septum, and a side arm connected to a dry-ice condenser and flushed with dry argon. With vigorous stirring, 510 mL of a 1.4 M solution of methyllithium in diethyl ether (Aldrich, salts free) were added via cannula in 15 min at the dry ice–acetone bath temperature. When the addition was completed, the bath was replaced by an ice bath and the stirring was continued for 1 h. All volatiles were then vacuum-transferred to a cold trap equipped with a 1-L round-bottom flask receiver containing a magnetic stirring bar. When almost dry salts appeared in the flask, the transfer was discontinued and the apparatus was again filled with argon. The receiver containing the propellane solution was disconnected from the cold trap and stoppered with a septum, and 27 mL of freshly distilled biacetyl was added from a syringe. The solution was stirred at ice-bath temperature and irradiated in a Pyrex vessel for 8 h with a 450-W medium-pressure Hanovia mercury lamp under dry argon. Volatiles were evaporated, and the semicrystalline residue was distilled on a Kugelrohr apparatus (80–85 °C/0.4 mmHg), yielding 36.2 g of wet white to pale yellow crystals. Crystallization of the crude **4** from heptane afforded 26.4 g of pure **4** in a 58% overall yield based on **5**: mp 67–69 °C; ^{1}H NMR δ 2.14 (s, 6 H), 2.24 (s, 6 H); ^{13}C NMR δ 25.79, 43.10, 51.81, 205.01; IR (C=O) 1708; MS, m/z (relative intensity) 152 (1, M^+), 137 (11), 109 (43), 95 (10), 43 (100), 39 (25); HRMS, m/z (calcd for $C_9H_{12}O_2$ 152.0837) 152.0839. Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.01; H, 7.97.

Bicyclo[1.1.1]pentane-1,3-dicarboxylic Acid (1). A 26.4-g portion of **4** was dissolved in 125 mL of dioxane and added over a period of 2 h to a stirred solution of sodium hypobromite prepared from 65 mL (1.25 mol) of bromine, 140 g (3.5 mol) of sodium hydroxide, and 1050 mL of water at 0–3 °C. After the addition of the diketone was completed, the reaction mixture was stirred for 1 h at 0 °C and then for 3 h at room temperature and finally for 1 h at 50 °C. Next, 6 g of sodium bisulfite were added, and the reaction mixture was extracted with 3 × 300 mL of chloroform, acidified with 225 mL of concentrated hydrochloric acid, and extracted with ether in a continuous extraction apparatus for 30–50 h. The ether was evaporated, the residue was dried under reduced pressure, and the crude product was washed with 50 mL of boiling chloroform. Cold suspension of the product was filtered, giving 24.6 g (90% yield) of the diacid **1**: mp 305 °C rapid dec, sealed tube (lit.[1] mp >260 °C subl); ^{13}C NMR (acetone-d_6) δ 38.08; 53.04, 170.59.

Bicyclo[1.1.1]pentane-1,3-dicarboxylic Acid (1) via Addition of Acetaldehyde to 2. A solution of **2** in diethyl ether prepared by the above procedure (210 mL, 3% in **2** according to integrated ^{1}H NMR intensities), 150 mL of acetaldehyde, and 0.4 g of benzoyl peroxide was stirred and irradiated as above for 6 h. Evaporation of solvents and excess acetaldehyde at reduced pressure (at the end, 50 °C/0.8 mmHg) furnished 15.06 g of crude **3** in the form of a yellowish oil (about 80% pure by GC): ^{1}H NMR δ 1.05 (d, J = 6.4 Hz, 3 H), 1.81 (d, J = 9.0 Hz, 3 H), 1.87 (d, J = 9.0 Hz, 3 H), 2.06 (s, 3 H), 3.74 (q, J = 6.4 Hz, 1 H); ^{13}C NMR δ (major peaks) 19.17, 25.95, 42.70, 43.41, 48.49, 66.21, 206.90; GC–MS, m/z (relative intensity) 139 (24, M – Me), 121 (63), 111 (27), 95 (30), 93 (68), 91 (59), 77 (81), 71 (100). An attempt at purification by short-path distillation (110–115 °C/0.4 mmHg) led to partial decomposition. Crude **3** (7.5 g) diluted with 25 mL of dioxane was slowly added to a vigorously stirred solution of sodium hypobromite prepared by slow addition of 18.5 mL (0.36 mol) of bromine to a well-stirred solution of 40.0 g (1.0 mol) of sodium hydroxide in 300 mL of water. Temperature during preparation of the hypobromite as well as the addition of **3** was maintained below 5 °C. The reaction mixture was stirred for 1 h at ice-bath temperature and then for 3 h at room temperature and finally for 1 h at 50 °C. Excess hypobromite was destroyed by addition of 5 g of sodium bisulfite, the mixture was extracted with 3 × 50 mL of chloroform and acidified with 55 mL of concentrated HCl, and the product was extracted with ether for 10 h. Ether was evaporated, the residue was dried under reduced pressure, and the crude diacid **1** was washed with 10 mL of boiling chloroform. Filtering off the cold suspension gave 2.76 g (35% yield) of the product.

1,3-Bis(chlorocarbonyl)bicyclo[1.1.1]pentane (6). A 24.6-g portion (0.157 mol) of the diacid **1** and 45 mL of thionyl chloride were refluxed until a clear solution was formed (about 10 h). Excess thionyl chloride was evaporated, and the crystalline residue was distilled on a Kugelrohr apparatus (120 °C/12 mmHg), giving 26.92 g (89% yield) of **6**: mp 55–57 °C; ^{1}H NMR δ 2.58 (s); ^{13}C NMR δ 44.57, 54.80, 169.55; IR (C=O) 1794; MS, m/z (relative intensity) 159 (1.4, M – Cl), 157 (4.4, M – Cl), 131 (1.3), 129 (4.0), 103 (11.6), 101 (32.4), 65 (100); HRMS, m/z (calcd for $C_7H_6ClO_2$ 157.0056) 157.0054. Anal. Calcd for $C_7H_6Cl_2O_2$: C, 43.55; H, 3.13; Cl, 36.74. Found: C, 43.48; H, 3.14; Cl, 36.76.

Dimethyl Bicyclo[1.1.1]pentane-1,3-dicarboxylate (7). First, 26.92 g (0.139 mol) of **6** was slowly added to 75 mL of stirred anhydrous methanol. Then, when the addition was completed, the mixture was refluxed for 30 min. Evaporation of methanol gave a crystalline solid, which after short-path distillation (125–130 °C/12 mmHg) gave 25.24 g (99% yield) of **7**: mp 92 °C; ^{1}H NMR δ 2.30 (s, 6 H), 3.67 (s, 6 H); ^{13}C NMR δ 37.46; 51.45, 52.68, 169.31; IR: 1739, 1211; MS, m/z (relative intensity) 153 (31, M – OMe), 152 (57), 125 (51), 124 (80), 96 (100), 66 (70), 64 (59); HRMS, m/z (calcd for $C_8H_9O_3$ 153.0552) 153.0549. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.78; H, 6.58.

3-Methoxycarbonylbicyclo[1.1.1]pentane-1-carboxylic Acid (8). To a gently refluxed and stirred solution of 25.24 g (0.137 mol) of the dimethyl ester **7** in 200 mL of methanol, a solution of 5.50 g (0.137 mol) of sodium hydroxide in 50 mL of methanol was added during 1.5 h. When the addition was completed, the mixture was stirred and refluxed for 1 h. Methanol was evaporated, and the white sodium salts were vacuum dried. The salts were dissolved in 150 mL of water, unreacted **7** was extracted with 4 × 50 mL of methylene chloride (3.00 g of **7** was recovered), and the aqueous phase was acidified with 12 mL of concentrated hydrochloric acid. The product was extracted with 4 × 50 mL of methylene chloride, and the extracts were dried with sodium sulfate. Evaporation of the solvent gave 18.12 g (88% yield corrected for recovered **7**) of crude product **8** (mp 137.5–140 °C). Crystallization from heptane–chloroform gave pure **8**: mp 139.5–140 °C (lit.[1] mp 139.5–140.2 °C); ^{1}H NMR δ 2.35 (s, 6 H), 3.69 (s, 3 H); ^{13}C NMR δ 37.43, 51.80, 52.69, 169.61, 174.73; MS, m/z (relative intensity) 153 (1, M – OH), 152 (4), 139 (13), 138 (14), 125 (10), 124 (16), 111 (17), 110 (31), 96 (53), 93 (22), 83 (29), 82 (100), 67 (52), 66 (62), 65 (98).

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Registry No. **1**, 56842-95-6; **2**, 35634-10-7; **3**, 105542-93-6; **4**, 115913-30-9; **5**, 98577-44-7; **6**, 115913-31-0; **7**, 115913-32-1; **8**, 83249-10-9; $(CH_3CO)_2$, 431-03-8; acetaldehyde, 75-07-0.

Heterogeneous Acid-Catalyzed Amination of Isobutene to *tert*-Butylamine

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Despite extensive studies on direct amination of lower alkenes[2,3] to form the corresponding alkylamines, this transformation has been achieved in a single step only by treatment with alkali metal amide catalysts.[3,4] While amination of ethene proceeds satisfactorily, isomerization and polymerization of the alkene substrate complicate the synthesis of propyl and butylamines.[5] We recently re-

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Table I. Effect of Catalyst Acidity on Amination of Isobutene[a]

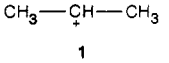
catalyst	concentration of strong acid sites[b]	conversion[c] 220 °C	240 °C	260 °C	280 °C	300 °C
SiO_2/Al_2O_3[d]	<0.05	<0.05	0.5	1.9	5.0	e
H–Y[f]	1.0	0.7	3.3	7.9	8.6	8.5
RE–Y[g]	0.9	1.0	3.5	8.9	9.1	8.5
H–mordenite[h]	1.4	0.9	2.9	5.9	7.7	8.3
Na–Y[i]	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

[a] All reactions were followed by GLC using the conditions described in the Experimental Section. [b] Millimole of ammonia chemisorbed at 200 °C/gram of catalyst; see text. [c] To *tert*-butylamine at 756 psia and 1000 h^{-1}; selectivity to *tert*-butylamine is >99%. [d] Davison 970 silica alumina. [e] Not determined. [f] Prepared from the sodium-exchanged form; see the Experimental Section. [g] Linde SK-500. [h] Norton Z900H. [i] Linde LZ-Y52.

ported the first acid-catalyzed amination of ethene to ethylamine via zeolite catalysis.[6] We now report our observations in attempts to extend this methodology to the preparation of *tert*-butylamine from isobutene.

Conversion of isobutene and ammonia to *tert*-butylamine is limited by thermodynamic equilibrium. Calculated product distributions based solely on the reported thermodynamic properties[7,8] of isobutene, ammonia, and *tert*-butylamine indicate that amination is favored by low temperature, high pressure, and high ammonia/isobutene ratio. However, high reaction temperatures are required for product desorption in the amination of simple olefins. For example, significant conversions of ethene to ethylamine required temperatures of 360–370 °C with zeolite catalysts.[6] In the presence of solid acid catalysts, amination of isobutene is observed at temperatures as low as 220 °C. Conversion to *tert*-butylamine with zeolite catalysts passes through a maximum at 260–280 °C and decreases to the equilibrium limit as the reaction temperature is raised to 300 °C (Table I, Figure 1). Over this temperature range, high selectivities (≥99%, based on isobutene) to *tert*-butylamine are obtained with a 2/1 ammonia/isobutene molar feed ratio. Oligomerization of isobutene is not observed below 280 °C and is not significant (<2%) below 300 °C. At lower ammonia/isobutene feed ratios (e.g., <1/1 mole ratio), acid-catalyzed polymerization of isobutene intervenes, and selectivity to *tert*-butylamine decreases rapidly.

Activity of solid acid catalysts for amination of isobutene generally correlates with the number of strong acid sites, as determined by temperature-programmed desorption of ammonia.[9] (The amount of ammonia chemisorbed at 200 °C is taken as a measure of the number of strong acid sites.) As a result of adventitious amorphous alumina formed in the pore structure during synthesis, H-mordenite displays lower activity than either H–Y or rare earth exchanged Y zeolites. Surprisingly, despite its low acidity, silica–alumina also catalyzes formation of *tert*-butylamine. Within the range of its thermal stability (≤220 °C), the activity of H-Nafion for isobutene amination is identical with that for silica–alumina. The necessity of acid catalysis is demonstrated by the negligible activity of the nonacidic sodium-exchanged Y zeolite. Consequently, formation of *tert*-butylamine involves a cationic intermediate on the catalyst surface. By analogy with the recent observation of isopropyl cation 1 upon treatment of H–Y zeolite with



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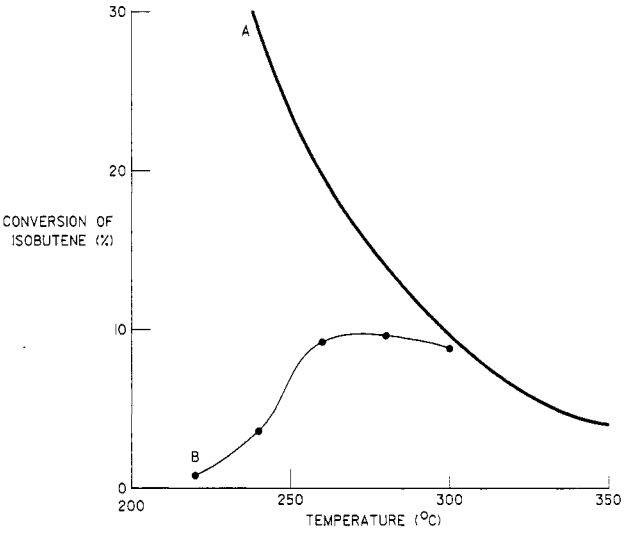
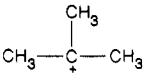


Figure 1. Equilibrium conversion of isobutene to *tert*-butylamine. Plot of conversion vs temperature for 2/1 ammonia/isobutene feed at 765 psia: (A) calculated equilibrium; (B) observed conversion with RE–Y.

propene at room temperature,[10] the cationic intermediate is probably the *tert*-butyl cation **2**. Formation of **2** results from protonation of isobutene by either a surface acid site or a chemisorbed ammonium ion. Reaction of **2** with ammonia, either adsorbed on the catalyst surface or from the gas phase, forms chemisorbed *tert*-butylamine. Subsequent product desorption would regenerate the catalytic site.



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Although equilibrium conversions to *tert*-butylamine are low, the simplicity and high selectivity of this process, coupled with the absence of inorganic coproducts, provide distinct advantages over the traditional two-step hydrogen cyanide based route to *tert*-butylamine.[11]

Experimental Section

All catalysts were commercially available except H–Y zeolite, which was prepared from the sodium form.[12] Ammonia and isobutene were obtained from Air Products (Specialty Gases, Hometown, PA) in high purity (>99.9%) and were used as received.

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Catalytic activity was evaluated in a Chemical Data Systems isothermal tubular reactor. The reactor consists of a 316 stainless steel tube (22.9 cm × 0.64 cm) mounted inside a close-fitting metal block, which is instrumented for temperature control. A thermowell extending axially next to the reactor measured reactor temperature. Reagents were metered to the reactor as liquids by using Isco Model 314 high-pressure syringe pumps. Prior to introduction to the reactor, the feeds were vaporized and mixed in a counter-current mixer maintained at 150 °C. Flow rates of ammonia and isobutene were adjusted to obtain the desired mole ratio of reactants and total flow rate (GHSV at STP).

Product analyses were carried out by on-line gas–liquid chromatography with a Varian Model 6000 Gas Chromatograph equipped with a 6 ft × $^1/_4$ in. 20% Carbowax 20M on Chromosorb T column and a VISTA 402 Chromatography Data System. Quantitation was based on comparison of peaks with external standards. Identities of major products were confirmed by GC–MS.

Catalyst samples (12–18 mesh) were heated (90 °C) in the reactor under nitrogen (10 sccm at 1 atmosphere) for 16–18 h. The temperature was then raised to the desired level over 3 h. Nitrogen was shut off. Ammonia was introduced, and the desired pressure was set with the back-pressure regulator. Isobutene was then introduced to obtain the desired feed ratio. Performance of each catalyst was evaluated over 24 h.

Catalyst acidity was determined by heating a sample of the powdered catalyst at 400 °C under nitrogen in a Du Pont Model 951 Thermogravimetric Analyzer. The sample was cooled to 20 °C, and ammonia was adsorbed onto it. Temperature-programmed desorption of ammonia indicated the number of strong acid sites (millimole of ammonia chemisorbed at 200 °C/gram of catalyst; see Table I).

Registry No. SiO_2, 7631-86-9; Al_2O_3, 1344-28-1; isobutene, 115-11-7; NH_3, 7664-41-7; *tert*-butylamine, 75-64-9.

Lithium Enolate Additions to the Tropone Nucleus

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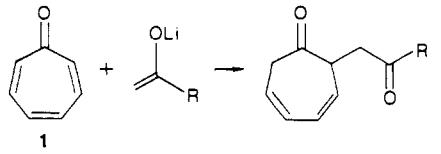
Nature is replete with examples of natural products that display a seven-membered carbocycle as a prominent structural feature. Although considerable progress has been made on the synthesis of many of these compounds,[1] only recently have strategies emerged that attempt to assemble the target molecules by starting from a pre-existing seven-membered ring system.[2] This situation is due, in part, to a paucity of appropriately functionalized candidates for starting materials. We have found 2,4,6-cycloheptatrien-1-one (tropone, 1) to be an excellent building block from which to construct complex carbon skeletons.[2a,b] In conjunction with our continuing efforts to exploit the unique reactivity of this compound in natural product synthesis, we herein describe an efficient protocol for appending *functionalized* substituents onto the troponoid nucleus via the addition of enolate nucleophiles.

To date direct substitution of tropones has, for the most part, been restricted to the addition of relatively unfunctionalized nucleophiles,[3] and it is surprising that, prior to our current work, enolates had not been examined in this context.[4] This methodology was developed in response to the more general inaccessibility of substituted tropones and dihydrotropone species and was designed to provide products amenable to further manipulation in a synthetic sequence.[5] To this end, the procedure exploits the unique proclivity of the troponoids for incorporating nucleophiles through additions to the conjugated trienone system in a 1,8-fashion.[6] This mode of addition is particularly attractive from a synthetic perspective since it results in the formation of products that retain a maximum level of functionalization.



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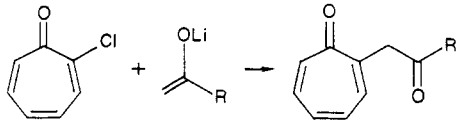
The chemistry described herein is equally efficient in producing 2-substituted tropones and dihydrotropones. Typically, substituted dihydrotropones can be prepared by the low-temperature addition of tropone (1) to a solution of the appropriate lithium enolate in THF. Table I displays the results of several enolate additions to the parent trienone. Of particular note is the clean regioselective formation of the 1,6-disubstituted adducts in entries 3 and 4.



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A similar procedure using 2-chlorotropone (2) yields the corresponding substituted tropone adducts. A presumed addition–elimination process ensues under these conditions to provide the tropone products directly.[5c,d] Attempts to isolate and identify any intermediates formed during these reactions have been unsuccessful to date. Inspection of these observations reveals that a wide range of functionalized substituents can be efficiently incorporated onto the tropone nucleus through the use of this technology.

Experimental Section

Proton and ^{13}C NMR spectra were recorded on a Nicolet QE-300 spectrometer. Chemical shifts are reported in parts per million downfield from tetramethylsilane (Me_4Si). Infrared spectra were obtained on a Nicolet 20-Dx spectrophotometer. THF was distilled from sodium benzophenone ketyl prior to use, and flash chromatography was done according to the method of Still.[7] Tropone was prepared by the procedure developed by Radlick[8] and 2-chlorotropone was prepared by Terborg's procedure.[5c]

General Procedure for the Addition of Lithium Enolates to Tropone or 2-Chlorotropone. To a solution of diisopropylamine (0.14 mL, 1.1 mmol) in 1 mL of dry THF at −78 °C was added *n*-BuLi (1.6 M in hexanes) (0.53 mL, 1.1 mmol). After the mixture was stirred for 1 h, 1 mmol of the appropriate carbonyl

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