Clean-Chemistry Synthesis of 2-Tetralones in a Single-Stage Acylation−Cycloalkylation Process

Anthony D. Gray and Timothy P. Smyth*

Department of Chemical and Environmental Sciences, University of Limerick, National Technological Park, County Limerick, Ireland

timothy.smyth@ul.ie

Received May 31, 2001

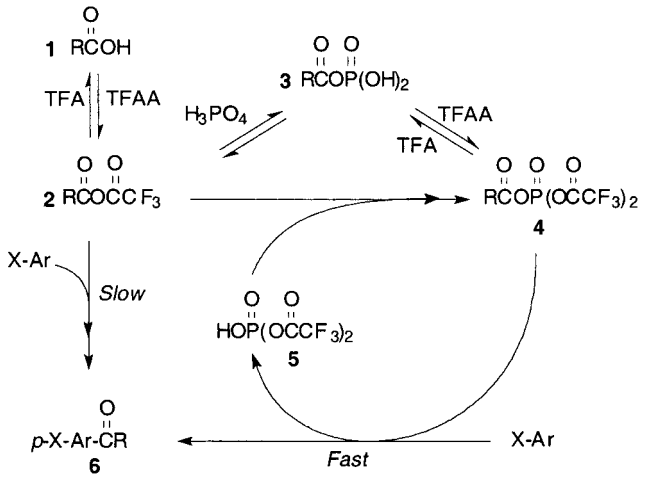
The preparation of substituted-2-tetralones by direct reaction of a 1-alkene with a substituted phenylacetic acid in a reaction system of trifluoroacetic anhydride (TFAA) and phosphoric acid is described. This single-stage process involves in situ formation of a mixed anhydride of the phenylacetic acid and acylation of the alkene by this species followed by cycloalkylation of the aromatic ring. This is a cleaner approach to the synthesis of 2-tetralones compared to Friedel−Crafts aliphatic acylation−cycloalkylation in that use of thionyl chloride, aluminum trichloride, and a chlorinated hydrocarbon solvent is eliminated. In addition, the atom efficiency is augmented by recovery of the spent TFAA as trifluoroacetic acid (TFA) and conversion of this back to TFAA by dehydration.

Introduction

We previously reported on the successful application of TFAA/H_3PO_4-mediated acylation of aromatics as a clean-chemistry alternative to the Friedel−Crafts process, wherein the use of thionyl chloride, aluminum chloride, and a chlorinated hydrocarbon solvent are all eliminated.[1] An acyl trifluoroacetate **2**, formed in situ from a carboxylic acid, is the acylation precursor which, on reaction with phosphoric acid, leads to the formation of an acyl bis(trifluoroacetyl)phosphate **4** (Scheme 1).

We obtained direct spectroscopic evidence (^{31}P and ^{19}F NMR data) that substantiated the role of **4** as the most active acylating agent in this reaction system. A value of 0.71 was estimated for σ_m of $OP(O)(OC(O)CF_3)_2$, which identifies the acyl carbonyl group in **4** as being more polarized than in $RC(O)OP(O)Cl_2$—an established reactive acylating agent.[2] Phosphoric acid is thus seen to act as a covalent catalyst rather than as a Brønsted acid in the TFAA/H_3PO_4 acylation reaction.[3] (Use of H_2SO_4 instead of H_3PO_4 led to sulfonation as well as acylation; we will report elsewhere our studies on the use of TFAA/H_2SO_4 as an aromatic sulfonation system.) The atom efficiency of the acylation process is augmented by recovery of the spent TFAA as trifluoroacetic acid (TFA) and conversion of this back to TFAA by dehydration.[4] We successfully applied this acylation process to the formation of a precursor structure (96% yield) in an industrially based synthesis of tamoxifen; in addition, reaction calorimetry indicated the viability of the process for scale-up.[1b]

Scheme 1



Friedel−Crafts chemistry has also been used industrially in the preparation of **9**, a 2-tetralone—for conversion onward to a pharmaceutically active material (Mibefradil)[5]—in a single-stage acylation−cycloalkylation process (eq 1) using ethylene. It was of interest, therefore, to ascertain if the TFAA/H_3PO_4 system could be applied, in a similar single-stage manner, to a general synthesis of 2-tetralones[6] starting with the appropriate carboxylic acid and alkene (eq 2). Herein, we report on the successful application of this process to the synthesis of a variety of 2-tetralones and detail some aspects of the scope of the reaction.

Results and Discussion

Initially, we examined the processes of alkene acylation using a carboxylic acid and of aromatic alkylation using

(1) (a) Smyth, T. P.; Corby, B. W. *J. Org. Chem.* **1998**, *63*, 8946−8951. (b) Smyth, T. P.; Corby, B. W. *Org. Process Res. Dev.* **1997**, *1*, 264−267.

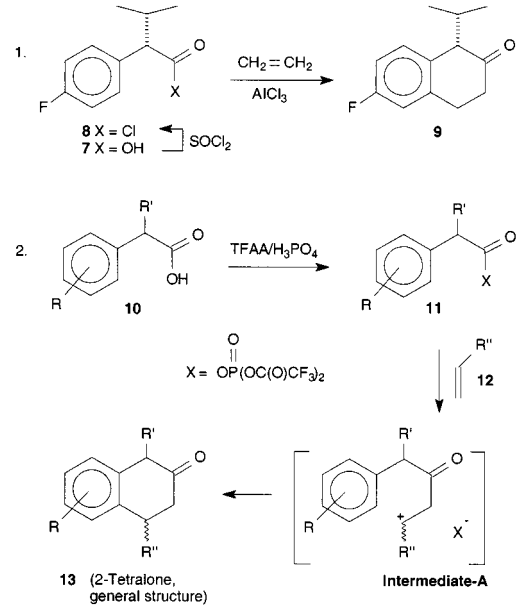
(2) Effenberger, F.; König, G.; Klenk, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 695−696.

(3) Acylation reactions using acyl trifluoroacetates were first reported in detail by Tedder: Tedder, J. M. *Chem. Rev.* **1955**, 787−827 and references therein. Catalysis by H_3PO_4 of aromatic acylation using acyl trifluoroacetates was first reported by Galli: Galli, C. *Synthesis* **1979**, 303.

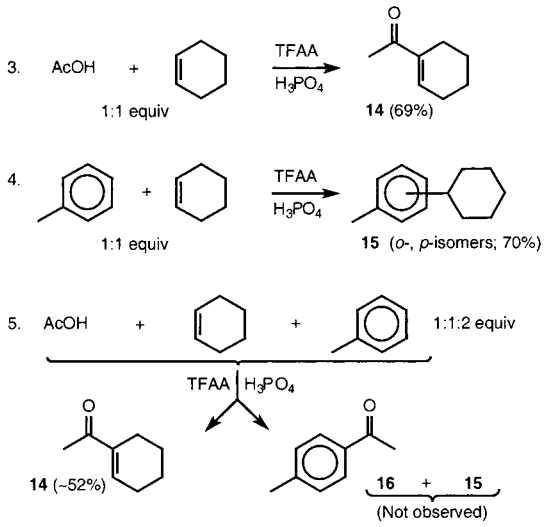
(4) TFAA is produced commercially by dehydration of TFA. Some processes use SO_3 as the dehydrating agent giving H_2SO_4 as a coproduct. For small-scale use, P_2O_5 is more convenient to use: Swarts, F. *Bull. Cl. Sci. Acad. R. Belg.* **1922**, 343.

(5) For general information see: http://cponline.gsm.com/.

10.1021/jo0158074 CCC: $20.00
Published on Web 09/18/2001

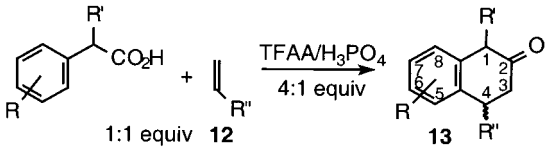


an alkene in the TFAA/H_3PO_4 system. 1-Acetyl-1-cyclohexene (**14**) was obtained in 69% yield after 10 min at room temperature in our reaction system (following aqueous workup) (eq 3); a yield of 48% was obtained in



the absence of phosphoric acid after 2.5 h at 37 °C.[7] The alkylation of toluene using cyclohexene gave a 70% yield of monoalkylated toluene **15** (*o*/*p*, 1:2) after 10 min at room temperature (eq 4). In a simple competition reaction, we established that alkene acylation was faster than aromatic alkylation and was also faster than aromatic acylation.[8] Thus, in a reaction system of acetic acid (1 equiv), cyclohexene (1 equiv), and toluene (2 equiv), acetylation of cyclohexene was found to be the predominant reaction: neither the alkylated nor the acetylated toluene products, **15** or **16**, was formed to any appreciable extent (eq 5).[9]

Table 1. General Results for TFAA/H_3PO_4-Mediated 2-Tetralone Formation



R[a]	R′	R″	2-tetralone yield (%)
H	H	*n*-C_4H_9	**13a** (55)
4-F	H	*n*-C_4H_9	**13b** (37)
4-Me	H	*n*-C_4H_9	**13c** (74)
4-MeO[b]	H	*n*-C_4H_9	**13d** (62)
3,4-diMeO[b]	H	*n*-C_4H_9	**13e**[c] (76)
H	CH_3	*n*-C_4H_9	**13f** (51)
H	H	-$(CH_2)_3$Br	**13g** (55)
4-Me	H	-$(CH_3)_2$	**13h** (70)

[a] The numbers here refer to the substituted phenylacetic acid. [b] H_3PO_4 (0.2 equiv) used. [c] GC analysis showed only one major peak. The ^{1}H NMR data was consistent with the 6,7-dimethoxy tetralone regioisomer rather than the 5,6-regioisomer.

This is the reactivity sequence required for formation of a 2-tetralone structure in a single-stage acylation−cycloalkylation process (eq 2). It was satisfying, therefore, to find that reaction of 1-hexene with phenylacetic acid (1:1 equiv) in TFAA/H_3PO_4 (4:1 equiv) at ambient temperature led to the rapid formation of 4-(1-butyl)-2-tetralone (**13a**) in 55% yield. The general results on 2-tetralone formation from reaction of a series of 1-alkenes with a set of phenylacetic acid structures are given in Table 1.[10] All products were characterized by ^{1}H NMR, HRMS, mass fragmentation pattern, and IR data (see the Experimental Section and Supporting Information for details). A typical set of data is given here for a sample of **13a**, which was found to be of 97% purity by GC analysis following purification by flash chromatography. The ^{1}H NMR (Figure 1a) showed chemical shift values for the hydrogen atoms at C-1, C-3, and C-4 that are very characteristic of 2-tetralone structures;[6,11] the chemical shift pattern of the (diastereotopic) C-3 hydrogens was observed to be solvent dependent (Figure 1b). The HRMS of **13a** gave a value of 202.13675 which is within 4.86 ppm of the calculated value; the characteristic peaks observed in the LRMS corresponded to the parent peak M, M − side chain at C-4, and M − (side chain and CO); a carbonyl stretching frequency was observed at 1717 cm^{-1}.

A successful outcome was obtained with isobutylene (Table 1, **13h**) by running the reaction in a pressure

(6) For general references to 2-tetralone formation using Friedel−Crafts acylation−cycloalkylation reactions, see: (a) Burckhalter, J. H.; Campbell, J. R. *J. Org. Chem.* **1961**, *26*, 4232−4235. (b) Prasad, R. S.; Roberts, R. M. *Synth. Commun.* **1991**, *21*, 385−393 and references therein. (c) Pendergast, W.; Johnson, J. V.; Dickerson, S. H.; Dev, I. K.; Duch, D. S.; Ferone, R.; Hall, W. R.; Humphreys, J.; Kelly, J. M.; Wilson, D. C. *J. Med. Chem.* **1993**, *36*, 2279−2291 and references therein. (d) Lee, S.; Frescas, S. P.; Nichols, D. E. *Synth. Commun.* **1995**, *25*, 2775−2780. (e) Tschaen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U.-H.; Frey, L.; Karady, S.; Shi, Y.-J.; Verhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324−4330. (f) Lin, C. H.; Ennis, M. D.; Hoffman, R. L.; Phillips, G.; Haadsmasvennson, S. R.; Ghazal, N. B.; Chidester, C. G. *J. Heterocycl. Chem.* **1994**, *31*, 129−139. (g) Yang, D. J.; Davisson, J. N. *J. Med. Chem.* **1985**, *28*, 1361−1365. (h) For an alternative method of 2-tetralone synthesis, see: Qandil, A. M.; Miller, D. W.; Nichols, D. E. *Synthesis*, **1999**, 2033−2035.

(7) Henne, A. L.; Tedder, J. M. *J. Chem Soc.* **1953**, 3628−3630.

(8) Acylation of toluene requires more vigorous reaction conditions (60 °C, 2.5 h).[1a]

(9) A small amount of cyclohexanol was also formed. Reaction of cyclohexene and of 1-hexene on their own in the TFAA/H_3PO_4 system generated the corresponding alcohols, following aqueous workup. Alcohol sideproducts occurred to a very minor extent in reactions leading to 2-tetralone formation: see GC traces included in the Supporting Information.

(10) 2-Tetralone products were formed—as determined by GCMS—with cyclohexene, and also with *cis*-3-hexene, as the alkene component. Purification proved to be problematic, however, in these instances.

(11) (a) Covarrubias-Zúñiga, A.; Cantú, F.; Maldonado, L. A. *J. Org. Chem.***1998**, *63*, 2918−2921. (b) Kolotuchin, S. V.: Meyers, A. I. *J. Org. Chem.* **2000**, *65*, 3018−3026.

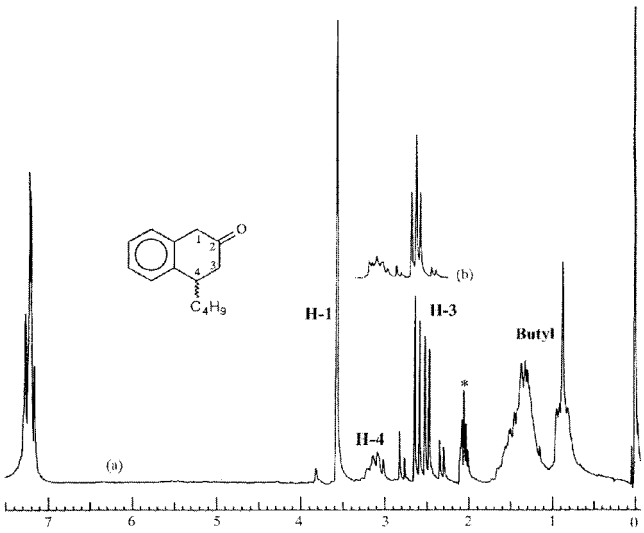


Figure 1. ^{1}H NMR of **13a** in (a) acetone-d_6 (*residual hydrogens) and (b) in $CDCl_3$.

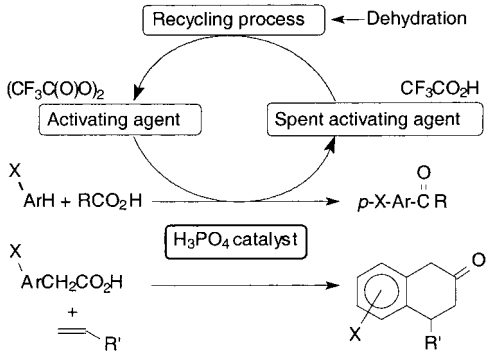
Table 2. Yield (%) of 13c as a Function of Time and of H_3PO_4 Concentration under Standard Reaction Conditions

H_3PO_4 (equiv)	3 h	6 h	9 h
1.0	74		
0.1	34	45	58
0.01	12		
0.00	4		

vessel (see the Experimental Section) wherein this alkene was, largely, liquified. The process of bubbling isobutylene through a solution of *p*-methylphenylacetic acid in TFAA/H_3PO_4 was not successful (the 2-tetralone product was formed in 11% yield); the removal, by entrainment, of volatile components such as TFAA and TFA was problematic in this instance. Likewise, passing a stream of ethylene through a reaction mixture of 3,4-dimethoxyphenylacetic acid (in TFAA/H_3PO_4) yielded only a trace of the 2-tetralone product (2.6%); in both cases, the bulk of the phenylacetic acid material was recovered.

The effect of varying the concentration of H_3PO_4 (with 4 equiv of TFAA throughout) was studied in the reaction of *p*-methylphenylacetic and 1-hexene; the findings are given in Table 2. The key dependence on H_3PO_4 concentration observed here mirrors that found in the case of the aromatic acylation reaction that we had studied earlier.[1a] In both cases, the concentration of the acyl bis(trifluoroacetyl)phosphate type structure (**11** in eq 2) is dependent on the concentration of H_3PO_4. In the multistep reaction leading to 2-tetralone formation, however, the concentration of the cycloalkylation precursor (**Intermediate-A** in eq 2) should be critical and should also be influenced by the concentration of H_3PO_4. The effect of varying the aromatic-ring substituent on the yield of 2-tetralone (Table 1) supports the view that cycloalkylation is a critical step in the overall process. Thus, it is unlikely that the ring substituent should have much influence on the rate of the aliphatic acylation step whereas it should have a significant influence on the rate of cycloalkylation. It is noteworthy that 0.2 equiv of H_3PO_4 was sufficient for effective catalysis of 2-tetralone formation with the activated phenylacetic acids bearing methoxy and dimethoxy substituents on the aromatic ring; this is similar to our earlier results on aromatic acylation.[1a]

Scheme 2



Use of reactive alkenes such as styrene and vinyl acetate was not successful as these components reacted with the acidic medium. Thus, styrene readily dimerized in TFAA/H_3PO_4, nonetheless, some (15%) 4-phenyl-2-tetralone was formed (as determined from the GCMS data). Vinyl acetate formed an acetyl trifluoroacetyl geminal diester resulting from the addition of TFA (to vinyl acetate)—no tetralone product was observed. It has been shown that vinyl ethers are efficiently trifluoroacylated by perfluoroacyl anhydrides[12] and therefore are not suited to acylation by an acyltrifluoroacetate.

Conclusions

Our results show that the TFAA/H_3PO_4 system can be usefully extended beyond aromatic acylation to a multistep reaction involving acylation of 1-alkenes coupled with cycloalkylation, in a single-stage process, leading to 4-substituted-2-tetralone formation. For both aromatic acylation and 2-tetralone formation the atom efficiency of the overall reaction is highest when using an activated aromatic ring in that relatively high yields are obtained with a catalytic quantity of H_3PO_4 (0.1−0.2 equiv). Common to both systems is the opportunity to recover the spent TFAA as TFA and convert this back to TFAA by dehydration (Scheme 2).

Experimental Section

^{1}H NMR spectra were recorded in acetone-d_6 (with tetramethylsilane as internal standard) unless otherwise stated. GC analyses were carried out on an RTX-1 column, 0.25 μm, 0.25 mm × 30 m; carrier gas: N_2, flow rate 5 mL min^{-1}; split ratio: 20/1; temperature program: 75 °C (2 min); 10 °C to 250 °C (10 min). This system was used to assay the yield of materials formed or isolated. GCMS analyses were carried out on a DB-5 column, 0.25 μm, 0.25 mm × 30 m; carrier gas: N_2, flow rate 1 mL min^{-1}; split ratio: 100/1; temperature program: 75 °C (2 min); 10 °C to 250 °C (10 min); mass selective detector operated at 70 eV electron impact. High-resolution mass spectra were recorded at the Mass Spectroscopy Service, University College, Cork.

All solvents except trifluoroacetic anhydride were rigorously dried and purified by distillation before use. 2-Tetralone products were purified by dry flash chromatography[13] and were generally obtained as yellow or yellow-brown oils after removal of solvent; their purity was assayed by GC.

(12) (a) Gorlov, D. V.; Kurykin, M. A.; Petrova, O. E.; *Russ. Chem. Bull.* **1999**, *48*, 1791−1792. (b) Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, 499−502.

(13) Casey, M.; Leonard, J.; Lygo B.; Procter, G. *Advanced Practical Organic Chemistry*; Blackie: Glasgow, 1990; Chapter 9.

General TFAA/H_3PO_4 Method. Trifluoroacetic anhydride (4.15 mL, 29.40 mmol) was added directly to the required carboxylic acid (7.35 mmol) to generate the mixed anhydride. This solution was stirred for 10 min. The mixed anhydride was cooled (ice water), and 85% phosphoric acid (0.85 g, 7.35 mmol) was added with stirring. After complete dissolution of the phosphoric acid, the alkene substrate (7.35 mmol) was added at such a rate that the temperature did not exceed 30 °C. The reaction mixture was cooled briefly and was then stirred at room temperature for 3 h (unless otherwise stated). (The removal of TFA by distillation as the initial isolation step is appropriate for large scale preparations.[1b] For the scale of the typical reaction carried here the following extraction procedure was used.) The reaction mixture was cooled (ice water) and water (25 mL) added. The solution was extracted with dichloromethane (25 mL), separated, washed with 30% NaOH (50 mL) and water (25 mL). The combined aqueous layers were extracted with a second portion of dichloromethane (25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. This general procedure was used for aliphatic acylation (formation of **14**), aromatic alkylation (formation of **15**) and 2-tetralone formation—the substrate was varied as required. The workup procedure above ensured removal of TFA, TFAA, H_3PO_4, any unreacted carboxylic acid and/or unreacted alkene. The weight of material recovered is given below as the mass balance and is listed as a percent of the starting weight of carboxylic acid and alkene minus the weight of one molecule of water for acylation and tetralone forming reactions. GC assay of material obtained at this stage gave the percent yield of the identified product(s). For spectroscopic analysis small samples of the 2-tetralones were purified by dry flash chromatography[13] using silica gel S 0.032−0.063 mm and *n*-hexane/diethyl ether as eluant. The ratio of *n*-hexane/diethyl ether of the solvent fraction (20 mL volume), in which the purified 2-tetralone product eluted, is stated. The purity of the samples was assayed using GC.

4-(1-Butyl)-2-tetralone (13a): obtained as a dark brown oil after workup (1.38 g, mass balance 93%, yield 55%); GC retention time 15.4 min; obtained as a yellow-brown oil after flash chromatography, eluted in the (85/15) fraction (purity assay 97%): δ 0.70−1.05 (br m, 3H, CH_3), 1.05−1.72 (br m, 6H, $-(CH_2)_3-$), 2.40 (dd, J = 4.6, 15.95 Hz, 1H, H-3 (diastereotopic)), 2.70 (dd, J = 5.35, 15.95 Hz, 1H, H-3 (diastereotopic)), 3.00−3.25 (br m, 1H, H-4), 3.57 (s, 2H, H-1), 7.13−7.35 (m, 4H, aromatic); MS(EI) *m*/*z* 202 (M), 145 (M − C_4H_9), 117 (M − C_4H_9/− CO); HRMS calcd for $C_{14}H_{18}O$ 202.13577, found 202.13675 (dev 4.86 ppm); IR (neat) 1717 cm^{-1}.

4-(1-Butyl)-6-fluoro-2-tetralone (13b): obtained as a dark brown oil after workup (1.56 g, mass balance 96%, yield 37%); GC retention time 15.08 min; obtained as a yellow-brown oil after flash chromatography, eluted in the (82.5/17.5) fraction (purity assay 93%), δ 0.70−1.05 (br m, 3H, CH_3), 1.05−1.70 (br m, 6H, -$(CH_2)_3$-), 2.42 (dd, J = 5.2, 18.8 Hz, 1H, H-3 (diastereotopic)), 2.75 (dd, J = 6.2, 18.8 Hz, 1H, H-3 (diastereotopic)), 3.00−3.25 (br m, 1H, H-4), 3.57 (s, 2H, H-1), 7.15−7.37 (m, 3H, aromatic); MS(EI) *m*/*z* 220 (M), 163 (M − C_4H_9), 135 (1M−C_4H_9/-CO); HRMS calcd for $C_{14}H_{17}FO$ 220.12634, found 220.12771 (dev 3.50 ppm); IR (neat) 1719 cm^{-1}.

4-(1-Butyl)-6-methyl-2-tetralone (13c): obtained as a dark brown oil after workup (1.42 g, mass balance 95%, yield 74%); GC retention time 16.29 min; obtained as a yellow oil after flash chromatography, eluted in the (83.75/16.25) fraction (purity assay 95%); δ 0.70−1.05 (br m, 3H, CH_3), 1.05−1.72 (br m, 6H, -$(CH_2)_3$-), 2.30 (s, 3H, 6-CH_3 and 0.5H, H-3), 2.37 (dd (partially masked at 2.30), J = 4.35, 15.7 Hz, 0.5H H-3 (diastereotopic)), 2.68 (dd, J = 4.98, 15.7 Hz, 1H, H-3 (diastereotopic)), 2.90−3.25 (br m, 1H, H-4), 3.50 (s, 2H, H-1), 6.96−7.16 (m, 3H, aromatic); MS(EI) *m*/*z* 216 (M), 159 (M − C_4H_9), 131 (M − C_4H_9/− CO); HRMS Calcd. for $C_{15}H_{20}O$ 216.15142, found 216.15072 (dev −3.24 ppm); IR (neat) 1717 cm^{-1}.

4-(1-Butyl)-6-methoxy-2-tetralone (13d): H_3PO_4 (0.2 equiv) used; obtained as a dark brown oil after workup (1.56 g, mass balance 91%, yield 62%); GC retention time 17.88 min; obtained as a dark yellow oil after flash chromatography, eluted in the (82.5/17.5) fraction (purity assay 95%); δ 0.70−1.05 (br m, 3H, CH_3), 1.05−1.72 (br m, 6H, $-(CH_2)_3-$), 2.39 (dd, J = 4.1, 15.55 Hz, 1H, H-3 (diastereotopic)), 2.68, (dd, J = 5.4, 15.55 Hz, 1H, H-3 (diastereotopic)), 2.95−3.28 (br m, 1H, H-4), 3.50 (s, 2H, H-1), 3.83 (s, 3H, CH_3O), 6.84 (s, 1H, aromatic), 6.76−7.3 (m, 2H, aromatic); MS(EI) *m*/*z* 232 (M), 175 (M − C_4H_9), 147 (1M − C_4H_9/− CO); HRMS calcd for $C_{15}H_{20}O_2$ 232.14633, found 232.14683 (dev 2.17 ppm); IR (neat) 1716 cm^{-1}.

4-(1-Butyl)-6,7-dimethoxy-2-tetralone (13e): H_3PO_4 (0.2 equiv) used; obtained as a dark brown oil after workup (1.83 g, mass balance 95%, yield 76%); GC retention time 19.80 min; obtained as a brown-yellow oil after flash chromatography, eluted in the (45/55) fraction (purity assay 95%); δ 0.70−1.05 (br m, 3H, CH_3), 1.05−1.72 (br m, 6H, $-(CH_2)_3-$), 2.45−2.85 (2dd (poorly resolved), 2H, H-3 (diastereotopic)), 2.90−3.20 (br m, 1H, H-4), 3.55 (s, 2H, H-1), 3.90 (s, 3H, CH_3O), 3.94 (s, 3H, CH_3O), 6.64 (s, 1H, aromatic), 6.75 (s, 1H, aromatic); MS(EI) *m*/*z* 262 (M), 205 (M − C_4H_9), 177 (1M − C_4H_9/− CO); HRMS calcd for $C_{16}H_{22}O_3$ 262.15689, found 262.15747 (dev 2.19 ppm); IR (neat) 1715 cm^{-1}.

1-Methyl-4-(1-butyl)-2-tetralone (13f): obtained as a dark brown oil after workup (1.25 g, mass balance 87%, yield 51%); GC retention time 15.70 and 15.76 min (two diastereomeric pairs of stereoisomers: 1:1.6); obtained as a clear oil after flash chromatography, eluted in the (86.25/13.75) fraction (purity assay 93%); $\delta(CDCl_3)$ 0.70−1.05 (br m, 3H, CH_3), 1.05−1.72 (br m, 6H, $-(CH_2)_3-$ overlapping with 1.45 (d, J = 6.67 Hz) and 1.49 (d, J = 6.67 Hz, 1-CH_3), 2.10−2.95 (4dd (partially overlapping), 2H, H-3 (diastereomeric and diastereotopic)), 2.95−3.25 (br m, 1H, H-4), 3.36−3.72 (2q (partially overlapping), J = 6.67 Hz, 1H, H-1 (diastereomeric)), 7.25 (s, 4H, aromatic); MS(EI) *m*/*z* 216 (M), 159 (M − C_4H_9), 131 (1M − C_4H_9/− CO); HRMS calcd for $C_{15}H_{20}O$ 216.15142, found 216.15107 (dev −1.60 ppm); IR (neat) 1717 cm^{-1}.

4-(1-(3-Bromopropyl))-2-tetralone (13g): obtained as a dark brown oil after work up (1.81 g, mass balance 92%, yield 55%); GC retention time 18.45 min; a dark yellow oil after flash chromatography, eluted in the (73.75/26.25) fraction (purity assay 92%); δ ($CDCl_3$) 1.49−2.09 (br m, 4H, $-(CH_2)_2-$), 2.52 (dd, J = 4.2, 16.35 Hz, 1H, H-3 (diastereotopic)), 2.78 (dd, J = 4.75, 16.35 Hz, 1H, H-3 (diastereotopic)), 2.98−3.25 (br m, 1H, H-4), 3.39 (t, J = 6.23 Hz, 2H, $-CH_2Br$), 3.60 (s, 2H, H-1), 6.98−7.49 (m, 4H, aromatic); MS(EI) *m*/*z* 266 (M: ^{79}Br), 268 (M: ^{81}Br), 145 (M − C_3H_6Br), 117 (M − C_3H_6Br/-CO); HRMS calcd for $C_{13}H_{15}BrO$ 266.03063, found 266.03119 (dev 2.13 ppm); IR (neat) 1715 cm^{-1}.

4,4-Dimethyl-6-methyl-2-tetralone (13h): isobuylene gas (3.2 mL, 33.5 mmol) was condensed, under nitrogen, into a cooled (−25 °C) graduated cylinder and rapidly transferred to a Parr hydrogenator vessel under nitrogen and held at −25 °C. A pre-prepared solution (see General TFAA/H_3PO_4 Method) of the mixed anhydride of *p*-methylphenylacetic acid (33.33 mmol) and H_3PO_4 was added slowly. The reaction mixture was then shaken at room temperature for 3 h using a Parr apparatus. **13h** was obtained as a dark brown oil after workup (5.64 g, mass balance 90%, yield 70%); GC retention time 13.32 min; obtained as a yellow oil after flash chromatography, eluted in the (92.5/7.5) fraction (purity assay 98%); δ ($CDCl_3$) 1.33 (s, 6H, (4,4-dimethyl), 2.36 (s, 3H, 6-CH_3), 2.51 (s, 2H, H-3), 3.64 (s, 2H, H-1), 7.05 (s, 2H, aromatic), 7.26 (s, 1H, aromatic); MS(EI) *m*/*z* 188 (M), 173 (M − CH_3), 145 (M − CH_3/− CO), 130 (M − $(CH_3)_2$/− CO); HRMS calcd for $C_{13}H_{16}O$ 188.12012, found 188.12037 (dev 1.36 ppm); IR (neat) 1719 cm^{-1}.

1-Acetyl-1-cyclohexene (14): acetic acid (2 g, 33.33 mmol) was used in the standard procedure (see General TFAA/H_3PO_4 Method) with a reaction time of 10 min. Compound **14** was obtained as a dark yellow oil after workup (3.97 g, mass balance 96%, yield 69%); GC retention time 6.95 min; obtained as a light yellow oil after distillation (2.98 g, 23.98 mmol, 96% purity), bp 41−42 °C/0.6 mm (lit.[7] bp 86−88 °C /28 mm); $\delta(CDCl_3)$ 1.50−1.74 (br m, 4H, $-(CH_2)_2-$), 2.11−2.35 (br m, 4H, $-(CH_2)_2-$), 2.27 (s, 3H, CH_3), 6.82−6.97 (br m, 1H, $-HC{=}C-$); MS(EI) *m*/*z* 124 (M), 109 (M − CH_3), 81 (M − CH_3/

CO) 43 (M − C_6H_9); IR (neat) 1666 cm^{-1}. This material was found to be identical (^{1}H NMR, GCMS) with an authentic sample (Aldrich).

1-Cyclohexyl-3-methylbenzene and 4-Cyclohexyl-1-methylbenzene (15). cyclohexene (0.89 g, 10.87 mmol) and toluene (1 g, 10.87 mmol) were used in the standard procedure (see General TFAA/H_3PO_4 Method) with a reaction time of 10 min. Obtained as a light yellow liquid after workup (1.61 g, mass balance 85%, yield 70%: *o*/*p*, 1:2); GCMS: at 10.89 min, MS(EI) *m*/*z* 174 (M), 83 (M − (C_6H_4 − CH_3)); at 11.00 min, MS(EI) *m*/*z* 174 (M), 83 (M − (C_6H_4 − CH_3)).

Competition Reaction. Acetic acid (1 g, 16.66 mmol), cyclohexene (1.4 g, 16.66 mmol), and toluene (3.03 g, 33.33 mmol) were used in the standard procedure (see General TFAA/H_3PO_4 Method) with a reaction time of 10 min. A yellow-brown oil was obtained after workup (2.25 g, yield of 1-acetyl-1-cyclohexene ~52%); GCMS: at 1.75 min 92 (M) toluene; at 2.75 min, 100 (M) cyclohexanol; at 5.33 min, 123 (M) unknown; at 6.53 min, 124 (M) 1-acetyl-1-cyclohexene; at 7.90 min 132 (M) unknown.

Acknowledgment. A.D.G. thanks Roche Ireland Ltd, Clarecastle, County Clare, and Enterprise Ireland for financial support through the Irish American Partnership Program. We thank Drs. Dennis Smith and John O'Reilly of Roche Ireland and Dr. Tony Daly, formerly of Roche Ireland, for their support throughout this work.

Supporting Information Available: ^{1}H NMR spectra of **13b**,**c**,**f**−**h**; GC traces for **13a** after aqueous workup and after chromatography and for the competition reaction involving acetic acid, cyclohexene, and toluene. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0158074