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Scalable, efficient process for the synthesis of (*R*)-3,5-bistrifluoromethylphenyl ethanol via catalytic asymmetric transfer hydrogenation and isolation as a DABCO inclusion complex

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Abstract—(*R*)-3,5-Bistrifluoromethylphenyl ethanol **2**, a key building block in the synthesis of aprepitant, has been synthesized from ketone **5** via catalytic asymmetric transfer hydrogenation using a simplified catalyst generation procedure. The process uses (1*S*,2*R*)-*cis*-1-aminoindan-2-ol **10** and dichloro(*p*-cymene)Ru(II)dimer **9** as the chiral ligand and metal source for the reduction. While the reduction provides **2** in 90–92% ee, an isolation of **2** as a 2:1 inclusion complex with DABCO was developed to allow for the upgrade of the enantiomeric excess to >99%.
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1. Introduction

Aprepitant **1** is an NK-1 receptor antagonist used for the treatment of chemotherapy-induced emesis. The structure of aprepitant contains three stereogenic centers, two of which are contained in its morpholine core (Scheme 1). Two recent reports from these laboratories described the use of chiral alcohol **2** as a key chiral building block for the synthesis of **1**. The first involved the coupling of **2** to acetal **3** followed by epimerization of the α-amino center to produce **1**.[1] The second involved the coupling of **2** to racemic lactam lactol **4** and then the use of the stereogenic center derived from **2** to establish the absolute and relative stereochemistry of the remainder of the molecule.[2] Essential to the development and implementation of both of these synthetic strategies was the availability of large quantities of **2** in high enantiomeric excess and chemical purity.

The most common approach for the enantioselective synthesis of aryl-ethanols such as **2** is the reduction of the corresponding acetophenone **5**. Various catalytic methods exist to effect this transformation including direct enantioselective hydrogenation[3] or borane reduction.[4] While these methods provide varying levels of performance, they generally require the use of air sensitive catalysts and or hazardous reagents.[5]

An alternative method for the reduction of acetophenones is the asymmetric transfer hydrogenation developed by Noyori.[6,7] This method uses isopropanol, a safe and benign hydride source, as the stoichiometric reductant in the reaction. One drawback of this method is the dilute conditions that the reactions are typically performed under. Dilute conditions are used to avoid incomplete conversion of the starting ketone and erosion of ee of the product, which result from the reversibility of the reaction.[6a] Formic acid has been used as an alternative reductant, however, the large amounts of base required to use this reductant were not compatible with ketone **5**.[6c,8]

In addition to the task of effecting a high yielding and highly enantioselective reduction of **5**, the synthesis of chiral alcohol **2** presented several challenges with respect to product isolation. Alcohol **2** has high solubility in most organic solvents and sublimes easily. The racemate of **2** crystallizes as a racemic compound,[9]

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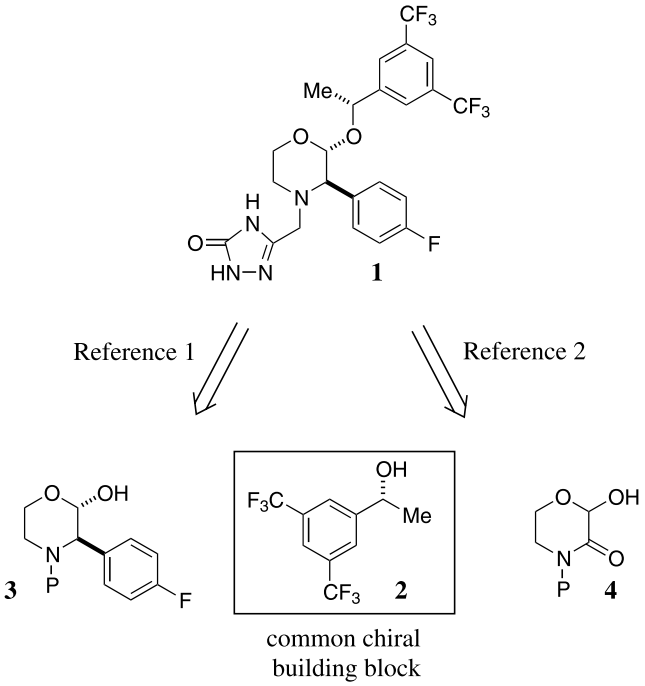


Scheme 1.

which is significantly more stable than the enantiomerically pure solid form of **2** (Table 1). This makes upgrade of enantiomeric excess by crystallization difficult to achieve without large losses to the mother liquors.

Table 1. Selected physical properties of chiral alcohol **2**

	Mp (°C)	Solubility (mg/g solvent)[a]
Enantiomerically pure **2**	52	52
Racemic **2**	72	21

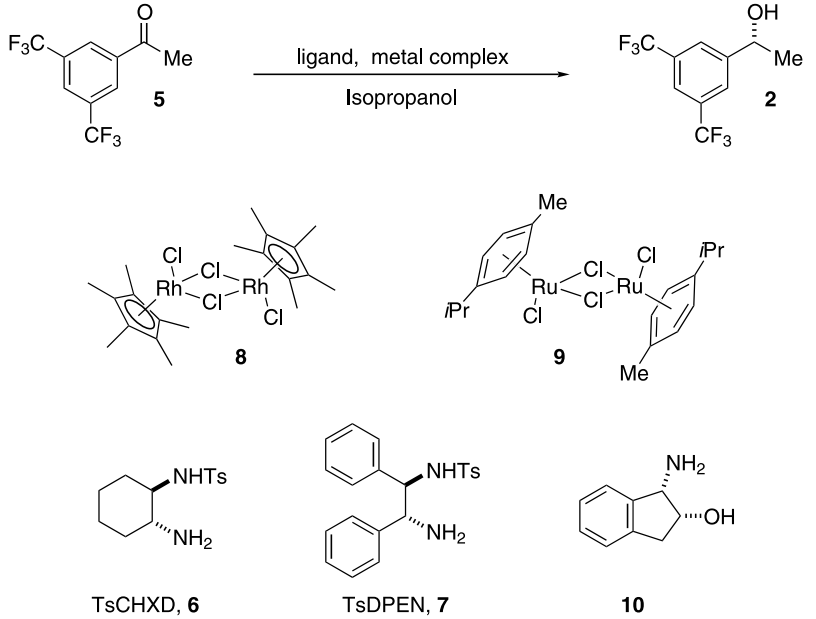
[a] Measured in heptane at ambient temperature (21°C).

While methods such as derivatization or kinetic resolution are useful for upgrading the enantiomeric excess of alcohols such as **2**, they all possess the liability of developing a separate chemical step. A method of purification was desired which would upgrade enantiomeric excess and chemical purity, provide higher melting point solids with a lower vapor pressure and would not require covalent derivatization of the chiral alcohol (a salt equivalent). The advantage of developing such a purification method would be to allow the isolation of material of consistent enantiomeric excess from any asymmetric synthesis of **2**.

2. Asymmetric reduction

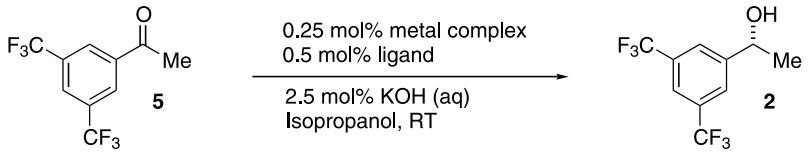
A variety of metal salts and ligands catalyze asymmetric transfer hydrogenation of acetophenones in IPA.[6a] Most notable are the monotosylated ligands **6** and **7** typically used in conjunction with either dichloropentamethylcyclopentadienyl(Cp*)Rh(III) dimer **8** or dichloro(*p*-cymene)Ru(II) dimer complex **9** (Scheme 2).[6] Complexes formed by these ligands and metal precursors have been shown to achieve high enantioselectivities on a wide variety of substrates. The monotosylated ligands **6** and **7** can be synthesized on multigram scale from the corresponding diamine or, in the case of **7**, purchased directly.

Chiral amino alcohols also catalyze the transfer hydrogenation with high selectivity and yield.[10] Of particular interest was the reported use of *cis*-aminoindanol **10** as a ligand for the asymmetric reduction[11] which, despite providing lower enantioselectivities on substrates like acetophenone (as compared to complexes prepared using ligands **6** and **7**), would be more readily available in these laboratories.[12] The preparation of the amino alcohol complex, which can be generated in situ, also was desirable from a processing perspective. The reported procedure for the use of **10** in transfer hydro-



Scheme 2.

Table 2. Screening of ligands **6**, **7** and **10** with metal precursors **8** and **9** for the asymmetric transfer hydrogenation of ketone **5**



Entry	Metal[a]	Ligand[a]	[**5**] (M)	Time (h)	Conv.[b]	Ee **2**[b]
1	Ru	TsDPEN **7**	0.1	24	99.2	77
2	Rh	TsDPEN **7**	0.1	2	98.8	90
3	Rh	TsDPEN **7**	0.5	24	97.9	84
4	Ru	TsCHXD **6**	0.1	2	99.3	78
5	Rh	TsCHXD **6**	0.1	2	99.2	94
6	Rh	TsCHXD **6**	0.5	2	98.2	91
7	Rh	*cis*-Aminoindanol **10**	0.1	2	99.0	72
8	Ru	*cis*-Aminoindanol **10**	0.1	2	98.9	93
9	Ru	*cis*-Aminoindanol **10**	0.5	2	69.3	91
10	Ru	*cis*-Aminoindanol **10**	0.5	4	98.0	91

[a] See Scheme 2 for complete structures.
[b] Conversion and ee were determined by chiral GC of the reaction mixture. See Section 5 for details.

genations was fairly complicated, involving the use of anhydrous and air-free conditions, high temperatures and a two-fold excess of the ligand. An investigation of the system revealed that the reaction could be performed under much less stringent controls.

Consistent results for the reduction of **5** were obtained when a simplified procedure was employed. Complexation of ligand **10** to the metal precursor **8** or **9** occurred readily at ambient temperature and the dilute concentrations under which the subsequent reductions were performed. Degassing of the solution was only found to be necessary once the catalyst had been activated with base. Ligand–metal complexes generated in solutions open to air performed as well as solutions generated under air-free conditions provided they were degassed by either bubbling of nitrogen through the solution (small scale) or evacuating the reaction vessel and backfilling the atmosphere with nitrogen several times (multi-kilo scale) prior to the addition of base. Lastly, the reaction did not require anhydrous conditions for optimum performance. Commercially available aqueous solutions of NaOH (5 M) could be used as the base source without any decrease in performance relative to KOH or KO*t*Bu solutions generated in dry isopropanol. The simplified catalyst generation procedure worked equally well when used with ligands **6** and **7** and both metal complex precursors.

The simplified catalyst generation procedure allowed for the rapid screening of the various ligand and metal combinations to find the optimum conditions for the reduction of **5**. Of particular interest was finding a catalyst/ligand combination which had good performance under more concentrated conditions.[13] The results of screening are summarized in Table 2. The ruthenium complexes showed only moderate enantioselectivity with monotosylated amines **6** and **7**. The Rh complex of TsCHXDN **6** gave the highest enantioselectivity at 0.1 M (94% ee) but the selectivity decreased when the reaction was performed under more concentrated conditions (91% ee). Interestingly, while the Rh complex of **10** performed poorly with *cis*-aminoindanol (72% ee), the Ru complex afforded good enantioselecticity both at 0.1 M (93% ee) and 0.5 M (91% ee).

Despite having similar performance in the reaction as (*R*,*R*)-**6**, *cis*-aminoindanol was chosen as the ligand for the process for several reasons. First, ligand **6** is not commercially available and although **6** can be synthesized from its diamine precursor, the yield of the reaction is poor. Alternatively, (1*S*,2*R*)-**10**, the enantiomer of *cis*-aminoindanol required to prepare (*R*)-**2**, was available in commercial quantities.[11,12]

The combination of ligand **10** and metal complex **9** catalyzes the reaction effectively at a substrate concentration of 0.5 M and a catalyst loading of 0.5 mol%. While the catalyst loading could be lowered from 0.5 to 0.25 mol%, the lower loading would often fail to give complete conversion most likely due to the presence of small amounts of catalyst poisons in different lots of **5** or adventitious air. A stalled reaction could be revived by charging additional catalyst, degassing the solution and then re-charging base. However in order to have a process that would reliably run to completion, the higher loading level (0.5 mol%) was used.

Despite the tendency for complications due to reversibility of the reaction at higher concentrations, the process was found to have a stable enantioselectivity up to 12 h of >90%, with no starting material and only a slight erosion of ee over 24 h (91–89% ee). This allowed for ample time to assay and quench the reac-

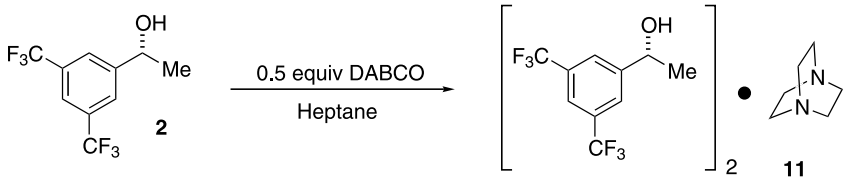
tion. Upon confirmation of complete conversion, the batch was quenched with 1 M HCl and could be held for prolonged periods (1–2 days) of time prior to resuming processing.

3. Isolation of chiral alcohol 2

As mentioned previously, enantiomerically enriched alcohol **2** was difficult to purify via direct crystallization. A means of non-covalently associating **2** in a complex with another moiety was desired to effectively alter the relative stability of racemic and enantiomerically pure alcohol **2**. Toda has described the upgrade of enantiomeric excess of tertiary acetylenic alcohols by crystallizing them as an inclusion complex with DABCO.[14] The crystal packing forces are the thermodynamic driving force for the formation of these complexes.[15] The alcohol is easily liberated by dissolving the complex in an organic solvent and then washing with a dilute aqueous acid to remove the amine.

Alcohol **2** readily forms an inclusion complex with DABCO (Scheme 3). Mixing the solid alcohol **2** (92% ee) with 0.5 equiv. of DABCO resulted in the solids melting and then re-solidifying. This material was found to be only slightly soluble in saturated hydrocarbon solvents such as hexanes or heptane. Dissolving the solids in hot hexanes followed by cooling to 0°C resulted in the formation of white crystals, which could be isolated by filtration. The solids had a higher melting point than alcohol **2** (69°C versus 52°C for **2**) and showed a 2:1 ratio of **2** to DABCO by ^{1}H NMR. Most interestingly the solids isolated were found to contain >99% ee chiral alcohol **2** and identified as DABCO complex **11**. The X-ray crystal structure of **11** is shown in Figure 1. The structure shows the two alcohol hydroxyls hydrogen bonded to the DABCO nitrogen with a bond length of 1.92 Å.

In order to develop a process for the isolation of **2** as its DABCO complex **11**, heptane was chosen as the crystallization solvent for the complex due to its lower volatility and more desirable processing characteristics. Upon completion of the reduction, the reaction solution was quenched with 1 M HCl (7L/ kg of **2**). In order to simplify processing, heptane was used as the extraction solvent and after two extractions of the aqueous layer, an 85% yield of the chiral alcohol **2** was obtained from ketone **5**, according to an HPLC assay.[16]



Scheme 3.

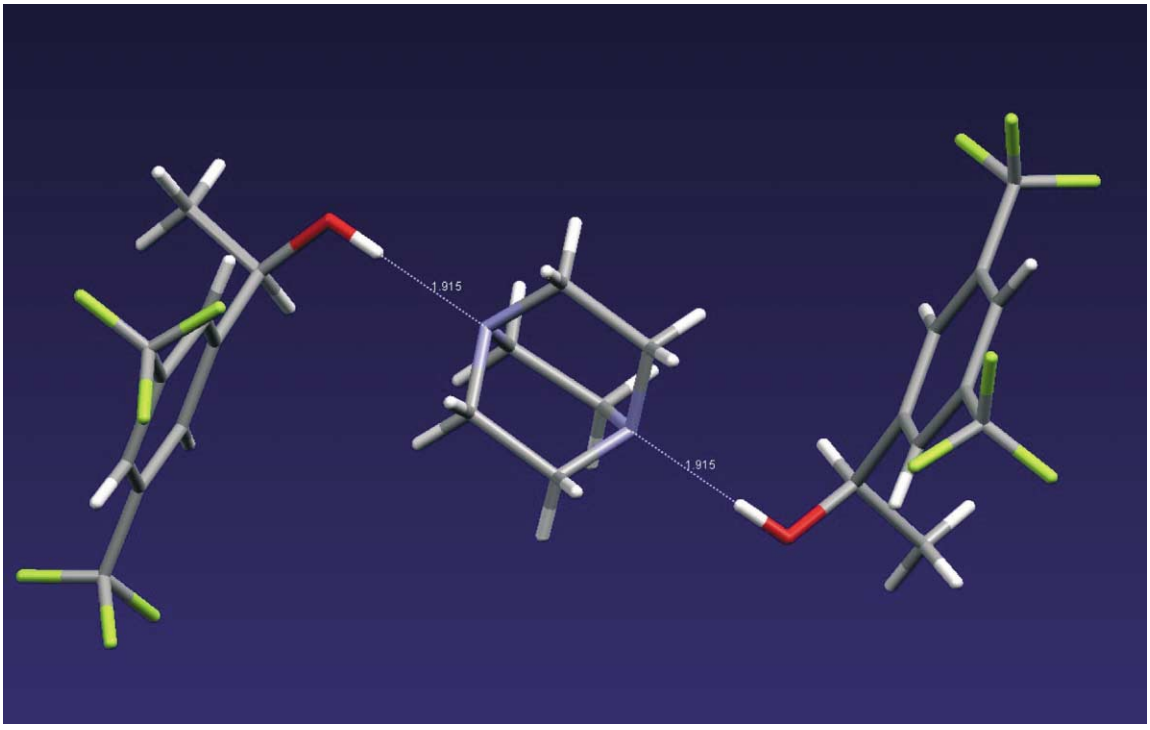


Figure 1.

The combined organic layers were charged with 0.55–0.65 equiv. of DABCO and concentrated to a volume of 4 L/kg of **2**. The solution was then distilled while flushing with heptane to remove residual IPA and water.[17] Crystallization upon cooling this solution afforded the DABCO complex in 75% yield (>99% ee, >98 wt% purity) from ketone **5**.[18]

This procedure was successfully performed on several multi-kilogram batches prior to implementation in the pilot plant. However during piloting of the isolation, complications were observed. When the crystallization slurry was filtered, the isolated solids were only 93–94% ee and the concentration of alcohol **2** in the mother liquors was much lower than expected. A careful investigation revealed that a new racemic compound had formed, complicating the isolation.

Prior to piloting, the DABCO complex of racemic **2** had been synthesized and shown to be a conglomerate system (Scheme 4). The X-ray powder diffraction pattern of the crystals isolated from the DABCO complex of racemic **2** was identical to those of enantiomerically pure **11**. The melting point (by differential scanning calorimetry) showed a characteristic depression relative to enantiomerically pure **11** (40°C versus 69°C (Table 3)). Most importantly the solubility of the conglomerate DABCO complex **12** was twice that of enantiomerically pure DABCO complex **11** (40 mg/g solvent in the process mother liquors at 0°C versus 20 mg/g for pure **11**). This allowed for an isolation of enantiomerically pure **11** with a theoretical mother liquor loss equal to the amount of racemic **2** present in the system.

Table 3. Selected physical properties of DABCO complexes **11**, **12** and **13**

	Mp (°C)	Solubility (mg/g solvent)[a]
Enantiomerically pure phase **11**	69	20
Racemic conglomerate **12**	40	40
Racemic compound **13**	52	16

[a] Measured in process mother liquors at 0°C.

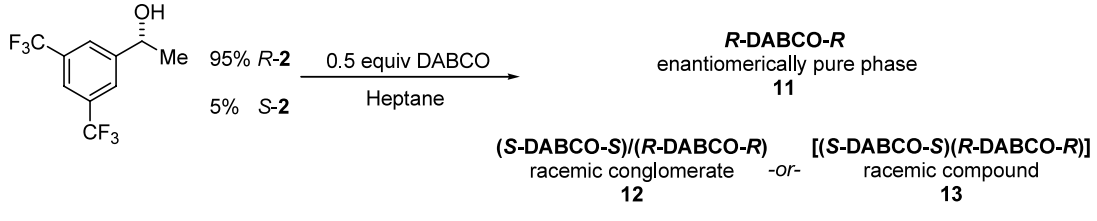
Examination of the isolated solids from the failed pilot plant batch via X-ray powder pattern showed additional new peaks, indicative of the presence of a new crystal form. When the racemic conglomerate DABCO complex **12** was slurried in heptane and spiked with a small amount of the isolated solids from the pilot plant containing this new crystal form, the X-ray powder pattern changed to that of a new racemic compound **13**.[9] The racemic compound **13** has a melting point different from that of the conglomerate **12** (52°C versus 41°C). Also its solubility is much lower than the conglomerate (16 mg/g in the process mother liquors at 0°C versus 40 mg/g for **12**).

The discovery of this new crystal form revealed that the crystallization as initially developed was metastable and had been under kinetic control prior to implementation in the pilot plant. The isolation had been carried out when (*S*)-**2** only crystallized as the much more soluble conglomerate complex **12**, the more stable racemic compound **13** did not have sufficient time to form. However, once the racemic compound **13** had formed, the vessels used for the preparation of **11** had been well seeded with form **13** and equilibration of racemate present in the system to **13** would be faster. In order to develop a robust process which provides exclusively **11** under thermodynamic control, the conditions of the isolation needed to be changed to dissolve all of (*S*)-**2** present as racemic compound **13** (16 mg/g solubility) and not (*S*)-**2** present as conglomerate **12** (40 mg/g solubility).

Changing the crystallization volume to 14 L/kg of **2** (as opposed to 4 L/kg of **2** used previously) allowed for the consistent isolation of solids containing >99% ee **2**.[19] While the larger volume leads to an additional 7–10% yield loss to the mother liquors, it insures that all of the undesired (*S*)-**2** remains dissolved in the mother liquors. These conditions were demonstrated during a subsequent pilot plant run affording a 69% yield of **11** (>99% ee, >97.3 wt%) from ketone **5** (79% recovery of **11**). The batches which had been isolated at 93–94% ee were easily upgraded to >99% ee **2** by slurrying in 14 L per kg of **2** and filtering the solids.

4. Conclusion

A process for the synthesis and isolation of chiral alcohol **2** as its DABCO inclusion complex in high chemical and enantiomeric excess has been described. Chiral alcohol **2** is synthesized from ketone **5** in 91% ee via asymmetric transfer hydrogenation reaction catalyzed by a *cis*-aminoindanol–Ru(*p*-cymene) complex. While the upgrade of the enantiomeric excess of **2** via direct crystallization with high yield is difficult, crystallization of **2** as its DABCO complex **11** under thermodynamic control, provided material with good



Scheme 4.

enantiomeric excess and chemical purity (99% ee, 98 LCAP) with good recovery (82–85%). Using this procedure, 90 kg of **11** was prepared on pilot scale.

5. Experimental

All solvents and reagents were purchased commercially and used without any further purification. Ketone **5** was purchased from Central Glass and DABCO was purchased from Manof Huntsman, both were used as received. Melting points were determined on an open capillary apparatus and are uncorrected. IR spectra were collected as KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm relative to tetramethylsilane. Reactions were monitored for enantiomeric excess and conversion by capillary GC on a commercially available B-Dex 120 column (0.25 mm ID, 60 m, Supelco). Reaction conversions and quantification was performed by HPLC analysis using a Zorbax SB-C8 column (4.6×250 mm) eluted with 50% acetonitrile and 50% 0.1% aqueous H_3PO_4.

5.1. Procedure for asymmetric transfer hydrogenation of 5

A 200 gal glass-lined vessel was charged with 200 kg of IPA (253 L). Ruthenium complex **9** (0.239 kg, 0.39 mol, 0.0025 equiv.) and ligand **10** (0.116 kg, 0.778 mol, 0.005 equiv.) were charged to the vessel followed by 10 kg (13.7 L) of IPA to rinse solids from the vessel walls. After a 1 h age, 40 kg of **5** (156 mol, 1.0 equiv.), was charged to the solution followed by a 10 kg IPA (13.7 L) rinse. The vessel was then degassed by six vacuum and nitrogen purges. 5N NaOH (0.92 kg, 0.77 L, 3.9 mol, 0.025 equiv.) was added to the solution. After 2 h the reaction was assayed to contain <0.2% area percent **5** and the ee of **2** was assayed at 90%. 307 kg (302 L) of 1N HCl was added to the vessel followed by 95 kg (139 L) of heptane. The layers were mixed and then separated. The aqueous layer was then extracted with a second portion of 95 kg (139 L) of heptane. The combined organic extracts were then washed with 220 kg of saturated NaCl solution. The combined organics were assayed to contain 35.1 kg of **2** (91% ee, 87% yield). The organic stream was used directly in the isolation of **11**.

5.2. Crystallization of DABCO complex 11

A solution of chiral alcohol (~350 L, 35.1 kg of **2** by assay, 136 mol with ee = 90%) in IPA/heptane extracts from the transfer hydrogenation was charged with 11.0 kg of DABCO (98 mol, 0.64 equiv.). The solution was concentrated to a volume of 150 L by vacuum distillation (50 torr) and flushed with heptane until nearly all of the IPA and water had been removed (<0.5 vol% IPA, water <1000 PPM by Karl Fisher titration). The concentration of the batch was adjusted to 66 g/L (15 volumes relative to **2**) and then heated to 45°C to dissolve all of the solids present. The batch was then cooled to 30°C and seeded with 300 g of **11** (0.8 wt% based on **2**). The slurry was then cooled to 0°C over 1 h and aged for an additional hour. The solids were filtered through a pressure filter and dried under vacuum at 20–25°C. 34.9 kg of **8** was isolated which was 98 wt% and >99% ee in a yield of 79% for the isolation. ^{1}H NMR: δ 7.85 (s, 2H), 7.79 (s, 1H), 5.00 (q, J = 6.5 Hz, 1H), 3.16 (s, 1H), 2.74 (s, 6H), 1.53 (d, J = 6.5 Hz, 3H). ^{13}C NMR: δ 149.0, 131.6 (q, J = 33 Hz), 125.5 (q, J = 3 Hz), 123.3 (q, J = 272 Hz), 121.0 (p, J = 4 Hz), 68.6, 46.7, 25.6. $[\alpha]_D^{20}$ +18.4 (*c* 0.125, MeOH). IR (cm^{-1}): 3117, 2974, 1382, 1275, 1185, 1120, 897. Elemental analysis calculated for $C_{26}H_{28}F_{12}N_2O_2$: C, 49.69; H, 4.49; F, 36.27; N, 4.46; O, 5.09. Found: C, 49.64; H, 4.25; N, 4.43; F, 36.30; O, 5.38. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 213817. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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13. The reactions were performed by adding the ligand and metal complex to the isopropanol reaction solvent. Following a 1 h age, **3** was added and the entire solution was degassed by bubbling a stream of nitrogen through the solution for 5 min. KOH was then added under nitrogen and the reaction was aged. Conversion and enantiomeric excess were monitored by chiral GC.
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15. DABCO is a relatively weak base. The pK_a of the two conjugate acids of DABCO are 8.8 and 3.0 for the singly and doubly protonated species, respectively.
16. 10–15% of **2** is lost to the aqueous cut. A better recovery of product can be obtained via an extraction with methyl *tert*-butyl ether, albeit with significant contamination with dissolved Ru.
17. Small amounts of water or IPA can have a drastic increasing effect on the solubility of **7**. Typically the IPA level was <0.5 v/v% and water was less than 1000 PPM.
18. The yield for the isolation from the crude stream of **2** was typically 88–90% prior to the formation of **13**.
19. This is based on an ee of 90% for alcohol **2** contained in the system. A lower ee of **2** in the starting system would require more solvent to dissolve all of **13**.