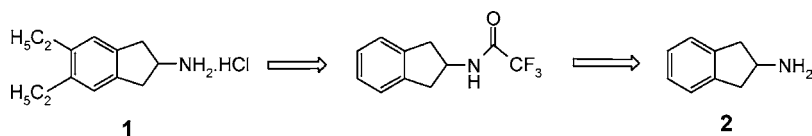
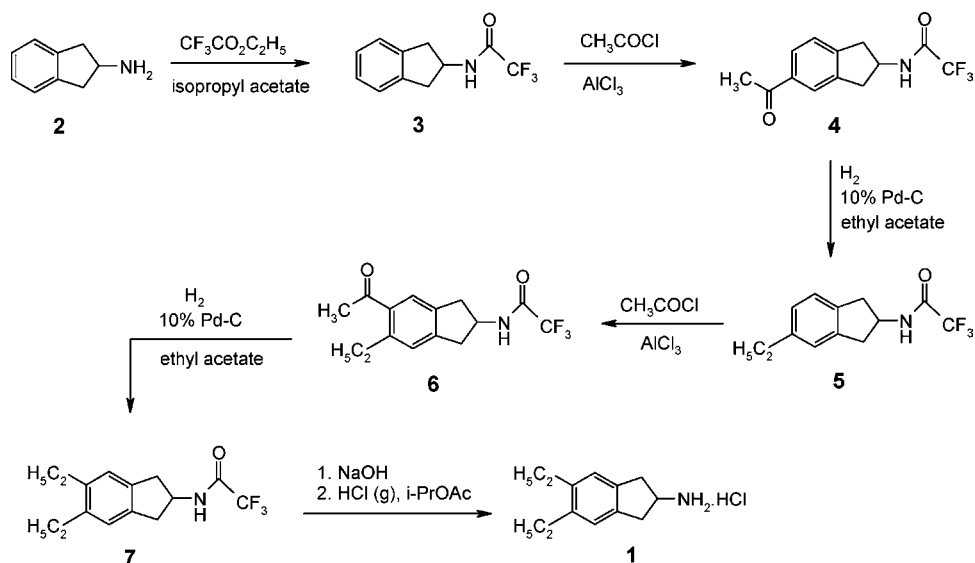


Scheme 1



Scheme 2



We next decided to investigate the Friedel–Crafts acylation using acetyl chloride both as the acetylating agent as well as the solvent. When the usual amounts of AlCl_3 (2.5 equiv), acetyl chloride (3.0 equiv), and **3** (1.0 equiv) were used for the reaction, the initial slurry became a solution, and then it solidified. On the other hand, with more acetyl chloride (≥ 6.0 equiv), the reaction proceeded well, and it remained a solution. Therefore, the amount of acetyl chloride was optimized to be 6.0 equiv and that of AlCl_3 2.5 equiv. Thus, AlCl_3 was added to cooled acetyl chloride (0–5 °C) in four equal portions. After the addition of AlCl_3 , substrate **3** was added in five equal portions to obtain a clear solution. After stirring at 0–5 °C for 1 h, the reaction mixture was diluted with heptane and reverse-quenched into a mixture of 1 N HCl and isopropyl acetate. The mixture was stirred at room temperature for 1 h and at 40–45 °C for 45 min. The product was isolated by cooling the mixture to room temperature and filtration. The yield of **4** was 90% with undetectable amounts of the undesired 4-regioisomer. The product contained 0.5% of aluminum. A use-test showed that it had no effect on the next hydrogenation step and was removed in the workup. To assess tolerability of the undesired 4-regioisomer in **4** on the quality of **1**, we observed that **4**, containing 3% of the undesired 4-regioisomer, afforded **1** of the desired purity. The 4-regioisomer can also be removed by reslurrying the crude **4** in isopropyl acetate and heptane (1/4.6) at 72–75 °C for 3 h.

With successful regioselective Friedel–Crafts acylation conditions in hand, our next goal was to reduce the acetyl group to the ethyl group. Such a conversion was reported in a patent by hydrogenation over Pd–C in THF.⁵

We examined the hydrogenation of **4** in ethanol and ethyl acetate. Both solvents gave satisfactory results. Ethyl acetate was selected for initial development. Degussa catalyst E101 NE/W, which is 10% Pd on carbon (50% wet), was used for the hydrogenation. The amount of catalyst, 10% of weight of the substrate **4**, was optimized for this hydrogenation. The reaction worked well under atmospheric pressure and at room temperature. Due to the operational difficulty of removing the oxygen in the headspace of the reactor by hydrogen at atmospheric pressure in the pilot plant, we decided to conduct this hydrogenation at 40 psig. The reaction was complete in 4 h. The corresponding alcohol intermediate was observed in the beginning of the reaction, but it was not detectable at the end of the reaction. To achieve maximum throughput, the reaction was performed in 3.5 mL of ethyl acetate per gram of **4**. At room temperature, **4** was not completely soluble in this amount of ethyl acetate. However, a complete solution was obtained as the reaction progressed. After the hydrogenation and removal of the catalyst by filtration, the solvent was switched to heptane, and the resulting suspension was stirred at 40 °C for 30 min and then slowly cooled to room temperature with efficient stirring. Product **5** was isolated by filtration in 91% yield with 99.8% HPLC purity. Any undesired 4-regioisomer of **5** was not efficiently removed in this process. It was mainly purified during the isolation of **7** in the second hydrogenation step.

The hydrogenation of **4** in ethanol was then carried out with a lesser amount of 5% Pd on carbon. The product was crystallized from a mixture of ethanol and water to afford **5** in 95.9% yield with no detectable amounts of the undesired regioisomer.

Similar to the previous Friedel–Crafts acylation of **3** to **4**, the acylation of **5** was first carried out in dichlo-

(5) Patsidis, K.; Palackal, S. J.; Alt, H. G. U.S. Patent 5,393,911, February 28, 1995.

romethane. The ratio of the desired regioisomer **6** to the undesired regioisomer was ~90 to 10 in the crude reaction mixture. Again, prolonged reaction at higher temperature (room temperature) resulted in a dark reaction mixture and decomposition. Thus, acetyl chloride (3.0 equiv) was added slowly at 0–5 °C to a mixture of AlCl₃ (2.5 equiv) in dichloromethane. Then, solid **5** was added in five equal portions at 0–5 °C to obtain a solution. The desired regioisomer **6** was obtained in 94% yield containing 6–7% of the undesired regioisomer. Since the undesired regioisomer was lowered to 1.2% during the isolation of **7** in the next hydrogenation step, crude **6** was used as such. However, **6** could be recrystallized from a mixture of dichloromethane and heptane (1:4 v/v) to achieve higher purity (<1.5% of the undesired regioisomer), but the yield was significantly lower (85%).

Similar to previous Friedel–Crafts acetylation, dichloromethane was eliminated by using acetyl chloride as a reagent as well as the solvent. While 2.5 equiv of AlCl₃ was satisfactory, 12.0 equiv of acetyl chloride had to be used. The reaction mixture was again quenched into a mixture of 1 N HCl and isopropyl acetate, and the product **6** was isolated in 94% yield by the addition of heptane, and it contained 9% of the undesired regioisomer.

The reduction of the acetyl group in **6** to the ethyl group was achieved by hydrogenation using 10% Pd/C catalyst in ethyl acetate. However, in this case we observed that the conversion of the alcohol intermediate to the ethyl group was much slower, and it required ~14 h to convert the alcohol intermediate to **7** at room temperature under 40 psig of hydrogen. We, therefore, decided to examine this hydrogenation at higher temperature. We found that the conversion of the alcohol intermediate to the product **7** was complete in 3 h at 50 °C. Thus, we optimized the reaction conditions that involved the hydrogenation first at the room temperature for 2 h, and then at 50 °C for 2.5 h, which converted all the alcohol intermediate to the product **7**. The workup was also similar to the previous hydrogenation. A solvent switch to heptane was carried out by concentrating the filtrate after removing the catalyst. The heptane suspension was stirred at 50–60 °C for 3 h. This procedure was highly efficient to remove the undesired regioisomer in the mother liquor. The reaction mixture containing 10% undesired regioisomer could be purified to give **7** with <2.5% of the regioisomer in 85% or higher yield.

The hydrogenation of **6** in ethanol was then carried out with a lesser amount of 5% Pd on carbon. The product was crystallized from a mixture of ethanol and water to afford **7** in 82.5% yield.

Having introduced the two ethyl groups at the 5- and 6-positions of 2-aminoindan, the final step was the deprotection of the trifluoroacetyl group. The deprotection of the trifluoroacetyl protecting group in **7** was studied under basic conditions. No significant hydrolysis was observed with NaOMe in refluxing methanol. In a biphasic solvent system using aqueous NaOH and an organic solvent, such as isopropyl acetate or toluene, the hydrolysis was incomplete, even in the presence of a phase-transfer catalyst (Bu₄NBr).

We found that a homogeneous mixture of 6 N NaOH and ethanol (1:1 v/v) at reflux led to a fast (1 h) and clean deprotection under nitrogen. After workup, a solution of the free base of **1** was obtained, which was concentrated to remove residual H₂O azeotropically. The free base of **1** was converted to the HCl salt by a slow addition of the free base solution to 1.43 equiv of a 2 N solution of HCl gas in isopropyl acetate at 20–30 °C. The salt formation can also be carried out using HCl gas above the surface rather than a solution. The crude **1** still contained some of the undesired regioisomer carried over from **6**. The crude product was then recrystallized from a mixture of ethanol and isopropyl acetate to afford pure **1** with no detectable regioisomeric impurity. Thus, 2.5% of the undesired regioisomer was efficiently removed to nondetectable amounts.

In summary, an efficient and economical synthesis of 5,6-diethyl-2,3-dihydro-1*H*-inden-2-amine hydrochloride (**1**) utilizing 2-aminoindan as a cheap and commercially readily available starting material is described (Scheme 2).⁶ The newly developed synthesis involves six steps with 49% overall yield, and it introduces two ethyl groups at the 5- and 6-positions via sequential regioselective Friedel–Crafts acetylations and hydrogenations of *N*-protected-2-aminoindan. The Friedel–Crafts acetylations can be carried out neat with high regioselectivity using acetyl chloride as the reagent as well as the solvent, thus avoiding the use of halogenated solvents.

Experimental Section

Melting points were measured on a Buchi 535 melting point apparatus. ¹H and ¹³C NMR spectra were recorded on a Bruker 300 instrument.

***N*-(2,3-Dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (3).** A 1-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, cooling bath, and nitrogen inlet–outlet, was charged with 2-aminoindan (**2**, 104.0 g, 781.0 mmol) and isopropyl acetate (200.0 mL). The solution was cooled to an internal temperature at 0–5 °C, and ethyl trifluoroacetate (133.0 g, 936.0 mmol) was added over 40 min while maintaining the internal temperature at 0–10 °C. The thick slurry was stirred at 0–10 °C for 2 h and then warmed to 20–25 °C over 30 min. Heptane (60.0 mL) was added, and the stirring was continued for an additional 30 min. The solids were collected by filtration, and washed with heptane (3 × 50.0 mL) or until the filtrate was colorless. The solids were dried at 60–65 °C in vacuo to afford *N*-(2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**3**, 149.2 g, 83.4%): mp 153–155 °C; ¹H NMR (CDCl₃, δ) 2.89 (dd, 2H, *J* = 4.4 and 16.4 Hz), 3.38 (dd, 2H, *J* = 7.1 and 16.4 Hz), 4.76 (m, 1H), 6.54 (br, 1H), 7.19–7.24 (m, 4H); ¹³C NMR (CDCl₃, δ) 39.97, 51.62, 125.30, 127.59, 140.24; Calc for C₁₁H₁₀F₃NO: C, 57.64; H, 4.40; N, 6.11; F, 24.87. Found: C, 57.55; H, 4.22; N, 6.07; F, 24.94.

***N*-(5-Acetyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (4).** *Procedure 1: Regioselective Friedel–Crafts Acetylation of 3 in Dichloromethane.* A 1-L, four-necked,

(6) Prasad, M.; Lohse, O.; Hu, B. WO 03/076387, March 7, 2003.

round-bottomed flask (rinsed with dichloromethane), equipped with a mechanical stirrer, digital thermometer, cooling bath, and nitrogen inlet–outlet, was charged with aluminum chloride (102.0 g, 765.0 mmol) and dichloromethane (280.0 mL) at 20–25 °C. The slurry was cooled to an internal temperature at 0–5 °C, and acetyl chloride (72.0 g, 917.0 mmol) was added over 20 min while maintaining the temperature at 0–5 °C. The white suspension was stirred at 0–5 °C for 15 min and *N*-(2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**3**, 70.0 g, 305.0 mmol) was added in five equal portions (14.0 g each) at 5-min intervals (total time = 25 min) while maintaining the internal temperature at 0–7 °C. Dichloromethane (20.0 mL) was added to wash off any solids sticking to the wall of the flask. The resulting tan solution was stirred at 0–5 °C for 1 h and then added to 1 N HCl (500.0 mL, precooled to 0–5 °C) in a 2-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, and a cooling bath, while maintaining the temperature at 0–25 °C. The 1-L, round-bottomed flask and the transferring tube were rinsed with dichloromethane (40.0 mL) and the dichloromethane added to the reaction mixture. The biphasic reaction mixture was warmed to 20–25 °C. The layers were separated, and the organic layer was washed with water (100.0 mL).

The organic layer was transferred to a 2-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet–outlet, a reflux condenser, and a heating mantle. The solution was warmed to an internal temperature at 40 ± 3 °C to achieve gentle refluxing. Heptane (1.2 L) was added slowly over a period of 50 min while maintaining the temperature at 40–55 °C to maintain a gentle reflux. The resulting slurry was stirred at 55–58 °C for an additional 30 min. The suspension was cooled to 20–25 °C over a period of 30 min with efficient stirring and stirred at 20–25 °C for an additional 2 h. The solids were collected by filtration, washed with a mixture of dichloromethane/heptane (2 × 100.0 mL, 20:80 v/v), and dried at 60–65 °C in vacuo to afford *N*-(5-acetyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**4**, 73.4 g, 88.7%): mp 112–114 °C; ¹H NMR (CDCl₃, δ) 2.52 (s, 3H), 2.94–3.01 (m, 2H), 3.36–3.44 (m, 2H), 4.80 (m, 1H), 7.23 (br, 1H), 7.27–7.32 (m, 1H), 7.74–7.77 (m, 2H); ¹³C NMR (CDCl₃, δ) 26.98, 39.44, 39.97, 51.58, 125.01, 125.25, 128.17, 136.75, 141.17, 143.36, 198.46; Calc for C₁₃H₁₂F₃NO₂: C, 57.57; H, 4.46; N, 5.16; F, 21.01. Found: C, 57.45; H, 4.48; N, 5.07; F, 20.93.

Procedure 2: Regioselective Friedel–Crafts Acetylation of **3 in Acetyl Chloride.** A 1-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, cooling bath, and nitrogen inlet–outlet, was charged with acetyl chloride (205.5 g, 2.62 mol) and cooled to an internal temperature of 0–5 °C. Aluminum chloride (145.5 g, 1.09 mol) was added in four equal portions (36.4 g each) at such a rate to maintain the internal temperature below 15 °C. The slurry was cooled to 0–5 °C and stirred for 15 min. *N*-(2,3-Dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**3**, 100.0 g, 0.436 mol) was added in five equal portions (20.0 g each) at 10-min intervals while maintaining the internal

temperature at 0–10 °C. The resulting tan solution was stirred at 0–5 °C for 1 h. To the solution was added heptane (400.0 mL) at 0–5 °C. The resulting biphasic mixture was added to a precooled (0 to –5 °C) mixture of 1 N HCl (650.0 mL) and isopropyl acetate (125.0 mL) in a 5-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, and a cooling bath, over a period of 20 min while maintaining the internal temperature at 0–25 °C. The 1-L round-bottomed flask was rinsed with acetyl chloride (20.0 mL), followed by heptane (110.0 mL), and the rinses were added to the batch. The reaction mixture was warmed to 22–24 °C over a period of 30 min, then heated to an internal temperature at 40–45 °C, and stirred at 40–45 °C for 1 h. The slurry was cooled to 21–25 °C and stirred for 1 h. The solids were collected by filtration, washed with heptane (2 × 200.0 mL), followed by 1 N HCl (350.0 mL) and deionized water (2 × 200.0 mL). The solids were dried at 60–65 °C in vacuo to afford *N*-(5-acetyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**4**, 106.1 g, 90.0%).

***N*-(5-Ethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**5**).** **Procedure 1: Hydrogenation of **4** in Ethyl Acetate.** A 1-L Buchi reactor was charged with *N*-(5-acetyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**4**, 100.0 g, 368.7 mmol), 10% Pd–C (10.0 g, 50% water), and ethyl acetate (350.0 mL) to obtain a suspension. The reactor was sealed and pressurized with N₂ to 40 psig. The N₂ was vented and the process repeated two more times. The reactor was again repressurized with N₂ to 40 psig, and agitation was started at 300 rpm. The reaction mixture was heated to 25 °C and held for 10 min to stabilize the temperature. Agitation was stopped, and the N₂ was vented. The reactor was pressurized with H₂ to 40 psig, which was then vented. This process was repeated two more times and the reactor was repressurized with H₂ to 40 psig. The in-line pressure regulator was set to maintain 40 psig of H₂ inside the reactor, and the hydrogen supply valve was opened. Agitation was started at 450 rpm. The heterogeneous reaction mixture was stirred at 23–25 °C and 450 rpm for 4 h. The hydrogen supply valve was closed, and the H₂ was vented. The reactor was purged three times with N₂, the reaction mixture was filtered over a pad of Celite (15.0 g), and the filtrate was saved. The reactor vessel was rinsed with ethyl acetate (210.0 mL) and filtered through the Celite pad. The cake was washed with ethyl acetate (210.0 mL).

The filtrates were combined and transferred to a 2-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet–outlet, and heating mantle. The combined filtrates were concentrated in vacuo at 35–40 °C to collect approximately 670 mL of solvent to obtain approximately 100 mL of a suspension. Heptane (870.0 mL) was added and the solution was concentrated to collect approximately 270 mL of solvent to obtain approximately 700 mL of a slurry. Heptane (270.0 mL) was added, and the suspension was concentrated to collect approximately 270 mL of solvent to obtain approximately 700 mL of a slurry. Heptane (270.0 mL) was added to obtain approximately 1000 mL of a suspension. The suspension was stirred at 35–40 °C for 30 min. The

suspension was cooled to 20–25 °C over a period of 30 min with efficient stirring. Stirring was continued at this temperature for an additional 2 h. The solids were collected by filtration, washed with heptane (100.0 mL) in two equal portions of 50 mL each, and dried at 60–65 °C in vacuo to afford *N*-(5-ethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**5**, 87.0 g, 91.0%): mp 112–114 °C; ¹H NMR (CDCl₃, δ) 1.23 (t, 3H, *J* = 7.5 Hz), 2.63 (q, 2H, *J* = 7.5 Hz), 2.80–2.88 (m, 2H), 3.29–3.38 (m, 2H), 4.75 (m, 1H), 6.63 (br, 1H), 7.04–7.09 (m, 2H), 7.16 (d, 1H, *J* = 7.7 Hz); ¹³C NMR (CDCl₃, δ) 16.25, 29.12, 39.68, 40.01, 51.80, 124.77, 125.09, 127.29, 137.42, 140.41, 143.96; Calc for C₁₃H₁₄F₃NO: C, 60.70; H, 5.49; N, 5.37. Found: C, 60.67; H, 5.48; N, 5.44.

Procedure 2: Hydrogenation of 4 in Ethanol. A reactor was charged with *N*-(5-acetyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**4**, 108.5 g, 400.0 mmol) and ethanol (94%; 542.0 mL). After inertizing the suspension with N₂, 5% Pd–C (5.42 g, 50% water) was added. After inertizing with N₂ the reactor was pressurized with H₂ to 3 bar at 25 °C internal temperature. The reaction mixture was hydrogenated until no H₂ was consumed. The hydrogen was replaced with N₂, the reaction mixture was filtered, and the filtrate was saved. The reactor vessel was rinsed with ethanol (109.0 mL) and filtered to wash the cake. The filtrates were combined and transferred to another flask. The reactor was washed with ethanol (50.0 mL). The combined filtrates were concentrated at 95–105 °C (jacket temperature) and 70–80 °C (internal temperature) to collect approximately 290.0 mL of solvent. Water (260.0 mL) was added at 70–80 °C (internal temperature) within 30–60 min. The clear solution was cooled to 65 °C and seeded at this temperature with **5**. The mixture was then cooled to 0–5 °C in 1 h, and stirred at this temperature for additional 2 h. The solids were collected by filtration, washed with a precooled (0 °C) mixture of ethanol and water (1:1 v/v; 102.0 mL), and dried at 50 °C in vacuo (20 mbar) for 20 h to afford *N*-(5-ethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**5**, 98.6 g, 95.9%).

***N*-(5-Acetyl-6-ethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**6**).** **Procedure 1: Regioselective Friedel–Crafts Acetylation of 5 in Dichloromethane.** A 2-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet–outlet, and heating cooling bath, was charged with aluminum chloride (194.4 g, 1457.7 mmol) and dichloromethane (525.0 mL). The mixture was stirred to give a suspension which was cooled to an internal temperature at 0 ± 5 °C over a period of 15 min. Acetyl chloride (137.3 g, 1749.2 mmol) was added over a period of 30 min while maintaining the internal temperature at 0 ± 5 °C. A suspension was obtained, which was stirred at this temperature for an additional 15 min. *N*-(5-Ethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**5**, 150.0 g, 583.1 mmol) was added in five equal portions (30.0 g each) while maintaining the internal temperature at 0 ± 5 °C. A solution was obtained when about half of the starting material was added. Dichloromethane (75.0 mL) was added to wash off any solids sticking on the

wall of the flask. The solution was stirred at 0–5 °C for an additional 1 h.

A 3-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet–outlet, and heating cooling bath, was charged with 1 N hydrochloric acid (1.0 L) and cooled to an internal temperature at 0–5 °C. The reaction mixture was added to hydrochloric acid solution over a period of 45 min while maintaining the internal temperature below 25 °C. Dichloromethane (2 × 90.0 mL) was used to rinse the reaction flask and the transferring pipe and was then added to the quenched mixture. The organic layer was separated and saved. The aqueous layer was extracted with dichloromethane (150.0 mL). The organic layers were combined and washed with water (500.0 mL).

The organic layer was transferred to a 2-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet–outlet, and heating mantle. The organic layer was concentrated at atmospheric pressure at 40 ± 3 °C to collect approximately 700 mL of solvent to obtain approximately 340 mL of solution. Heptane (1.125 L) was added over a period of 15 min while maintaining the internal temperature at 40–50 °C (gentle refluxing) with efficient stirring. A solid precipitated out. The resulting suspension was stirred at 55 ± 3 °C (gentle refluxing) for an additional 30 min. The suspension was cooled to an internal temperature at 20–25 °C over a period of 1 h with efficient stirring. The suspension was stirred at 20–25 °C for an additional 2 h. The solids were collected by filtration, washed with a mixture of heptane/dichloromethane (2 × 100.0 mL, 5:1, v/v), and dried at 60–65 °C in vacuo to afford *N*-(5-acetyl-6-ethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**6**, 165.1 g, 94.0%): mp 124–127 °C; ¹H NMR (CDCl₃, δ) 1.18 (t, 3H, *J* = 7.5 Hz), 2.53 (s, 3H), 2.79–2.94 (m, 4H), 3.34–3.42 (m, 2H), 4.79 (m, 1H), 6.73 (br, 1H), 7.15 (s, 1H), 7.47 (s, 1H); ¹³C NMR (CDCl₃, δ) 16.43, 23.72, 27.45, 30.32, 39.48, 39.99, 51.67, 125.64, 127.19, 137.65, 137.74, 144.07, 144.12, 202.50; Calc for C₁₅H₁₆F₃NO₂: C, 60.20; H, 5.39; N, 4.68; F, 19.04. Found: C, 60.04; H, 5.54; N, 4.47; F, 18.89.

Procedure 2: Regioselective Friedel–Crafts Acetylation of 5 in Acetyl Chloride. A 250-mL, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, cooling bath, and nitrogen inlet–outlet, was charged with acetyl chloride (37.68 g, 480 mmol) and cooled to an internal temperature at 0 ± 5 °C. Aluminum chloride (13.33 g, 100 mmol) was added in four equal portions (3.33 g each) while maintaining the internal temperature below 15 °C. The resulting solution was cooled to 0 ± 5 °C and stirred for 5 min. *N*-(5-Ethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**5**, 10.29 g, 40 mmol) was added in five equal portions (2.06 g) at 10 min intervals while maintaining the internal temperature at 0–10 °C. The tan solution was stirred at 0 ± 5 °C for an additional 30 min. The reaction mixture was added to a precooled (0–5 °C) mixture of 1 N HCl (120.0 mL) and isopropyl acetate (13.0 mL) in a 500-mL, three-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, and

a cooling bath, over a period of 20 min while maintaining the internal temperature at 0–25 °C. The 250-mL round-bottomed flask was rinsed with acetyl chloride (3.0 mL) followed by heptane (13.0 mL) and added to the batch. The resulting slurry was warmed to 40–45 °C over a period of 30 min and then stirred for additional 1 h. Heptane (39.0 mL) was added, and the slurry was stirred at 40–45 °C for an additional 15 min. The slurry was cooled to 20–25 °C and stirred for 1 h. The solids were collected by filtration, washed with a mixture of heptane/isopropyl acetate (2 × 10.0 mL, 80:20 v/v), followed by 1 N HCl (36.0 mL) and deionized water (2 × 25 mL). The solids were dried at 60–65 °C in vacuo to afford *N*-(5-acetyl-6-ethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**6**, 11.3 g, 94.0%).

***N*-(5,6-Diethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**7**).** *Procedure 1: Hydrogenation of 6 in Ethyl acetate.* A 1-L Buchi reactor was charged with *N*-(5-acetyl-6-ethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**6**, 160.0 g, 534.6 mmol), 10% Pd–C (16.0 g, 50% water), and ethyl acetate (560.0 mL) to obtain a suspension. The reactor was sealed and pressurized with N₂ to 40 psig, which was then vented. This process was repeated two more times. The reactor was repressurized with N₂ to 40 psig, and agitation was started at 650 rpm. The reaction mixture was heated to 25 °C and held for 10 min to stabilize the temperature. Agitation was stopped, and the N₂ was vented. The reactor was pressurized with H₂ to 40 psig and then vented. This process was repeated two more times. The reactor was repressurized with H₂ to 40 psig and the in-line pressure regulator set to maintain 40 psig of H₂. The hydrogen supply valve was opened, and agitation was started at 650 rpm. The heterogeneous reaction mixture was stirred at 20–25 °C and 650 rpm for 2 h. The reaction mixture was heated to an internal temperature at 45–50 °C over a period of 30 min. The mixture was stirred at this temperature for an additional 3 h. The reaction mixture was cooled to 20–25 °C over a period of 30 min. The hydrogen supply valve was closed, and the H₂ was vented. The reactor was purged three times with N₂. The reaction mixture was filtered over a pad of Celite (24.0 g). The filtrate was saved. The reactor was rinsed with ethyl acetate (336.0 mL) which was filtered through the Celite pad. The cake was washed with ethyl acetate (336.0 mL). The filtrates were combined and transferred to a 5-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet–outlet, and heating mantle. The filtrates were concentrated in vacuo at 35–40 °C to collect approximately 1140 mL of solvent to obtain approximately 240 mL of a suspension. Heptane (1.4 L) was added, and the suspension was concentrated in vacuo at 35–40 °C to collect approximately 680 mL of solvent to obtain approximately 960 mL of a slurry. Heptane (1.6 L) was added to obtain approximately 2,560 mL of a suspension. The suspension was stirred at an internal temperature at 45–50 °C for 3 h. The suspension was cooled to an internal temperature at 20–25 °C over a period of 1 h with efficient stirring and stirred at this temperature for additional 2 h. The solids were collected by filtration, washed with heptane (2

× 250.0 mL), and dried at 60–65 °C in vacuo to afford *N*-(5,6-diethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**7**, 133.5 g, 87.5%): mp 155–156 °C; ¹H NMR (CDCl₃, δ) 1.21 (t, 6H, *J* = 7.5 Hz), 2.63 (q, 4H, *J* = 7.5 Hz), 2.82 (dd, 2H, *J* = 3.9 and 16.2 Hz), 3.33 (dd, 2H, *J* = 7.1 and 16.2 Hz), 4.75 (m, 1H), 6.53 (br, 1H), 7.06 (s, 2H); ¹³C NMR (CDCl₃, δ) 15.86, 25.85, 39.87, 51.79, 125.10, 137.80, 141.31; Calc for C₁₅H₁₈F₃NO: C, 63.15; H, 6.36; N, 4.91; F, 19.98. Found: C, 63.02; H, 6.30; N, 4.85; F, 19.64.

Procedure 2: Hydrogenation of 6 in Ethanol. A reactor was charged with *N*-(5-acetyl-6-ethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**6**, 119.72 g, 400.0 mmol) and ethanol (94%; 912.0 mL). After inertizing the suspension with N₂, 5% Pd–C (5.99 g, 50% water) was added. After inertizing with N₂ the reactor was pressurized with H₂ to 3 bar. The reaction mixture was hydrogenated at 40 °C (internal temperature) until no H₂ was consumed. The hydrogenation was then continued at 50 °C for an additional 1 h. The hydrogen was replaced with N₂, the reaction mixture was filtered at 40–50 °C, and the filtrate was saved. The reactor vessel was rinsed with ethanol (158.0 mL) at 40 °C and filtered to wash the cake. The filtrates were combined and transferred to another flask at >35 °C. The reactor was washed with hot (40–50 °C) ethanol (70.0 mL). The combined filtrates were heated to 75–78 °C (internal temperature), and water (456.0 mL) was added at 70–80 °C (internal temperature) within 30–60 min. The slightly cloudy solution was cooled to 60 °C (the product started crystallizing out as flakes). The mixture was stirred at 60 °C for 30 min and then heated to 65–67 °C (internal temperature). Stirring was continued at 65–67 °C for additional 1 h (during this time a homogeneous suspension was formed). The mixture was then cooled to 50 °C in 1 h, and then to 20 °C as quickly as possible. The mixture was stirred at this temperature for additional 2 h. The solids were collected by filtration, washed with a mixture of ethanol (89.0 mL) and water (35.5 mL), and dried at 55–60 °C in vacuo (20 mbar) for 20 h to afford *N*-(5,6-diethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**7**, 94.15 g, 82.5%).

5,6-Diethyl-2,3-dihydro-1*H*-inden-2-amine Hydrochloride (1**).** A 2-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet–outlet, and heating cooling bath, was charged with *N*-(5,6-diethyl-2,3-dihydro-1*H*-inden-2-yl)-2,2,2-trifluoroacetamide (**7**, 100.0 g, 350.5 mmol), 200-proof ethanol (500.0 mL), and 6 N NaOH (500.0 mL). The mixture was stirred under nitrogen to give a solution and heated to an internal temperature at 78 ± 3 °C over a period of 30 min to achieve gentle refluxing. The solution was stirred at this temperature for an additional 1 h. The solution was cooled to an internal temperature at 30–35 °C and concentrated in vacuo at 35 ± 5 °C to collect approximately 520 mL of solvent to obtain approximately 485 mL of a biphasic mixture (an oil layer floating on top of the aqueous layer). This mixture was cooled to 20–25 °C, and isopropyl acetate (500.0 mL) was added. After stirring for 5 min the organic layer was separated and saved. The aqueous layer was

extracted with isopropyl acetate (500.0 mL). The organic layers were combined and washed with water (300.0 mL).

The organic layer was concentrated in vacuo at 35 ± 5 °C to collect approximately 230 mL of solvent to obtain approximately 800 mL of a solution. This solution was added to a solution of HCl gas in isopropyl acetate (250.0 mL, 2 N, prepared by dissolving 18.3 g of hydrogen chloride gas in 250.0 mL of isopropyl acetate) over a period of 40 min while maintaining an internal temperature at 25 ± 5 °C. Solids formed immediately. The suspension was stirred at 20–25 °C for 2 h. The solids were collected by filtration, washed with isopropyl acetate (2×100.0 mL), and dried at 60–65 °C in vacuo to afford crude 5,6-diethyl-2,3-dihydro-1*H*-inden-2-amine hydrochloride (**1**, 78.3 g).

A 2-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet–outlet, and a heating/cooling bath, was charged with 5,6-diethyl-2,3-dihydro-1*H*-inden-2-amine hydrochloride (78.0 g) and 200-proof ethanol (624.0 mL). The suspension was stirred and heated to an internal temperature at 78 ± 3 °C to achieve gentle refluxing. To the resulting solution was added isopropyl acetate (624.0 mL) at a rate to maintain the internal temperature at 78 ± 3 °C. A precipitate

formed. The resulting suspension was stirred at this temperature for an additional 1 h. The suspension was cooled to an internal temperature at 20–25 °C over a period of 2 h with efficient stirring, and the stirring was continued for an additional 2 h. The solids were collected by filtration, washed with a mixture of isopropyl acetate/ethanol (2×100.0 mL, 70:30 v/v), and dried at 60–65 °C in vacuo to afford pure 5,6-diethyl-2,3-dihydro-1*H*-inden-2-amine hydrochloride (**1**, 70.8 g, 89.0%): mp >250 °C; ¹H NMR (CD₃OD, δ) 1.18 (t, 6H, *J* = 7.5 Hz), 2.63 (q, 4H, *J* = 7.5 Hz), 2.98 (dd, 2H, *J* = 4.5 and 16.4 Hz), 3.34 (dd, 2H, *J* = 7.1 and 16.4 Hz), 4.06 (m, 1H), 4.87 (br, 3H), 7.08 (s, 2H); ¹³C NMR (CD₃-OD, δ) 16.57, 26.88, 38.89, 53.31, 126.21, 138.24, 142.72; Calc for C₁₃H₂₀ClN: C, 69.15; H, 8.93; N, 6.20; Cl, 15.70. Found: C, 69.08; H, 8.80; N, 6.12; Cl, 15.75.

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