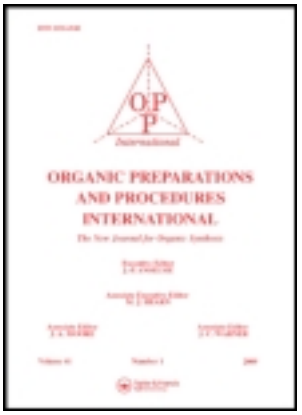

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OPPI BRIEF

Large-scale Synthesis and Purification of *trans*-4-*tert*-Butyl-1-Phenylcyclohexanol, an Organic Gelation Agent

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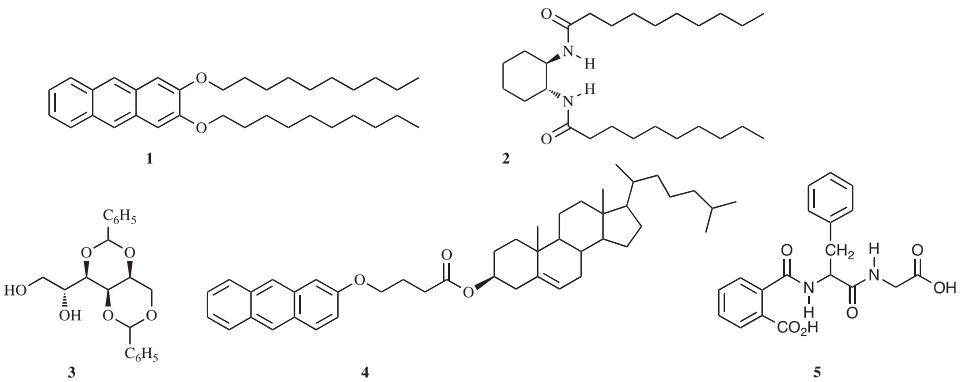
A relatively small number of organic compounds can be used to convert organic liquids into gels[1,2] and are referred to as low-mass organic gelators, distinguished from polymeric gelling agents. The gelling properties of such materials are typically discovered inadvertently; even now, it is difficult to design molecules with this behavior. *Scheme 1* gives some examples of known organic gelators (**1–5**). Structurally, they tend to have long unbranched alkyl chains (**1**,[3] **2**[4]) and/or significant degrees of hydrogen bonding (**2**, **3**,[5] **4**,[6] **5**[7]). These



Scheme 1
Representative Organogelators.

materials exhibit a wide range of gelation behavior, with some compounds useful for gelling only very non-polar liquids and others effective for immobilizing a wider range of fluids. The gelled state is achieved by first dissolving the gelator in the appropriate hot liquid, followed by cooling. The gelation resembles crystallization in that there is often an

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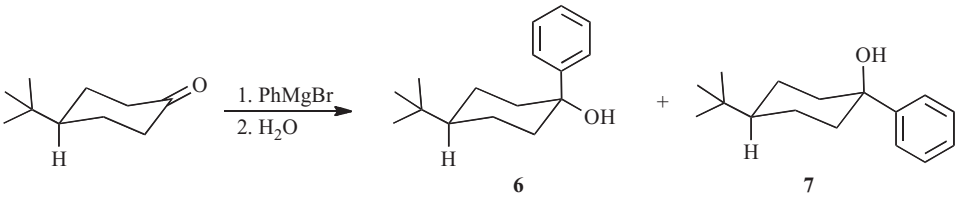
irreproducible delay between cooling and the onset of gel formation. These molecules function through the same general mechanism, namely by aggregation primarily in one dimension, yielding long fibers that overlap extensively. Depending on the cross-sectional diameter of the aggregates, the resulting gels may be clear or cloudy, the latter ones being more common.

trans-4-*tert*-Butyl-1-phenylcyclohexanol (**6**) is perhaps the smallest and most rigid molecule known[8–10] to gel organic solvents, and one of the simplest structurally. This compound has been known for several decades[11,12] before its gelation abilities were recognized. Low concentrations (0.5–1 wt%) can be used to convert a wide variety of saturated hydrocarbons to transparent gels that resist gravity indefinitely and give sharp, concentration-dependent melting points. For example, a mineral oil gel containing 1 wt.% of **6** exhibits a melting point of 52–53°C. Aromatic hydrocarbons and even halocarbons, ethers and esters can be immobilized at higher concentrations (2–5%). Protic solvents (*e. g.*, methanol, ethanol) are entirely resistant to gelling, the compound simply precipitating upon cooling instead. The gels are technically *metastable*, and precipitation of the gelling agent can occur if seeded, mechanically agitated, and/or warmed somewhat, etc. Very slow evaporation of a dilute hexane solution of **6** can yield fibers up to several centimeters in length. However, mineral oil gels are very resistant to precipitation, generally being stable for months or even years at room temperature.



Scheme 2
Preparation of *trans*- and *cis*-4-*tert*-Butyl-1-phenylcyclohexanol.

Gelling agent **6** is best prepared[11,12] by reaction of the phenylmagnesium bromide with 4-*tert*-butylcyclohexanone, both available in bulk quantities. The reaction inevitably produces both *trans* (**6**) and *cis* (**7**) isomers of the product (*Scheme 2*), though (fortunately) the *trans* isomer generally predominates (*see below*). Preliminary tests suggest that the *cis* isomer does not interfere with the gelling ability of the *trans* isomer, but resistance to crystallization under these conditions has not been evaluated. The isomers exhibit significant differences in polarity on silica gel TLC, with the *trans* isomer being more polar (R_f 0.14 vs. 0.28 for the *cis*, using 10% ethyl acetate in hexanes). However, in addition to serious limitations on scale, column chromatography is plagued by the tendency of compound **6** to gel the solvent used to dissolve it for application to the column. For column chromatography, dichloromethane proved to be the best solvent for the application and separation, but only rather small amounts (< few grams) of **6** could be purified in this way. To provide samples for industrial testing, we sought a relatively large-scale synthesis and purification of the material.

In order to optimize the fraction of *trans* isomer formed, we studied various procedures for the reaction. Optimization was studied on a one-mmol scale, with the results analyzed

by capillary gas chromatography, which easily resolved the isomers. The critical variables, in decreasing order of importance, were (a) the use of phenylmagnesium bromide versus phenyllithium, (b) the use of ether versus THF, and (c) the order of addition. We found phenylmagnesium bromide to be much superior to phenyllithium, giving nearly always better than 62% *trans*, while phenyllithium gave 50% or less of the desired *trans* isomer. Diethyl ether was always superior to THF, especially when the ketone was added to the Grignard reagent. In addition to poorer *trans*:*cis* ratios, THF always gave a larger amount of unreacted ketone, presumably the result of enolization. The order of addition affected mostly the amount of residual ketone, with the best results obtained from addition of the ketone to the organometallic reagent. The predominance of the less stable *trans* isomer was enhanced somewhat by the presence of magnesium bromide, prepared *in situ* from magnesium and 1,2-dibromoethane. However, the simplest conditions that gave complete conversion and a high *trans*:*cis* ratio were the addition of an ethereal solution of the ketone to a 1 M ethereal solution of the Grignard reagent at -78°C, and these were chosen for the scale-up process.

The challenges for a large-scale synthesis are (a) to maximize production while avoiding inconveniently large volumes of solvent, (b) to avoid if possible the necessity of an aqueous work-up, and (c) to obtain the gel-active *trans* isomer essentially free of the inactive *cis* isomer *without* chromatography. All of these goals were realized. We were able to carry out the Grignard reaction on a $>$ 2 mole scale in a 5-liter round bottom flask, and quantitatively cause the precipitation of the magnesium salt by-product, and purify the crude product by differential solubility/filtration.

After many smaller scale reactions, the following protocol was developed. On a 2.4 mole scale, commercial phenylmagnesium bromide (3 M in ether) was diluted to $\sim$0.7 M with anhydrous ether in a 5-liter, three-neck round bottom flask equipped for mechanical stirring and under a nitrogen atmosphere. Cooling this to -78°C gave a stirrable suspension of the Grignard reagent, to which was added a $\sim$2.5 M solution of 4-*tert*-butylcyclohexanone (2.2 mol) in ether. The mixture was allowed to slowly warm to room temperature overnight, and the resulting thick suspension was treated with water. As the mildly exothermic hydrolysis was complete, there generally came a point where the ethereal solution would dramatically clear and all of the magnesium salts would coagulate on the walls of the flask, but with no second liquid phase evident. This sometimes occurred with as little as 80 mL of water (1.9 equiv. relative to Grignard used) but usually at closer to 360 mL (8.4 equiv) of water. As long as the ethereal solution was warm ($\sim 30^{\circ}$C), the organic products were completely soluble, and simple vacuum filtration through granular sodium sulfate provided a slightly yellow solution. On one occasion, after addition of 8 equiv of water, the magnesium salts did not coagulate and a suspension was still present. But vacuum filtration of the warm (30°C) ethereal solution to remove the rather granular magnesium salts was still easily performed, followed by rinsing with a little ether to make sure that the salt did not retain any of the desired product. In either case, evaporation of the filtrate gave essentially a quantitative yield (96–99%, 490–505 g) of the crude *cis*/*trans* mixture ($\sim$62–68% *trans*), free of unreacted ketone by capillary GC analysis.

Since chromatography could only provide small amounts of pure *trans* or *cis* isomer, we studied crystallization. Of some of the common solvents (aliphatic and aromatic hydrocarbons, ethers, ethyl acetate, alcohols), crystallization was possible only from alcohols;

for all others, cooling of a warm solution resulted in a gel. We found that hot (60°C) 85:15 ethanol:water would dissolve the mixture of isomers readily, but upon cooling the fibrous *trans* isomer precipitated in such a way that the solvent could not be efficiently removed from the solid. It was later learned that the *cis* isomer (**7**) could often be crystallized from > 60% *cis*-enriched samples, as discussed below.

Since the *trans* isomer was more polar than the *cis* (based on TLC observations), it was decided to measure the solubility of each in hydrocarbon solvents at room temperature. As long as the mixtures were not heated, gelation was avoided, and the *cis* isomer was significantly more soluble. For example, in hexanes the *cis* isomer was much more soluble (22 mg/mL) than was the *trans* isomer (5.2 mg/mL). A variety of hydrocarbons (pentane, cyclopentane, 2-methylbutane, cyclohexane, 2,3-dimethylbutane) were also studied, but the relative solubilities were nearly the same as observed for hexanes. Thus, a simple method to obtain highly pure *trans* isomer was to simply stir the powdered crude product with sufficient hexanes (14.5 mL per gram) to dissolve all of the *cis* isomer. This inevitably washed away some of the *trans* isomer as well, but the operation was simple if not entirely efficient. On the largest scale attempted, 100 g of powdered crude product in a 2 L Erlenmeyer flask was suspended and stirred with 1450 mL of hexanes for ∼20 min, then collected *in vacuo* on a 600 mL coarse fritted funnel until dripping stopped; then the solid was broken up and suspended again in 620 mL more hexanes, stirred and filtered as before to give 50.7 g (∼82% recovery) of the *trans* isomer, >99% pure by capillary GC analysis. Thus, on the 2.2 mole scale described above, the yield of pure *trans* isomer was 248–256 g, or 49–50% yield overall.

The hexanes were easily recycled by distillation. The resulting *cis*-enriched mixture (>60% *cis*) could be recrystallized from 85:15 ethanol:water to yield the crystalline *cis* isomer; however, filtration must be done before the *trans* isomer begins to precipitate (evident as fibrous rather than crystalline material). In theory, the resulting *trans*-enriched filtrate could then be concentrated and treated with hexanes to obtain more of the pure *trans* isomer, but we did not study that level of recovery.

Experimental Section

Phenylmagnesium bromide (3 M in ether) and 4-*tert*-butylcyclohexanone were obtained from Aldrich Chemical and used as received. Anhydrous ether was obtained from Mallinckrodt and used as received. The Grignard reagent and anhydrous ether were transferred by cannula under nitrogen or argon. Hexanes (VWR) were ACS grade and distilled before use. NMR analyses were performed in acetone-d_6 at 500 MHz for ^{1}H (referenced to TMS) and at 125.7 MHz for ^{13}C (referenced to solvent at 29.84 ppm). Quantitative GC analyses were carried out using a 30 m × 0.25 mm HP-5 capillary column with helium carrier at 15 psi, and FID detection.

***trans*- and *cis*-4-*tert*-Butyl-1-phenylcyclohexanol (6 and 7).** To a two neck 5-L round-bottom flask equipped with a mechanical stirrer and under nitrogen was added phenylmagnesium bromide (800 mL, 3 M in ether; 2.4 mol) solution (viscous) using a 12 gauge cannula, followed by 2.8 L of anhydrous ether. The mixture was cooled to −78°C in a Dry Ice-acetone bath, resulting in a stirrable suspension. A solution of 4-*tert*-butylcyclohexanone (340 g, 2.2 mol, 0.92 equiv. relative to Grignard) in anhydrous

ether (500 mL) under nitrogen was then introduced using a cannula over a 20–40 minute period. The resulting very thick grey suspension was allowed to warm to room temperature overnight with stirring. With the flask immersed in a room temperature water bath, water was added using a cannula to the thick white suspension with stirring until the mixture thinned considerably and the magnesium salts coagulated on the walls of the flask; this typically occurred at somewhere between 80 mL and 360 mL (1.9–8.4 equiv) of water added. The slightly yellow ethereal solution was filtered through a pad of anhydrous granular sodium sulfate. On one occasion, the solution failed to become clear during the addition of water (possibly because of more efficient stirring), in which case the suspension was filtered through a pad of anhydrous sodium sulfate to remove the magnesium salts. In either case, it is important that the ethereal solution be sufficiently warm (25–30°C) to keep the organic products soluble during the decantation/filtration process. Concentration was carried out by atmospheric pressure distillation on a rotary evaporator followed by pump vacuum (<1 Torr). This provided a nearly quantitative yield (490–505 g, 96–99%) of a *cis*/*trans* mixture (62–68% *trans*), containing only traces of impurities by capillary GC. It is important to maintain a clean injection port liner, as used liners may sometimes cause significant amounts of dehydration (primarily of the *trans* isomer) during injection. A temperature program of 100°C to 240°C at 10°C per minute was used, and the observed elution order (retention time) was: ketone (5.5 min), alkene dehydration product (11.8 min), *trans* isomer **6** (12.3 min), and *cis* isomer **7** (12.8 min). On silica TLC, the *trans* isomer exhibited R_f 0.14 vs. 0.28 for the *cis*, using 10% ethyl acetate in hexanes.

Pure *trans*-4-*tert*-butyl-1-phenylcyclohexanol (6). The vacuum-dried *cis*/*trans* mixture was powdered using a mortar and pestle, and sifted through a 16-mesh wire gauze to remove chunks (which were re-submitted for powdering). A weighed amount of the powder was suspended in hexanes (14.5 mL per gram of powder) and the thick suspension was magnetically stirred 15 minutes, then the solid was collected on a coarse fritted funnel until dripping stops (important). Using a plastic spatula (to avoid damaging the frit), the solid was then broken up in the fritted funnel (important), the solid was stirred with an additional 6.2 mL of hexanes per gram (based on original weight) until a uniform suspension resulted, and the filtration repeated (until dripping stops). The recovery is approximately 50% of the original weight, or 72–82% of the *trans* isomer present originally. On the scale above, 248–256 g (1.07–1.10 mol, 49–50% overall yield) of *trans*-4-*tert*-butyl-1-phenylcyclohexanol (**6**) was obtained, mp. 157.5–158.0°C, lit 156.5–157.5,[11] 158–159.[12] The purity is typically 99.3 ± 0.1% *trans* by capillary GC analysis. ^{1}H NMR (acetone-d_6): δ 0.78 (s, 9H), 0.96–1.08 (m, 2H), 1.14–1.22 (m, 1H), 1.66–1.76 (m, 4H), 2.48–2.56 (m, 2H), 3.75 (s, 1H), 7.22 (tt, J = 7.8, 1.2 Hz, 1H), 7.31–7.35 (m, 2H), 7.54–7.58 (m, 2H). ^{13}C NMR (acetone-d_6): δ 25.6, 27.9, 32.7, 39.8, 48.7, 72.8, 127.4, 127.5, 128.8, 146.4. MS (EI): 232 (M^+, 7%), 133 (100%), 120 (8%), 105 (15%).

The alkene dehydration product gave the following GC-MS (EI): 214 (M^+, 45%), 158 (33%), 143 (48%), 130 (100%), 115 (43%), 91 (80%).

Pure *cis*-4-*tert*-butyl-1-phenylcyclohexanol (7). The hexanes filtrate from the purification of the *trans* isomer was concentrated by rotary evaporation or distillation, followed by drying on the vacuum pump (<1 Torr), to give ∼260 g of *cis*-enriched material. This material was dissolved in ethanol (1 L) with heating (∼70°C) and water was added with stirring until the mixture just clouded; approximately 230 mL was required. The mixture

was allowed to cool to room temperature and stand overnight. The crystalline material was collected and washed once with cold ethanol to give 90 g (0.38 mol, 17.6% yield, 47–57% recovery of the *cis* isomer originally present) of *cis*-4-*tert*-butyl-1-phenylcyclohexanol (**7**), mp. 117.5–118.0, lit 117–118,[11] 117.[12] It was observed that sometimes the fibrous *trans* isomer would begin to precipitate on prolonged standing, and it is important that the filtration be performed before this occurs, but the difference is easily evident. ^{1}H NMR (acetone-d_6): δ 0.92 (s, 9H), 1.1–1.2 (m, 1H), 1.62–1.70 (m, 4H), 1.76–1.82 (m, 4H), 3.66 (s, 1H), 7.17 (tt, $J = 7.3$, 1.2 Hz, 1H), 7.26–7.31 (m, 2H), 7.53–7.56 (m, 2H). ^{13}C NMR (acetone-d_6): δ 23.6, 28.0, 33.0, 40.3, 48.3, 72.6, 125.5, 126.8, 128.6, 151.8. MS (EI): 232 (M^+, 8%), 133 (100%), 120 (8%), 105 (15%).

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