to oxidation. In addition, however, an apparently important role of TMOF is to lower the dielectric constant of the reaction medium, thus favoring SN2 as opposed to SN1 reactions of the methoxythallated intermediates. Thus, we have been able to effect the cinnamaldehyde rearrangements reported above by using a solvent combination whose dielectric constant is similar to MeOH/TMOF (e.g., MeOH/hexane, MeOH/*p*-dioxane, MeOH/CCl_4), although they proceed more slowly.[14] In marked contrast, the use of solvent mixtures of high dielectric constant (i.e., MeOH/CH_3CN) led to complex mixtures of products.

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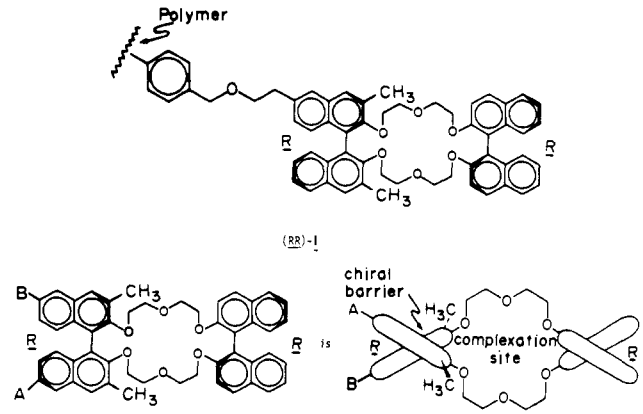
Total Chromatographic Optical Resolutions of α-Amino Acid and Ester Salts through Chiral Recognition by a Host Covalently Bound to Polystyrene Resin[1]

Sir:

We report here the covalent attachment of host (*RR*)-**1** to macroreticular cross-linked polystyrene *p*-divinylbenzene resin, and the use of the resin for total optical resolutions (both preparative and analytical) of amino acids and ester salts.[2]



1, A = B = H; 2, A = B = Br; 3, A = B = CH_2CH_2OH; 4, A = CH_2CH_2OH; B = H; 5, A = CH_2CH_2-PS-CH_2Cl (PS = polystyrene), B = H; 6, A = CH_2CH_2-PS-CH_2OCH_3, B = H

Optically pure (*R*)-2,2′-dihydroxy-3,3′-dimethyl-1,1′-binaphthyl[3] was brominated in dichloromethane (−78° to 25°) to give (90%) (*R*)-6,6′-dibromo-3,3′-dimethyl-2,2′-dihydroxy-1,1′-binaphthyl,[4] mp 115–119° ($CHCl_3$ solvate), $[\alpha]^{25}_{578}$ −68°.[5] This dibromide when refluxed for 17 h in $(CH_2)_4O$-KOH with mole for mole optically pure (*R*)-2,2′-bis-(1,4-dioxa-6-tosyloxyhexyl)-1,1′-binaphthyl[3] gave cycle (*RR*)-**2**[4] (69%), mp 135-143° (solvate from benzene–