Multigram Synthesis of *N*-Alkyl *Bis*-Ureas for Asymmetric Hydrogen Bonding Phase-Transfer Catalysis

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Editorial Summary: Gouverneur *et al.* present a protocol for multigram synthesis of two chiral urea-based hydrogen bonding phase-transfer catalysts for asymmetric nucleophilic fluorinations of target compounds, including detailed synthesis and purification procedures.

Proposed Tweet: #NewNProt for the multigram synthesis of *N*-alkyl bis-ureas for asymmetric hydrogen bonding phase-transfer catalysis

Proposed Teaser: Multigram synthesis of bis-urea organocatalysts

KEY REFERENCES USING THIS PROTOCOL

Pupo, G. *et al.* Asymmetric nucleophilic fluorination under hydrogen bonding phase-transfer catalysis. *Science,* **360**, 368–642 (2018), DOI: 10.1126/science.aar7941.

Pupo, G *et al.* Hydrogen bonding phase-transfer catalysis with potassium fluoride: enantioselective synthesis of β-fluoroamines. *J. Am. Chem. Soc.*, **141**, 2878–2883 (2019), DOI: 10.1021/jacs.8b12568.

Roagna, G. *et al.* Hydrogen bonding phase-transfer catalysis with ionic reactants: enantioselective synthesis of γ-fluoroamines. *J. Am. Chem. Soc.* **142**, 14045–14051 (2020), DOI 10.1021/jacs.0c05131.

ABSTRACT

Fluorine is a key element being present in as many as 35% of agrochemicals, 20–25% of marketed drugs. The availability of reliable synthetic protocols to prepare catalysts which allow the efficient incorporation of fluorine in organic molecules is therefore essential for broad applicability. Herein, we report a protocol for the multigram synthesis of two representative enantiopure *N*-alkyl *bis*-urea organocatalysts derived from (*S*)-(–)-1,1′-binaphthyl-2,2′-diamine [(*S*)-BINAM]. These tridentate hydrogen-bond donors are highly effective phase-transfer catalysts to solubilise safe and inexpensive metal alkali fluorides (KF and CsF) in organic solvents for enantioselective nucleophilic fluorinations. The first catalyst, characterised by *N*-isopropyl substitution, was obtained using a two-step sequence consisting of reductive amination followed by urea coupling from commercially available starting materials (14 g, 48% yield, 5 d total synthesis time). The second catalyst, featuring *N*-ethyl alkylation and *meta*-terphenyl substituents, was accessed *via* a novel, scalable, convergent route which concluded with the coupling between *N*-ethylated (*S*)-BINAM and a preformed isocyanate (52 g, 52% overall yield). On this scale, the synthesis requires approximatively 10 d. This can be reduced to 5 d by performing some steps in parallel. Compared to the previous synthetic route, this protocol avoids chromatographic purifications and affords the desired catalysts in very high purity and strongly improved yields.

INTRODUCTION

In the last two decades, hydrogen bonding has emerged as a powerful interaction for asymmetric catalysis, leading to the design of numerous hydrogen bond donor (HBD) organocatalysts.[1,2,3] In this context, (thio)ureas occupy a prominent position due to their facile and modular synthesis which allows the rapid generation of air and moisture-stable catalyst libraries, as well as the inclusion of additional functionalities. Representative (thio)urea catalysed

reactions include 1,2- and 1,4-additions as well as acyl transfer, concerted cycloadditions, and S_N1 substitution *via* oxocarbenium ions.[3,4]

The suitability of (thio)ureas in enantioselective synthesis arise from their ability to interact with the reactants through strong directional hydrogen bonding interactions.[2] As a result, Lewis basic electrophiles, such as carbonyl compounds, nitroalkenes, and imines are activated *via* LUMO lowering (Figure 1A).[2] An alternative mode of electrophile activation, pioneered by the Jacobsen group,[4] employed these catalysts for *in situ* generation of cationic electrophiles. This involved anion abstraction followed by the formation of a chiral ion pair which is subsequently attacked by an external nucleophile (Figure 1A).[5] More recently, our laboratory disclosed that the fluoride anion-binding ability of ureas [6, 7] can be exploited in phase transfer catalysis to bring inorganic alkali metal fluorides into solution. [8, 9, 10] This novel strategy for the activation of insoluble nucleophiles combining hydrogen bonding and phase-transfer catalysis (HB-PTC) was applied to challenging asymmetric nucleophilic fluorination with KF and CsF. Such approach complements asymmetric catalytic methodologies employing F_2-derived reagents, offering the advantage of using cheap and abundant fluorine sources.[11] The proposed catalytic cycle starts with the interaction of the chiral HBD with the inorganic salt resulting in the formation of a soluble HBD-fluoride complex (**I**, Figure 1B) which can undergo ion metathesis with a charged electrophile to give the reactive ion pair **II**. Irreversible fluorination affords the enantioenriched product and releases the active catalyst. *In situ* generated *meso*-episulfonium and aziridinium ions were successfully desymmetrised using CsF and KF under HB-PTC (Figure 1C).[8,9] The enantioenriched β-fluorosulfides and β-fluoroamines were obtained in yields up to 98% and e.r. (e.r. = enantiomeric ratio) up to 97:3, the latter up to the decagram scale. *meso*-Azetidinium salts also underwent enantioselective fluorination under HB-PTC, affording a range of γ-fluoroamines in yields up to 99% and e.r. up to 97.5:2.5 (Figure 1C).[10]

For these transformations, the highest level of enantioselectivity was consistently obtained with *N*-alkyl *bis*-ureas derived from (*S*)-(–)-1,1′-binaphthyl-2,2′-diamine ((*S*)-BINAM) such as (*S*)-**1** and (*S*)-**2** (Figure 1C). Analogues lacking the *N*-alkyl substituent gave reduced enantiocontrol, an observation that we rationalised following an in-depth study of their respective binding mode to fluoride in solution.[12] This study indicated that *N*-alkyl *bis*-ureas such as (*S*)-**1** and (*S*)-**2** form well-defined tridentate complexes with fluoride, which is in contrast to non-alkylated *bis*-urea catalysts featuring four NH groups.[12] To expand the applicability of HB-PTC, a suitable scale-up strategy amenable to the synthesis of decagram quantities of these catalysts was required, and should stimulate new developments in the field. Herein, we provide a protocol for the multigram synthesis of catalysts (*S*)-**1** (14 g) and (*S*)-**2** (52 g). The sequence applied to access (*S*)-**2** has been significantly improved with respect to the original route.[9]

EXPERIMENTAL DESIGN

The synthesis of catalysts (*S*)-**1** and (*S*)-**2** was previously reported by our group, giving access to 2.45 g of (*S*)-**1** (52% overall yield)[8] and 2.10 g of (*S*)-**2** (37% overall yield).[9] Catalyst (*S*)-**1** is conveniently obtained in two steps from commercially available (*S*)-BINAM (2). The first step is a one-pot reductive amination between unprotected (*S*)-BINAM and acetone with $NaBH_4$ in the presence of aqueous H_2SO_4 to afford (*S*)-**3**, a reaction optimised based on a literature procedure.[13] A 10-fold increase of the reaction scale had no detrimental effect on yields (60% *versus* 57% yield).[8] Caution is required during the addition of the hydride source because of the generation of flammable hydrogen gas. We recommend performing this step under a flow of inert gas (nitrogen or argon) at 0 ºC and adding $NaBH_4$ slowly and portion-wise. The second step of the protocol is the coupling with commercially available 3,5-*bis*(trifluoromethyl)phenyl isocyanate. To avoid formation of achiral 1,3-*bis*(3,5-*bis*(trifluoromethyl)phenyl)urea (Schreiner's urea catalyst, Figure 2), which itself is a competent catalyst in HB-PTC,[8] it is critical to perform the coupling under anhydrous conditions. Slow addition of the isocyanate is recommended to maintain consistent stirring; indeed, isocyanate addition generates a heterogeneous reaction mixture which progressively becomes homogeneous as the reaction proceeds. This protocol allowed access up to 14 g of catalyst (*S*)-**1** in a single batch (see details in the PROCEDURE, stages A–B). Catalyst purity was assessed by HPLC analysis.

Our reported synthetic route to catalyst (*S*)-**2** consisted of a two-step protocol from unprotected (*S*)-BINAM, consisting of *bis*-urea formation followed by *N*-monoalkylation with iodoethane (EtI).[9] This reaction sequence was implemented based on discouraging attempts to access synthetically useful amounts of catalyst (*S*)-**2** from the reaction of *mono*-ethylated diamine **5** with an isocyanate generated *in situ* from achiral aniline **6**. Following

this protocol, sufficient quantities (~ 2.51 g) of *bis*-urea (*S*)-**2** were obtained for screening purposes, however the final *N*-alkylation step required extensive chromatographic purification to separate the desired (*S*)-**2** from the other *mono* and *bis N*-alkyl regioisomers, making it unsuitable for large scale preparation. This state of play led us to revisit *bis*-urea formation from *mono*-ethylated diamine **5** for the large-scale synthesis of (*S*)-**2**. With the aim of obtaining decagrams of catalyst (*S*)-**2**, we optimised the step leading to urea formation to obtain bis-urea (*S*)-**2** as the sole product upon full conversion of the starting material, thus removing the need for chromatographic purification of the final catalyst. This led to the improved synthetic route reported in 3, where the key step is the coupling of (*S*)-N^2-ethyl-[1,1'-binaphthalene]-2,2'-diamine **5** with preformed isocyanate **7**. This protocol was successfully scaled up and enabled the preparation of ~50 g of (*S*)-**2** (details in the PROCEDURE section, stages C–G).

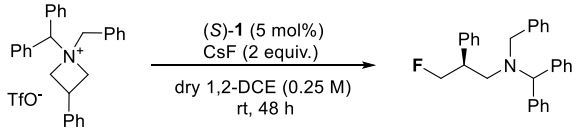
Specifically, (*S*)-N^2-ethyl-[1,1'-binaphthalene]-2,2'-diamine **5** (3, top) was obtained in moderate yields (~ 60–65%) by applying a three-step protection-alkylation-deprotection sequence[8] (Stages C–D of the PROCEDURE). No noticeable differences in yields were observed between small (2.5 g) and large (40 g) scale reactions. Unreacted starting material (~25%) could be recovered and recycled. Care is required in the alkylation step (stage D) to ensure adequate stirring due to the heterogeneous nature of the reaction. Suzuki-Miyaura cross-coupling of 3,5-dibromoaniline and 3,5-*bis*(trifluoromethyl)phenyl boronic acid gave access to achiral aniline **6** (stage E). Notably, a 10-fold reduction in catalyst loading (0.5 mol %) with respect to our original report was effective and greatly simplified the purification of intermediate **6**. Conversion of aniline **6** into isocyanate **7** was performed using solid triphosgene[14] in a biphasic medium (aq. $NaHCO_3$ and CH_2Cl_2, stage F). These conditions allowed the facile isolation of the desired product **7** by layers separation at the end of the reaction. Vigorous stirring is required to ensure interphase mass transfer and prevent stirrer blockage. Recrystallisation of isocyanate **7** was essential to ensure reproducibility in the subsequent urea coupling. This last step (stage G) afforded (*S*)-**2** in > 90% purity, which was enhanced upon recrystallisation to 99% as determined by HPLC analysis. (*S*)-**2** was obtained in 52% overall yield from (*S*)-BINAM, which compares favourably with our previous report (37% overall yield).

The reactions reported in the PROCEDURE are based on the large-scale (>10 g) synthesis of catalyst (*S*)-**1** and (*S*)-**2**. The same protocol can be applied to access both catalysts on a smaller scale (≤ 1 g) using smaller glassware and substituting the overhead stirrer used in stage F with a magnetic stirring bar. On a small scale, the recrystallization of (*S*)-**2** can be replaced with chromatography over silica gel (Eluent: *n*-pentane:EtOAc = 100: 0 to 80: 20, gradient). The reported "expected times" refer to the large-scale syntheses; reaction times are expected to be similar on a reduced scale, but purification times will be substantially shortened. Examples of application of catalysts (*S*)-**1** and (*S*)-**2** in asymmetric nucleophilic fluorination of azetidinium triflates and *in situ* formed aziridinium ions can be found in BOX 1 and BOX 2, respectively. These reactions can be used to test the performance of the catalysts.

BOX 1: Representative example of enantioselective fluorination with CsF *via* HB-PTC with catalyst (*S*)-1

Time: 50 h; **Scale:** 0.1 mmol of substrate.

The standard procedure for the enantioselective fluorination of *meso*-azetidinium triflates with CsF is provided using a 1.5:1 *cis*:*trans* mixture of 1-benzhydryl-1-benzyl-3-phenylazetidin-1-ium trifluoromethanesulfonate **8** as model substrate (see scheme below). The reaction can be used to test the performance of catalyst (*S*)-**1**. Catalyst (*S*)-**2** affords (*S*)-*N*-benzhydryl-*N*-benzyl-3-fluoro-2-phenylpropan-1-amine **9** in low yield and enantioselectivity.



8
1.5:1 *cis*:*trans*

(*S*)-**9**

Additional materials:

- Catalyst (*S*)-**1**. The synthesis is reported in the PROCEDURE (steps A–B).
- 1-benzhydryl-1-benzyl-3-phenylazetidin-1-ium trifluoromethanesulfonate (**8**, prepared as described in a previous report.[10] Note: a mixture of diastereoisomer can be successfully used).
- Cesium fluoride CAS No 13400-13-0 (CsF, 99.9% trace metal basis, Sigma-Aldich, Cat. No. 289345).
- Anhydrous 1,2-dichloroethane (1,2-DCE, 99.8% extra-dry, AcroSeal™, Acros Organics, Cat. No. 326841000).
- Big vial (7 mL) with screw cap.

- Small vial (1.75 mL) with screw cap.
- 12 mm stirring bar.
- Stirring plate.
- 1 mL syringe.
- Needles (0.80x120 mm).
- Column (diameter: ~1.5 cm).
- Silica gel (Merck, 60, particle size 0.040-0.063 mm, Cat. No. 1.11567.1000).
- *n*-Pentane (≥ 99.0% purity, for HPLC, Sigma-Aldrich, Cat. No. 34956).
- Diethyl Ether (Et_2O, ≥ 99.8% purity, contains BHT as inhibitor, puriss. p.a. ACS reagent, reag. ISO, reag. Ph. Eur., Sigma-Aldrich, Cat. No. 34858).
- HPLC instrument (Shimadzu *i*-Prominence LC-2030, PDA detector), normal phase.
- HPLC column with chiral stationary phase (DAICEL CHIRALCEL® OJ-H).
- *n*-Heptane (for HPLC, ≥ 99%, Sigma-Aldrich, Cat. No. 34873).
- Ethanol, absolute (EtOH, ≥ 99.8%, analytical reagent grade, Fischer chemical Cat. No. E/0650/17).

Procedure:

1) Inside a fumehood, grind ~1 g of CsF using an oven-dried pestle and mortar. Transfer the powdery CsF in an oven-dried vial and store the vial in a desiccator. Grinded CsF can be stored in a desiccator for months. **Critical step** CsF is hygroscopic. The use of oven-dried glassware is suggested to minimise the amount of water adsorbed during the process, which should be done quickly. **Critical step** To ensure efficient phase-transfer, the surface area of CsF should be maximised, so a very fine powder is crucial for this step.
2) Place a 12 mm stirring bar in the big vial (7 mL). **Critical step** efficient stirring is fundamental. Check in advance that the stirring bar properly fits in the vial.
3) Weigh 53.9 mg (0.1 mmol) of substrate **8** and transfer it to the big vial.
4) Weigh 4.2 mg (5 mol%) of catalyst (*S*)-**1** and transfer it to the big vial.
5) Place the 1.75 mL small vial (1.75 mL) with the cap on the balance and zero it.
6) In the closed small vial weigh 31 mg (2 equiv.) of CsF. **Critical step** CsF is hygroscopic. Close the cap of both the CsF bottle and vials between each weigh and clean the spatula on a piece of clean paper before taking more CsF from the bottle to not contaminate it.
7) Transfer the CsF to the big vial. Gently tap the bottom of the small vial to ensure quantitative transfer.
8) Transfer 400 μL of anhydrous 1,2-DCE to the big vial using a syringe. **Critical step** It was found that addition of water to the reaction (1 equiv.) had a detrimental effect on the yield but did not affect the enantioselectivity.[10] From a practical point of view, the use of anhydrous 1,2-DCE in combination with CsF as provided from the supplier afforded higher yields of (*S*)-**9** compared to the use of non-anhydrous 1,2-DCE. No substantial improvements were observed in strictly anhydrous conditions (dry glassware and dry CsF).
9) Seal the vial and wrap some parafilm around the cap.
10) Place the vial on a stirring plate at about 0.5 cm from the plate itself. Set the stirring speed at 900 rpm. **Critical step:** this is the single most important point of the set-up. The stirring bar should evenly rotate and not jump in the vial.
11) Wait 48 h.
12) Directly purify the reaction mixture by flash column chromatography. See step 21 of the PROCEDURE (Stage A) for how to pack a column. Transfer the content of the vial on top of the column. Wash the vial with two aliquots of CH_2Cl_2 (200 μL each). Cover the top of the column with 1 cm of sand.
13) Purify the compound using a *n*-pentane: Et_2O = 100:0 to 90:10 vol/vol. Collect the eluate in 5 mL tubes. Check the content of the tubes by using either UV-light or $KMnO_4$ stain.
14) Combine the fractions containing the pure product and remove the solvent using a rotary evaporator (water bath temperature: 40 °C, pressure: 700 to 5 mbar, gradient).
15) Dry the product under high vacuum to determinate accurately the yield.
16) To evaluate the enantiomeric ratio, dissolve 1 mg of pure product in 1 mL of *n*-heptane (HPLC grade) and analyse it using a chiral stationary phase HPLC. (Column: DAICEL CHIRALCEL® OJ-H, Heptane:EtOH = 95:5, 1 mL/min; t_1 = 8.83 min (minor), t_2 = 13.52 min (major).

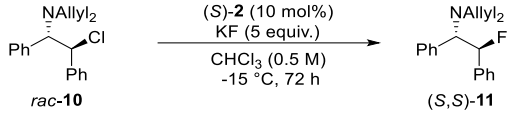
Expected results: (*S*)-*N*-benzhydryl-*N*-benzyl-3-fluoro-2-phenylpropan-1-amine **9** was obtained as a colourless oil following this procedure in 98% yield and 96:4 e.r.

Analytical data: [10]
Colourless oil

[α]$_D$ = +10.1 (c 0.3 in $CHCl_3$ at 25 °C)
^{1}H NMR (400 MHz, CDCl3) δ ppm: 7.40 – 7.36 (m, 4H), 7.22 – 7.22 (m, 14H), 7.07 – 7.02 (m, 2H), 5.00 (s, 1H), 4.62 (ddd, *J* = 47.6, 9.0, 5.5 Hz, 1H), 4.52 (ddd, *J* = 47.5, 9.0, 6.4 Hz, 1H), 3.69 (d, *J* = 1.0 Hz, 2H), 3.23–3.12 (m, 1H), 2.91 (dd, *J* = 13.3, 7.3 Hz, 1H), 2.75 (ddd, *J* = 13.3, 7.5, 2.1 Hz, 1H)
^{19}F NMR (377 MHz, CDCl3) δ ppm: - 221.09 (tdd, *J* = 47.5, 21.1, 1.7 Hz)
^{13}C NMR (101 MHz, CDCl3) [overlapping signals] δ ppm: 140.80, 140.62 (d, *J* = 3.7 Hz), 140.47, 139.56, 129.51, 129.26, 129.03, 128.54, 128.44, 128.40, 128.35, 128.25, 127.27, 127.10, 127.03, 85.70 (d, *J* = 171.4 Hz), 69.40, 55.57, 52.85 (d, *J* = 6.1 Hz), 45.14 (d, *J* = 18.4 Hz)
IR (Et_2O cm^{-1}) 3028, 2926, 2834, 1601, 1493, 1452, 1261, 1027, 762, 743, 698
HRMS (ESI+) *m/z* calculated for $C_{29}H_{29}FN^+$ $[M+H]^+$ 410.2279, found 410.2278

BOX 2: Representative example of enantioselective fluorination with KF *via* HB-PTC with catalyst (*S*)-2

Time: 75 h; **Scale:** 0.2 mmol of substrate
The standard procedure for the enantioselective fluorination of racemic β-chloroamines with KF is provided using *rac*-*N*,*N*-diallyl-2-chloro-1,2-diphenylethan-1-amine **10** as model substrate (see scheme below). The reaction can be used to test the performance of catalyst (*S*)-**2**. Catalyst (*S*)-**1** is also active in this transformation but affords *N*-allyl-*N*-((1*S*,2*S*)-2-fluoro-1,2-diphenylethyl)prop-2-en-1-amine **11** in moderate enantioselectivity (86:14 e.r.)..



Additional materials:

- Catalyst (*S*)-**2**. The synthesis is reported in the PROCEDURE (steps C–G).
- *rac*-*N*,*N*-diallyl-2-chloro-1,2-diphenylethan-1-amine (*rac*-**10**, prepared as described in a previous report).[9]
- Potassium fluoride CAS No. 7789-23-3 (KF, 99.9% metal basis, Alfa Aesar, Cat. No. 11389867). **Critical step** if the KF is not provided as a fine powder, it is recommended to grind it immediately prior to use with an oven dried pestle and mortar. Store the excess powdery KF in a desiccator.
- Chloroform ($CHCl_3$, 99.9%, extra-dry, stabilised, AcroSeal™, Acros Organics, Cat. No. 10071511).
- Aluminum Oxide (activated, basic, Brockmann 1, standard grade, ~150 mesh, 58Å, Sigma-Aldrich, Cat. No. 199443).
- 5 mL Schlenk tube. **Critical** step any container of ~5 mL capacity that can be immersed in the bath and guarantee good stirring can be used. In our laboratory Schlenk tubes proved to be optimal.
- Glass stopper (the appropriate size of the tube).
- 25 mL round bottom flask.
- 7 mL vial with screw cap (2x).
- 1.75 mL vial with screw cap.
- 1 cm oval stirring bar. **Critical step** the stirring bar needs to perfectly fit in the Schlenk tube to ensure optimal stirring.
- 5 cm oval stirring bar (for the cooling bath).
- Stirring plate.
- Dewar (big enough to contain the cooling coil of the cryostat).
- Cryostat.
- Isopropanol, technical grade.
- 1 mL syringe.
- 10 mL syringe (2x).
- Cotton.
- Needles (0.80x40 mm and 0.80x120 mm).
- Column (diameter: ~2 cm).
- Silica gel (Merck, 60, particle size 0.040-0.063 mm, Cat. No. 1.11567.1000).
- *n*-Hexane (≥ 95%, analytical reagent grade, Fisher Chemical Cat. No. H/0355/17).
- Diethyl Ether (Et_2O, ≥ 99.8% purity, contains BHT as inhibitor, puriss. p.a. ACS reagent, reag. ISO, reag. Ph. Eur., Sigma-Aldrich, Cat. No. 34858).
- Dichloromethane (CH_2Cl_2, ≥ 99.8% purity, for HPLC, contains amylene as stabiliser, Sigma-Aldrich, Cat. No. 24856).
- HPLC instrument (Shimadzu *i*-Prominence LC-2030, PDA detector), normal phase.
- HPLC column with chiral stationary phase (DAICEL CHIRALPAK® IA- 3).

- *n*-Heptane (for HPLC, ≥ 99%, Sigma-Aldrich, Cat. No. 34873).
- 2-Propanol, (^{i}PrOH, for HPLC ≥ 99.9%, Sigma-Aldrich, Cat. No. 34863).

Procedure:

1) Place the Dewar containing a stirring bar on the stirring plate. Fill the Dewar with technical grade ^{i}PrOH. Insert the cooling system of the cryostat and the temperature probe in the bath, ensuring that both are fully covered by the ^{i}PrOH.
2) Set the temperature to -15 °C and turn on the stirring (500 rpm). Let the temperature stabilise (around 30 min. Time might vary depending on the performance of the cryostat).
3) Use some cotton to block the hole of a 10 mL syringe and fill it with 2 cm of basic alumina. Insert a needle in the syringe. Clamp the syringe to a stand and place a 7 mL vial below it, clamped too. Filter ~2 mL of anhydrous $CHCl_3$ through the alumina pad and collect the eluate in the vial. Close the cap. **Critical step**: This is to neutralise residual HCl in the solvent. $CHCl_3$ does not need to be anhydrous, but we noticed that the use of AcroSeal™ or SureSeal™ bottles gave more reproducible results.
4) Place the vial containing the $CHCl_3$ in the ^{i}PrOH bath to cool to -15 °C.
5) Roll a piece of weighing paper and fit it inside the Schlenk tube. This will prevent the solids from sticking to the tube walls. Roll a second piece of weighing paper in a funnel shape and place it on top of the tube, as shown in the image below.

6) Ensure that the Schlenk tap is closed.
7) Place a 1 cm oval stirring bar in the Schlenk tube. **Critical step:** the stirring bar needs to perfectly fit in the Schlenk tube to ensure optimal stirring.
8) Weigh 62.4 mg (0.2 mmol) of substrate *rac*-**10** and transfer it to the 10 mL Schlenk tube.
9) Weigh 28 mg (10 mol%) of catalyst (*S*)-**2** and transfer it to the 5 mL Schlenk tube.
10) Place the 1.75 mL vial with the cap on the balance and zero it.
11) In the 1.75 mL vial weigh 60 mg (5 equiv.) of KF. **Critical step:** KF is hygroscopic. Close the cap of both the KF bottle and vials between each weigh and clean the spatula on a piece of clean paper before taking more KF from the bottle to not contaminate it.
12) Transfer the KF to the Schlenk tube. Gently tap the bottom of the vial to ensure quantitative transfer. Be careful to not drop the vial inside the Schlenk tube.
13) Remove the weighing paper and seal the tube with the glass stopper. **Critical step:** Once the KF has been transferred to the tube, avoid leaving it unnecessarily open.
14) Transfer 400 µL of cold (-15 °C) $CHCl_3$ to the Schlenk tube.
15) Seal the tube with the glass stopper by giving it a small twist. Wrap some parafilm around the joint.
16) Transfer the tube to the ^{i}PrOH bath. **Critical step:** This needs to be done quickly, to avoid increase of the temperature of the reaction mixture which might affect the enantiopurity of the final product.
17) Increase the stirring speed to 900 rpm. Ensure that the Schlenk tube is optimally placed and that the stirring bar is moving evenly. **Critical step:** this is the single most important point of the set-up. You might want to verify the stirring in advance with a mock tube containing *i*PrOH and record the position of the clamps and the tube. The stirring bar should evenly rotate and not jump in the tube.
18) Wait 72 h.
19) Prepare a vial containing a 1:1 mixture of Et_2O and CH_2Cl_2 and place it in the Dewar to cool to -15 °C.
20) Meanwhile prepare a silica plug using a 10 mL syringe following step 3 but replacing the alumina with silica. 1 cm plug would be sufficient.
21) Put the contents of the reaction vial on top of the silica plug. Wash the tube at least 3 times with the cold (–15 °C) mixture of CH_2Cl_2:Et_2O = 1:1 from step 19, transferring all on top of the plug. **Critical step:** don't clamp the syringe too tight. This would deform the plastic resulting in the plunger not fitting and potentially leading to loss of product.

22) Filter the reaction mixture through the plug and collect it in a 25 mL round bottom flask. Evaporate the solvent to dryness. **PAUSE point:** if it is not possible to purify the compound immediately, store the flask in the freezer at –20 °C.
23) See step 21 of the PROCEDURE (Stage A) for how to pack a column and perform a dry loading. Scale down the amount of silica: for the column, aim to have a 15–17 cm height of silica; for the dry loading, add the equivalent of a teaspoon of sand to the crude reaction mixture dissolved in CH_2Cl_2.
24) Purify the compound by flash column chromatography using a gradient of *n*-hexane: Et_2O = 100:0 to 99.6:0.4 vol/vol. Collect the eluate in 5 mL tubes. Check the content of the tubes by using either UV-light or $KMnO_4$ stain. **Critical step:** the main impurity could be unreacted starting material (usually the reaction is complete by this time), which has a similar polarity to the product.
25) Combine the fractions containing the pure product and remove the solvent using a rotary evaporator (water bath temperature: 40 °C, pressure: 200 to 5 mbar, gradient).
26) Dry the product under high vacuum to accurately determine the yield.
27) To evaluate the enantiomeric ratio, dissolve 1 mg of pure product in 1 mL of Heptane (HPLC grade) and analyse it using a chiral stationary phase HPLC. (Column: DAICEL CHIRALPAK® IA-3, Heptane:^{i}PrOH = 99.75:0.25, 1 mL/min; t_1 = 3.37 min (minor), t_2 = 3.61 min (major).

Expected result: *N*-allyl-*N*-((1*S*,2*S*)-2-fluoro-1,2-diphenylethyl)prop-2-en-1-amine **11** was obtained as a colourless oil following this procedure in 71% yield and 95:5 e.r.

Analytical data: [9]
Colourless oil
[α]$_D$ = +27.5 (c 0.5 in $CHCl_3$ at 25 °C)
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 – 7.06 (m, 10H), 5.82 (dd, *J* = 47.2, 7.2 Hz, 1H), 5.69 (dddd, *J* = 17.5, 10.1, 7.6, 4.9 Hz, 2H), 5.11 – 4.99 (m, 4H), 4.15 (dd, *J* = 18.2, 7.2 Hz, 1H), 3.47 – 3.40 (m, 2H), 2.83 (dd, *J* = 14.3, 7.6 Hz, 2H)
^{19}F NMR (377 MHz, CDCl3) δ = -179.25 (dd, *J* = 47.2, 18.2 Hz, 1F)
^{13}C NMR (101 MHz, CDCl3) δ = 138.7 (d, $J_{C\text{-}F}$ = 20.3 Hz), 137.1, 136.6 (d, $J_{C\text{-}F}$ = 4.5 Hz), 129.7 (d, $J_{C\text{-}F}$ = 1.2 Hz), 128.2 (d, $J_{C\text{-}F}$ = 2.0 Hz), 128.1, 128.0, 127.4, 127.0 (d, $J_{C\text{-}F}$ = 6.7 Hz), 117.1, 95.3 (d, $J_{C\text{-}F}$ = 178.6 Hz), 67.3 (d, $J_{C\text{-}F}$ = 20.9 Hz), 54.0 (d, $J_{C\text{-}F}$ = 2.1 Hz)
IR (Et_2O cm^{-1}) 3066, 3031, 2923, 2814, 1641, 1495, 1453, 1418, 1205, 1124, 1080, 1031, 918, 759, 698, 607
HRMS (APCI$^+$) *m/z* calculated for $C_{20}H_{23}FN^+$ $[M+H]^+$ 296.18090, found 296.18069

MATERIALS

REAGENTS

! CAUTION All chemicals used in the PROCEDURE are potentially dangerous. Consult the safety data sheet of each reagent prior to performing the synthesis. Operators should wear personal protective equipment (lab coats, gloves and eye protection) and all the operations should be carried out in a chemical fume hood. The solid and liquid waste produced during the experiments should be disposed appropriately according to local regulation.

For the synthesis of (S)-N^2-isopropyl-[1,1'-binaphthalene]-2,2'-diamine **3**

- (*S*)-(–)-1,1′-binaphthyl-2,2′-diamine [(*S*)-BINAM)], CAS No. 18531-95-8 (>99% ee, 95% purity, Fluorochem, Cat. No. 212800).
- Sulfuric acid (H_2SO_4) aqueous solution 20% vol/vol **! CAUTION** Corrosive. It may cause severe skin burns.
- Sodium borohydride ($NaBH_4$), CAS No. 16940-66-2 (≥ 96%, purum, Sigma-Aldrich, Cat. No. 71320) **! CAUTION** Reacts with water with formation of hydrogen gas (flammable!). May damage fertility and the unborn child.
- Acetone, CAS No. 67-64-1 (≥ 99.8% purity, Chromasolv™ for HPLC, Honeywell Riedel-de Haën, Cat. No. 15664510).
- Tetrahydrofuran (THF, ≥ 99.9% purity, contains 250 ppm BHT as inhibitor, puriss. p. a., ACS reagent, Reag. Ph. Eur. Sigma-Aldrich, Cat. No. 87368).

For the synthesis of catalyst (*S*)-**1**

- 3,5-*Bis*(trifluoromethyl)phenyl isocyanate, CAS No. 16588-74-2 (98% purity, Alfa Aesar, Cat. No. L09582).
- Anhydrous Dichloromethane (CH_2Cl_2).

For the synthesis of N,N'-([1,1'-binaphthalene]-2,2'-diyl)bis(2,2,2-trifluoroacetamide) **4**

- (*S*)-(–)-1,1′-binaphthyl-2,2′-diamine [(*S*)-BINAM)], CAS No. 18531-95-8 (>99% ee, 95% purity, Fluorochem, Cat. No. 212800).
- Trifluoroacetic anhydride, CAS No. 407-25-0 (99% purity, Fluorochem, Cat. No. 001272) **! CAUTION** Corrosive and toxic upon inhalation.
- Anhydrous dichloromethane (CH_2Cl_2).
- Methanol (MeOH) (for HPLC ≥ 99.9%, Sigma-Aldrich Cat. No. 34860).

For the synthesis of (S)-N²-ethyl-[1,1'-binaphthalene]-2,2'-diamine **5**

- Iodoethane (EtI), CAS No. 75-03-6 (99% purity, Fluorochem, Cat. No. 148250) **! CAUTION** Acute and chronic toxicity. Avoid breathing the vapours.
- Potassium carbonate (K_2CO_3), CAS No. 584-08-7 (Sigma-Aldrich, Cat. No. P1472).
- Potassium hydroxide (KOH), CAS No. 1310-58-3 (≥ 85% purity, ACS reagent, pellets, Sigma-Aldrich, Cat. No. 221473) **! CAUTION** Corrosive. This reagent causes severe skin burns and eye damage.
- Acetone (≥ 99.8% purity, Chromasolv™ for HPLC, Honeywell Riedel-de Haën, Cat. No. 15664510).
- Ethanol absolute (≥ 99.8% purity, analytical reagent grade, Fisher-Scientific, Cat. No. 12478740).

For the synthesis of 3,3'',5,5''-tetrakis(trifluoromethyl)-[1,1':3',1''-terphenyl]-5'-amine **6**

- 3,5-dibromoaniline, CAS No. 626-40-4 (95% purity, Fluorochem, Cat. No. 212023).
- 3,5-*bis*(trifluoromethyl)phenyl boronic acid, CAS No. 73852-19-4 (98% purity, Fluorochem, Cat. No. 005569).
- Palladium(II) acetate [$Pd(OAc)_2$], CAS No. 3375-31-3 (>98% purity, Fluorochem, Cat. No. 035785).
- Dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (SPhos), CAS No. 657408-07-6 (98% purity, Fluorochem, Cat. No. 078390).
- Potassium carbonate (K_2CO_3), CAS No. 584-08-7 (Sigma-Aldrich, Cat. No. P1472).
- Degassed tetrahydrofuran (THF, ≥ 99.9% purity, contains 250 ppm BHT as inhibitor, puriss. p. a., ACS reagent, Reag. Ph. Eur. Sigma-Aldrich, Cat. No. 87368).
- Degassed water (H_2O, Milli-Q, 18 MΩ/cm; Millipore).

For the synthesis of 5'-isocyanato-3,3'',5,5''-tetrakis(trifluoromethyl)-1,1':3',1''-terphenyl **7**

- *Bis*(trichloromethyl) carbonate (triphosgene), CAS No. 32315-10-9 (98% purity, reagent grade, Alfa-Aesar, Cat. No. A14932) **! CAUTION** Fatal upon inhalation. **Perform all the operations involving triphosgene inside the fume hood.**
- Sodium hydrogen carbonate solution ($NaHCO_3$, saturated aqueous solution).
- Dichloromethane (CH_2Cl_2, ≥ 99.8% purity, for HPLC, contains amylene as stabiliser, Sigma-Aldrich, Cat. No. 24856).

*For the synthesis of catalyst (S)-**2***

- Anhydrous pyridine.
- 3Å Molecular sieves, powder (Alfa Aesar, Cat. No. B22658).
- Anhydrous tetrahydrofuran (THF).

SOLVENT AND REAGENTS FOR WORK-UP AND PURIFICATIONS

- Ethyl acetate (EtOAc, ≥99.7% purity, for HPLC, Sigma-Aldrich, Cat. No. 34858).
- Diethyl ether (Et_2O, ≥99.8% purity, contains BHT as inhibitor, puriss. p.a. ACS reagent, reag. ISO, reag. Ph. Eur., Sigma-Aldrich, Cat. No. 34858).
- Dichloromethane (CH_2Cl_2, ≥ 99.8% purity, for HPLC, contains amylene as stabiliser, Sigma-Aldrich, Cat. No. 24856).
- *n*-Pentane (≥ 99.0% purity, for HPLC, Sigma-Aldrich, Cat. No. 34956).
- Brine solution (NaCl saturated aqueous solution).
- Hydrochloric acid solution (HCl, 1 M in water).
- Potassium hydroxide solution (KOH, 1 M in water).
- Ammonium chloride (NH_4Cl) saturated aqueous solution.
- Celite filter aid (Alfa Aesar, Cat. No. B22658).
- $MgSO_4$ (Sigma-Aldrich, Cat. No. M7506).
- Silica gel (Merck, 60, particle size 0.040-0.063 mm, Cat. No. 1.11567.1000).
- Silicon dioxide (sand) (Sigma Aldrich, Cat. No. 18649).
- Silica gel pre-coated aluminum sheets (Merck Kieselgel 60 F_{254} plates Cat. No. 1.05554.0001) for TLC analysis.

- Deuterated chloroform ($CDCl_3$, Sigma Aldrich, Cat. No. 18649).

EQUIPMENT

- Schlenk line (i.e. dual nitrogen-vacuum manifold with vacuum line).
- High vacuum pump.
- Water aspirator.
- Heat gun (alternatively oven maintained at 100 °C).
- Rotary evaporator (Büchi).
- UV-lamp (λ = 254 nm and λ= 365 nm).
- Technical and analytical balances (Mettler Toledo).
- Weighing paper.
- Thermometer (range: -10 °C to 150 °C).
- Laboratory stands, clamps and bossheads.
- Cork rings.
- Magnetic stir plate with heating functionality (IKA) and temperature probe (VWR).
- PTFE coated stir bars (oval and octagon, various size).
- Overhead stirrer, PTFE shaft and PTFE stirrer blade (7.5 cm).
- Ice -bath (various size).
- Oil bath (various size, 2/3 filled with mineral oil).
- LabJack.
- Three-Neck round bottom flasks (500 mL, 1 L, 3 L).
- Two- Neck round bottom flasks (100 mL, 500 mL).
- Single-Neck round bottom flasks (500 mL, 1 L, 2 L).
- Dropping funnel with pressure equalizing tube (100 mL, 500 mL).
- Reflux condenser.
- Quickfit® cone/screw thread adapter (various sizes, Fischer Scientific).
- Quickfit® right angled adapters (various sizes, Fischer Scientific).
- Quickfit® side arm adapter (various sizes, Fischer Scientific).
- Plastic conical joint clips (various size).
- Glass stoppers (various sizes).
- Rubber septa (various sizes).
- Graduated cylinders (100 mL, 250 mL, 500 mL).
- Disposable graduate syringes (various size).
- Disposable injection needles (0.80x40 mm and 0.80x120 mm).
- Cannula.
- Spatula (various size).
- Separating funnels (1 L, 2 L).
- Erlenmeyer flask (500 mL, 1 L).
- Funnels (various size).
- Buchner funnels (various sizes).
- Rubber cones (various sizes).
- Chromatographic columns (various sizes).
- Glass tubes .
- TLC eluting chamber.
- Disposable Pasteur pipettes.
- Disposable glass vials with caps (~ 1 mL and ~ 5 mL).
- NMR spectrometer capable of obtaining ^{1}H-NMR, ^{19}F-NMR and ^{13}C-NMR(Bruker AVIIIHD 400, AVIIIHD 500 or VII 500).
- Reverse phase HPLC (Thermo Fischer Dionex Ultimate 3000 and Shimadzu LC-20AD).
- Column Kinetex 5µ C-18 100Å (250 x 4.6mm) and Luna C-18 analytical.

REAGENTS SET UP

Degas solvents

To degas solvents, follow the instructions below (**Error! Reference source not found.**4A):

1. Pour an excess of solvent in a round bottom flask containing a stirring bar.
2. Close the flask with a rubber septum and pierce it with an outlet needle.

3. Connect a needle (0.8 x 120 mm) to the nitrogen or argon line and insert it in the flask, as close as possible to its bottom and below the liquid meniscus.
4. Degas the solvent by vigorously bubbling nitrogen or argon into the solvent while stirring to ensure homogeneous dispersion. Degas for at least 30 min immediately before use.

For frequent use, degassed solvents could be stored indefinitely in a Schlenk tube under inert gas at room temperature. Nevertheless, we do not recommend storage of ethereal solvents for prolonged time (> 6 months) due to the risk of formation of explosive peroxides.

Activated 3Å MS

Heat the MS under vacuum at 200 °C for at least 18 h (overnight).

Activated MS could be stored indefinitely in a Schlenk tube under inert gas at room temperature.

EQUIPMENT SET UP

Drying glassware on a Schlenk line

To use a Schlenk line to dry glassware (Figure 4B), follow the instructions below. Alternatively, the glassware can be dried in an oven maintained at > 100 °C for at least 3 h.

1. Ensure that the taps of the Schlenk line are closed. Turn on the high vacuum pump and wait 5 min.
2. After 5 min, fill the trap of the vacuum line with liquid nitrogen. **! CAUTION** It is necessary to evacuate the line before cooling the trap with liquid nitrogen to avoid condensing liquid oxygen, as this might react explosively with grease or other organic materials. For the same reason, never leave the vacuum line open to air, but ensure that a larger amount of inert gas is present in the system.
3. Insert the stirring bar into the appropriate flask as described in the PROCEDURE (steps 24, 39 and 145). **! CAUTION** Be gentle and let the stirring bar slide on the flask walls rather than dropping it to avoid cracking of the flask.
4. Secure the flask to a metal stand using a clamp at about 50 cm from the fume hood bottom. DO NOT use a rubber-coated clamp, as this might melt during the next steps.
5. Assemble the other parts (e.g. dropping funnels, reflux condenser, glass stoppers,…) as described in the PROCEDURE (steps 24, 39 and 145). **! CAUTION** Inspect all the glassware to ensure the absence of cracking which might cause the implosion of the glass.
6. Connect the tubing of the Schlenk line to the glassware using a Quickfit® right angled adapter.
7. Ensure that all the openings are closed with a glass stopper.
8. Open the connection to the vacuum.
9. Under vacuum, heat the glassware to 360 °C with the heat gun for at least 5 min. Direct the heat flow uniformly around the whole glassware, especially at the bottom, where the stirring bar is resting, and around the joints. **! CAUTION** Hot glassware.
10. Let the glassware cool to room temperature, under vacuum.
11. When the flask is cold, backfill the flask with inert gas and wait 1 min.
12. Repeat the vacuum-inert gas cycle two times.

Transferring liquid between two flasks using a cannula

To use a cannula to transfer liquid between two flasks (Figure 4C) follow the instructions below:

1. Connect the container with the solvent/solution to be transferred to the Schlenk line. If the container has a tap (Figure 4C I), connect the tap to the Schlenk line and evacuate and backfill the tubing of the Schlenk prior to opening the flask tap. Alternatively, if the solvent/solution is contained in a single neck round bottom flask with a rubber septum, use a bottomless 1 mL syringe and a needle to connect the flask to the Schlenk line (4C II). Let the inert gas flow through the needle for 1-2 min prior to piercing the septum.
2. Dry the receiving flasks as described in "***Drying glassware on a Schlenk line***"
3. Under a positive flow of nitrogen, replace the glass stopper with a rubber septum. Insert a bleed needle into the septum to allow the small amount of air trapped in it to be flushed out. Fold the septum over the joint.
4. Replace the bleed needle with a clean and dry cannula (a hollow piece of PTFE or stainless steel) into the septum, maintain a positive flow of nitrogen to purge the cannula. Wait 1-2 min.
5. Insert the other side of the cannula into the flask containing the solvent through the rubber septum.
6. Close the flow of nitrogen into the receiving flask.
7. Add a bleed needle in the septum of the receiving flask.

8. Lower the cannula below the liquid meniscus in the solvent flask. The solvent should start flowing into the receiving flask. **CRITICAL STEP:** To facilitate transfer of the liquid, raise the solvent flask above the receiving flask and apply an overpressure to it adjusting the inert gas flow of the Schlenk. (4C III).
9. Transfer the required amount of solvent.
10. To stop the liquid flux, raise the cannula in the solvent flask above the liquid meniscus.
11. Reopen the flow of nitrogen into the receiving flask.
12. Remove the bleed needle.
13. Remove the cannula from the receiving flask. Clean and dry it immediately (this is particularly important if it has been used to transfer a solution).

Purity determination of bis-ureas (S)-1 and (S)-2 by reverse phase HPLC

Analysis of (*S*)-**1**.
Dissolve 1 mg of catalyst (*S*)-**1** in 2 mL of a H_2O:CH_3CN 30:70 mixture. Use Column Kinetex 5µm C-18 for HPLC analysis. Condition the column with a H_2O:CH_3CN 30:70 mixture for 30 min. Use the following HPLC method for quality control: 45 min linear gradient H_2O:CH_3CN 30:70 – 0:100, 1 mL/min. Detection at 254 nm. The purity of (*S*)-**1** is expressed as its normalized peak area percentage (Figure 5A).

Analysis of (*S*)-**2**.
Dissolve 1 mg of catalyst (*S*)-**2** in 1 mL of CH_3CN. Use Column Luna C-18 (analytical) for HPLC analysis. Condition the column with a H_2O:CH_3CN 15:85 mixture for 30 min. Use the following HPLC method for quality control: H_2O:CH_3CN = 15:85 to 2:98 over 3 min, then hold at 2:98 for 15 min. 1 mL/min. Detection at 254 nm. The purity of (*S*)-**2** is expressed as its normalized peak area percentage (Figure 5B).

PROCEDURE

Synthesis of catalyst (*S*)-1

Stage A: Synthesis of (S)-N^2-isopropyl-[1,1'-binaphthalene]-2,2'-diamine 3 **TIMING:** 8 h
CRITICAL Stage A of this procedure uses 10 g of (*S*)-BINAM to produce about 6.8 g of (*S*)-**3**.

1) Insert a 40 mm oval shaped stirring bar into a 500 mL three-neck round-bottom-flask. Insert a thermometer in one of the side necks and connect the other side neck to the nitrogen line with a Quickfit® right angled adapter.
2) Transfer 140 mL (measured with a graduated cylinder) of THF to the flask.
3) Transfer 3.6 mL (49 mmol, 1.4 equiv.) of acetone to the flask *via* a syringe.
4) Cool the solution to 0 °C using an ice bath.
5) At 0 °C, carefully add 70 mL of aqueous solution of H_2SO_4 (20% vol/vol), corresponding to 20 mL of H_2SO_4 solution for every mole of (*S*)-BINAM (Step 7). Adjust the addition rate to keep the temperature below 20 °C. The solution should remain colourless (no colour change should be observed).
6) Remove the ice bath and stir the solution at room temperature (~21 °C) for 45 min.
7) After 45 min, add 10 g (35 mmol, 1 equiv) of (*S*)-BINAM as a solid. (*S*)-BINAM is fully soluble and a brown solution is obtained.
8) Cool the solution to 0 °C using an ice bath.
9) When the temperature is stabilised at 0 °C (~ 5–10 min), add solid $NaBH_4$ portion-wise over 45 min (13 g, 350 mmol, 10 equiv.). This causes both gas evolution and formation of an inorganic precipitate. The reaction mixture colour gets lighter (greyish). **! CAUTION** Beside reducing the iminium to form the desired product, $NaBH_4$ reacts exothermically with H_2SO_4 with evolution of hydrogen (6). Wait for gas evolution to stop before adding more reducing agent. On this scale (10 g) it is suggested to run the reaction under a flow of nitrogen to mitigate the fire hazard associated with hydrogen evolution. **? TROUBLESHOOTING**

10) Remove the ice bath and stir the reaction mixture for a further 60 min at room temperature (~21 °C).
11) After 60 min, cool the reaction to 0 °C with an ice bath.
12) At 0 °C, carefully add 250 mL of aqueous KOH (1 M) to reach pH ~8 (monitored by pH paper). The reaction mixture gets even lighter in colour (off white); the precipitate is still present.
13) Transfer the reaction mixture into a 1 L separating funnel, rinsing the reaction flask with EtOAc (3 x 70 mL). Shake vigorously. **! CAUTION** vent the separatory funnel multiple times during the process to avoid pressure build-up.
14) Separate the phases (Top: organic, collect in an Erlenmeyer flask; bottom: aqueous, transfer back into the separating funnel). **? TROUBLESHOOTING**
15) Extract the aqueous phase two more times with EtOAc (2 x 100 mL) following Steps 13–14. Collect the organic phases together in the Erlenmeyer flask.
16) Transfer the combined organic phases to the separating funnel and wash the organic layer with brine (300 mL).
17) Collect the organic layer (top) in an Erlenmeyer flask and dry it with $MgSO_4$. If the solid sticks to the flask walls, add more $MgSO_4$. Let it rest for 5 min.
18) Meanwhile connect a 1 L round bottom flask to a water aspirator with Quickfit® adapters, tubing, and side arm, and place a Büchner fritted funnel (diameter: ~6 cm) on top of it.
19) Filter the organic phase through the frit. Rinse the Erlenmeyer flask and the solid with EtOAc.
20) Reduce the solution to dryness using a rotary evaporator (water bath temperature: 40 °C, pressure: 200 to 5 mbar, gradient).
    PAUSE POINT: crude **3** is obtained as a greyish solid (~14 g). It can be kept at room temperature under air until further purification (normally done within 72 h).
21) Purify crude **3** using dry loading Flash Column Chromatography. If bigger columns are available in the laboratory, the whole crude can be charged at once. Conversely, if only smaller columns are available, the crude can be divided into a larger number of smaller fractions and the quantity of silica and sand decreased accordingly.

- *Dry loading*: Weigh ~7 g of crude **3** (from Step 20) in a 100 mL round bottom flask. Dissolve the solid in ~15 mL of CH_2Cl_2. Add ~15 g of sand. Remove the solvent using a rotary evaporator until a powdery solid is obtained (water bath temperature: 40 °C, pressure: 600 to 5 mbar, gradient). To avoid bumping, the pressure should be maintained at 600 mbar until all solvent has been evaporated. Leave the solid to fully dry at 5 mbar for further 5 min.
- Pack a chromatographic column with a slurry of silica gel and *n*-pentane (column diameter = ~7 cm, height of silica = 14 cm).
- Transfer the sand with absorbed crude on top of the column. Scratch the wall of the flask to transfer the content quantitatively.
- Add 5 mL of CH_2Cl_2 and ~ 3–5 g of sand to the flask. Remove the solvent using a rotary evaporator and when the sand is dry transfer it into the column.
- Add ~2 cm of clean sand on top of the column.
- Elute the column with a gradient of *n*-pentane: EtOAc = 96:4 to 90:10 vol/vol. Collect the eluate in a 500 mL Erlenmeyer flask.

- Maintain *n*-pentane: EtOAc = 96:4 vol/vol until all the side product (*bis*-alkylated aniline) has been collected (R_f = 0.84, *n*-pentane: EtOAc = 95:5 vol/vol, Table 1). Discard the fractions.
- Increase the polarity to *n*-pentane: EtOAc = 90:10 vol/vol to collect the product (R_f = 0.56, *n*-pentane: EtOAc = 90:10 vol/vol, Table 1).
- Combine the fractions containing the pure product and remove the solvent using a rotary evaporator until a solid is obtained (water bath temperature: 40 °C, pressure: 800 to 5 mbar, gradient).

Table 1: Chromatographic purification of (*S*)-**3** over silica gel: R_fs (TLC) of product and common impurities.

Compound	**Eluent**	**R_f**	**Visualization: UV light λ= 254 nm and 365 nm**
bis-Alkylated aniline (side product)	*n*-Pentane: EtOAc = 95:5 vol/vol	0.84	Blue spot (254 nm)
(*S*)-**3** (product)	*n*-Pentane: EtOAc = 95:5 vol/vol	0.26	Blue spot (254 nm)
(*S*)-**3** (product)	*n*-Pentane: EtOAc = 90:10 vol/vol	0.56	Blue spot (254 nm)

22) If necessary, repeat step 21 for the remaining crude.

CRITICAL STEP: To maximise yield, if mixed fractions are obtained, concentrate them separately from the pure ones. Repeat steps 21. The column size should be adjusted depending on the amount of material to be purified.

PAUSE POINT: (*S*)-N^2-isopropyl-[1,1'-binaphthalene]-2,2'-diamine **3** is obtained as a white solid (6.8 g). It can be stored at room temperature under air for > 1 year. **? TROUBLESHOOTING**

Stage B: Synthesis of Catalyst (S)-1 **TIMING:** ~ 56 h
CRITICAL: Stage B of this procedure uses 6.8 g of (*S*)-3 to produce about 14 g of (*S*)-**2**.

CRITICAL: Anhydrous conditions required. The presence of water results in the formation of a side product, 1,3-bis(3,5-bis(trifluoromethyl)phenyl)urea (Schreiner's urea catalyst, Figure 7), which is difficult to remove and catalytically active as a phase-transfer catalyst. See the Equipment setup section for instructions on how to dry the glassware.

23) Insert a 20 mm oval shaped stirring bar into a 100 mL two-neck round bottom flask. Fit a water condenser on the central neck and connect the system to the Schlenk line with a Quickfit® right angled adapter placed on top of the condenser. Place a glass stopper on the side neck.
24) Follow the procedure for drying the glassware in Equipment setup (Figure 4B).
25) Under a flow of nitrogen, transfer 6.8 g (21 mmol, 1 equiv.) of (*S*)-N^2-isopropyl-[1,1'-binaphthalene]-2,2'-diamine **3** (from Step 21) to the flask. **? TROUBLESHOOTING**
26) Replace the glass stopper on the side neck with a rubber septum.
27) Transfer ~50 mL of anhydrous CH_2Cl_2 into the flask *via* a cannula (see Equipment setup, Figure 4C). (*S*)-N^2-isopropyl-[1,1'-binaphthalene]-2,2'-diamine **3** is soluble in CH_2Cl_2 and a brown solution is obtained.
28) Cool the solution to 0 °C with an ice batch while stirring.
29) At 0 °C, add 7.8 mL (42 mmol, 2 equiv.) of 3,5-*bis*(trifluoromethyl)phenyl isocyanate dropwise over 10–15 min. **CRITICAL STEP:** Addition of the isocyanate causes an immediate precipitation of a white solid, which then reacts further with formation of a yellow solution within ~30 min by the end of addition. If the rate of addition of the isocyanate is too fast, precipitation of the intermediate might cause the blockage of the stirring bar. **? TROUBLESHOOTING**
30) Replace the ice-bath with a mineral oil bath. Make sure that the meniscus of the reaction mixture is at the same level as the oil in the bath. **CRITICAL STEP** Wipe the exterior of the flask with some tissue to remove the water prior to immersing it into the oil bath.
31) Set the temperature of the oil bath to 40 °C.
32) Stir the reaction mixture at reflux for 48 h leaving the connection to the Schlenk line open and the flow of nitrogen at minimum, to not create a closed system. The solution gets darker (brown) over time.
    CRITICAL STEP: We suggest monitoring the reaction after 36 h *via* TLC. *Sample preparation:* Cool the reaction mixture to 30 °C. Increase the nitrogen flow and replace the glass stopper with a rubber septum. Use a 1 mL syringe to pierce the septum and collect 50-100 µL (approximately the dead volume of the needle) from the stirred reaction mixture and transfer it in a vial containing 500 µL of CH_2Cl_2 and a drop of MeOH to quench eventual residual isocyanate. TLC eluent: *n*-pentane:AcOEt = 90:10 vol/vol (R_f product: 0.10, R_f SM: 0.56).
33) After disappearance of the starting material (~36–48 h), add 1 mL of MeOH to the reaction mixture. No colour change is observed. **CRITICAL STEP:** addition of MeOH converts unreacted isocyanate into the corresponding (methyl (3,5-bis(trifluoromethyl)phenyl)carbamate) **12** (Figure 7) preventing the formation of Schreiner's urea during the work up. The carbamate is more easily separable from the desired product by column chromatography over silica gel.
34) Stir for 15 min at room temperature (~21 °C).
35) Concentrate the solution to dryness using a rotary evaporator (water bath temperature: 40 °C, pressure: 600 to 5 mbar, gradient).
    PAUSE POINT: crude (*S*)-**1** is obtained as an off-white solid (~17 g). It can be kept at room temperature under air until further purification (normally done within 72 h).
36) Purify crude (*S*)-**1** using dry loading Flash Column Chromatography following Step 21 with the following modifications:
    - Elute the column with a gradient of *n*-pentane: EtOAc = 95:5 to 85:15 vol/vol. Collect the eluate in 20 mL tubes.
    - Maintain *n*-pentane: EtOAc = 95:5 vol/vol = until all the impurities have been collected (for their R_fs see Table 2). Note that the solubility of some of these impurities is poor in the eluent system, which causes tailing. Discard the fractions.

- Gradually increase the polarity to *n*-pentane:EtOAc = 85:15 vol/vol to collect the product. (R_f = 0.49, *n*-pentane:EtOAc = 80:20 vol/vol, Table 2).
- Combine the fractions containing the pure product and concentrate the solution to dryness using a rotary evaporator (water bath temperature: 40 °C, pressure: 800 to 5 mbar, gradient). We suggest spotting multiple times the content of each test tube on the TLC plate to detect the presence of trace impurities. If the fractions are contaminated, collect them separately and, for maximum yield, repeat step 36. Consider *n*-pentane:Acetone = 90:10 vol/vol as alternative eluent system.
- Dry the solid under high vacuum at 70 °C for 48 h to remove the residual EtOAc.

Table 2: Chromatographic purification of (*S*)-**1** over silica gel: R_fs (TLC) of product and common impurities.

Compound	**Eluent**	**R_f**	**Visualization: UV light λ= 254 nm and 365 nm**
Methyl-(3,5-bis(trifluoromethyl)phenyl)carbamate **12**	*n*-Pentane: EtOAc = 90:10 vol/vol	0.40	Blue spot (254 nm)
(*S*)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(2'-(isopropylamino)-[1,1'-binaphthalen]-2-yl)urea **13**	*n*-Pentane: EtOAc = 90:10 vol/vol	0.47	Blue spot (254 nm)
1,3-bis(3,5-bis(trifluoromethyl)phenyl)urea (Schreiner's urea catalyst)	*n*-Pentane: EtOAc = 90:10 vol/vol	0.25	Blue spot (254 nm)
(*S*)-**1** (product)	*n*-Pentane: EtOAc = 90:10 vol/vol	0.10	Blue spot (254 nm)
(*S*)-**1** (product)	*n*-Pentane: EtOAc = 80:20 vol/vol	0.49	Blue spot (254 nm)

37) If necessary, repeat step 36 for the remaining crude.
PAUSE POINT: (*S*)-**1** is obtained as a white solid (14 g). It can be stored at room temperature on the bench for > 1 year. **? TROUBLESHOOTING**

38) Determine purity of (*S*)-**1** by reverse-phase HPLC using the following method (for further details, see Equipment set-up). Retention times of (*S*)-**1** and expected impurities are reported in table 3.
- *HPLC analysis:* Column Kinetex 5µ C-18; eluent: 45 minutes linear gradient H_2O:CH_3CN 30:70 – 0:100, 1 mL/min. Detection at 254 nm

Table 3: Retention times for reverse-phase HPLC analysis of (*S*)-**1** and expected impurities generated in the urea formation step.

Methyl-(3,5-bis(trifluoromethyl)phenyl)carbamate **12**	5.1 min
1,3-bis(3,5-bis(trifluoromethyl)phenyl)urea (Schreiner's urea)	13.3 min
(*S*)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(2'-(isopropylamino)-[1,1'-binaphthalen]-2-yl)urea **13**	24.4 min
(*S*)-**1**	27.3 min

? TROUBLESHOOTING

~~**Figure 7**~~

Synthesis of catalyst (*S*)-2

Stage C: Synthesis of (S)-N-N'-([1,1'-binaphthalene]-2,2'-diyl)bis(2,2,2-trifluoroacetamide) 4
TIMING: 20 h
CRITICAL: Stage C of this procedure uses 40 g of (*S*)-BINAM to produce about 65.8 g of (*S*)-**4**.
CRITICAL: Anhydrous conditions required. See the Equipment setup section for instructions on how to dry the glassware.

39) Insert a 40 mm oval shaped stirring bar into a 500 mL three-neck round bottom flask. Fit a 100 mL dropping funnel in the middle neck and a Quickfit® right angled adapter and a glass stopper in the side ones. Seal the dropping funnel with a glass stopper. Connect the Quickfit® right angled adapter to the Schlenk line (Figure 4B).
40) Follow the procedure in the Equipment setup for drying the glassware (Figure 4B).

41) Under a flow of nitrogen, transfer 40 g (0.14 mol, 1 equiv.) of (*S*)-BINAM into the flask.
42) Add 280 mL of anhydrous CH_2Cl_2 (measured with a graduated cylinder). Use the solvent to wash the flask neck. (*S*)-BINAM is not fully soluble, and a suspension is obtained at this stage.
43) Replace the stopper in the flask with a glass joint holding a thermometer (range: –10 to 150 °C). The thermometer should be immersed in the solvent but well above the stirring bar, to avoid breaking it.
44) Cool the suspension to 0 °C using an ice batch while stirring.
45) Ensure that the tap of the dropping funnel is closed! Transfer 49 mL (0.35 mol, 2.5 equiv.) of trifluoroacetic anhydride into the dropping funnel. **! CAUTION** Trifluoracetic anhydride is corrosive.
46) At 0 °C, add the trifluoroacetic anhydride dropwise over a period of 30 min. **CRITICAL STEP** Slow down the addition rate if the temperature of the reaction mixture increases above 10 °C.
47) Remove the ice-bath and let the reaction mixture warm to room temperature (~21 °C).
    CRITICAL STEP Place an empty bowl under the reaction flask and let it sit on a cork ring to reduce the weight held by the clamp.
48) Stir for 18 h (overnight) at room temperature. The product is more soluble than the starting material: at the end of the reaction a brown solution is obtained.
49) After 18 h transfer the solution into a 500 mL single-neck round bottom flask.
50) Rinse the three-neck flask with CH_2Cl_2 (2 x 20 mL) and transfer the solvent into the single-neck flask.
51) Concentrate the solution to dryness with a rotary evaporator located in a fume hood (water bath temperature: 40 °C, pressure: 600 to 5 mbar, gradient). **! CAUTION** Trifluoroacetic acid is a by-product of the reaction and it is extremely corrosive and volatile.
    PAUSE POINT: The product is a powdery off-white solid (65.8 g). It can be stored at room temperature under air for > 1 year. **? TROUBLESHOOTING ?**

Stage D: Synthesis of (S)-N^2-Ethyl-[1,1'-binaphthalene]-2,2'-diamine 5
TIMING: 34 h

CRITICAL: Stage D of this procedure uses 65.8 g of (*S*)-4 to produce about 26.3 g of (*S*)-**5**.

52) Place the stirring plate on a LabJack. Connect the temperature probe to the stirring plate.
53) Place an oil bath filled about halfway with mineral oil on the stirring plate and immerse the temperature probe into the oil at ~ 50 mm from the bottom of the bath. Insert a flat PTFE coated stirring bar in the bath.
54) Weigh 68.5 g of trifluoroacetamide **4** (0.14 mmol, 1 equiv.) into a 2 L single-neck round bottom flask equipped with a 60 mm oval shaped stirring bar.
55) Add 560 mL of acetone (measured with a graduate cylinder) to the flask.
56) Lower the flask so that the meniscus of the reaction mixture is at the same level of the mineral oil in the bath. **CRITICAL STEP:** Leave enough space for the stirring bar in the oil bath to freely rotate without touching the flask, as this could cause it to break. Note that the volume in the flask will increase after the addition of the other reagents, so adjustment will be necessary. We suggest evaluating the relative size of the flask and bath before starting the experiment and filling the bath with mineral oil.
57) Stir the mixture at room temperature (~21 °C) until the trifluoroacetamide **4** dissolves (~5-10 min). A brown solution is obtained.
58) Add 110 g of K_2CO_3 (0.28 mol, 2 equiv.) portion-wise while stirring. **CRITICAL STEP**: Portion-wise addition is required to prevent blockage of the stirring bar.**? TROUBLESHOOTING**
59) Add 13.5 mL of EtI (0.168 mol, 1.2 equiv.) while stirring. **! CAUTION** Ethyl iodide is an alkylating agent. It should be used under a fume-hood. Fill the used syringe with a basic solution of MeOH/aqueous $NaHCO_3$ and leave it under the fume hood for at least 24 h before disposal.
60) Fit a water condenser to the flask and connect it to the nitrogen line *via* a Quickfit® squared angle joint.
61) Set the oil bath temperature to 50 °C.
62) Stir the reaction mixture at reflux °C for 18 h (overnight) leaving the connection to the Schlenk line open and the flow of nitrogen at minimum, so to not create a close system. No changes were observed after 18 h at reflux.
    CRITICAL STEP: The reaction does not reach completion. 18 h was found to be optimal to ensure good conversion and avoid excessive overreaction. Consistent yields have been obtained on scales from 2.5 g to 40 g.
63) After 18 h, remove the oil bath and cool the reaction to room temperature.
64) Filter the reaction mixture through a frit (diameter ~10 cm) under vacuum to remove residual solid K_2CO_3. This will prevent bumping during the evaporation. Collect the filtrate in a 2 L round bottom flask.
65) Wash the solid with EtOAc (50 mL). **CRITICAL STEP:** For maximum yield repeat this step two times.

66) Concentrate the reaction mixture to dryness using a rotary evaporator (water bath temperature: 40 °C, pressure: 500 to 5 mbar, gradient).
PAUSE POINT: The crude product is obtained as a brown solid. It can be used immediately in step 67 or stored at room temperature under air for at least 72 h.
67) Dissolve the residue in 450 mL of EtOH.
68) Add a 60 mm oval shaped stirring bar to the flask and stir at room temperature (~21 °C) until full dissolution (~5–10 min). If residual K_2CO_3 is present, the reaction mixture will appear cloudy, but this does not affect the subsequent reaction.
69) Cool the reaction mixture to 0 °C.
70) At 0 °C, slowly add 110 mL of aqueous KOH (65% wt/vol) while stirring.
71) Replace the ice-bath with a mineral oil bath. **! CAUTION** Wipe the exterior of the flask with some tissue to remove the water prior to immersing it into the oil bath.
72) Set the bath temperature to 70 °C.
73) Stir the reaction mixture at 70 °C for 18 h (overnight) leaving the connection to the Schlenk line open and the flow of nitrogen at minimum, so to not create a close system. A white solid is formed during the reaction.
CRITICAL STEP: We recommend monitoring the reaction progression *via* TLC (eluent *n*-pentane:Et_2O = 80:20). Detection: UV light, λ= 254 nm. Starting materials have characteristic brownish spot at this wavelength, while the products are characterised by bright blue spots. (R_f of product: 0.22, eluent *n*-pentane:EtOAc = 90:10 vol/vol). *Sample preparation:* Cool the reaction mixture to 60 °C. Use a 1 mL syringe to collect 50–100 μL (approximately the dead volume of the needle) from the stirred reaction mixture and transfer it in a vial containing 1 mL of CH_2Cl_2 to obtain a solution.
74) After 18 h, remove the oil bath and cool the reaction to room temperature.
75) Transfer the reaction mixture into a 2 L separating funnel, rinsing the reaction flask with ethyl acetate (3 x 100 mL).
76) Add 200 mL of ethyl acetate and 300 mL of water. Shake vigorously. **! CAUTION** vent the separatory funnel multiple times during the process to avoid pressure built-up.
77) Separate the phases (Top: organic, collect in an Erlenmeyer flask; bottom: aqueous, transfer back into the separating funnel). **! CAUTION** the aqueous solution is very basic and corrosive! At the end of the work-up carefully neutralise it with a saturated solution of ammonium chloride prior of disposing into the aqueous waste. **? TROUBLESHOOTING**
78) Extract the aqueous phase three more times with EtOAc (3 x 100 mL). Collect the organic phases together in the Erlenmeyer flask.
79) Transfer the combined organic phases to the separating funnel and wash them with brine (300 mL).
80) Filter the organic phase trough a $MgSO_4$ pad (diameter: ~ 15 cm, height: ~ 5cm) under vacuum filtration. Collect the filtrate in a 2 L round bottom flask.
81) Reduce the solution to dryness using a rotary evaporator (water bath temperature: 40 °C, pressure: 200 to 5 mbar, gradient).
PAUSE POINT: crude **5** is obtained as an off-white solid. It can be kept at room temperature under air until further purification (normally done within 72 h).
82) Divide the crude product into 4 fractions of ~10 g each and purify each fraction by dry loading flash column chromatography. Follow Step 21 with the following modifications:
    - Elute the column with a gradient of *n*-pentane: EtOAc = 97:3 to 90:10 vol/vol. Collect the eluate in 500 mL Erlenmeyer flask.
    - Maintain *n*-pentane:EtOAc = 97:3 vol/vol until all the side product (*bis*-alkylated aniline) has been collected. (R_f = 0.22; *n*-pentane:EtOAc = 97:3 vol/vol, Table 4). Discard the fractions.
    - Increase the polarity to *n*-pentane:EtOAc = 90:10 vol/vol to collect the product. (R_f = 0.31; *n*-pentane:EtOAc = 90:10 vol/vol, Table 4).
    - To collect unreacted (*S*)-BINAM, increase the polarity to *n*-pentane:EtOAc = 80:20 vol/vol (R_f = 0.29, *n*-pentane:EtOAc = 80:20 vol/vol, Table 4).
83) Repeat step 83 for the remaining crude **5**.
CRITICAL STEP: For maximum yield, if mixed fractions are obtained, concentrate them separately from the pure ones according to step 81. Repeat step 82.
PAUSE POINT: (*S*)-N^2-Ethyl-[1,1'-binaphthalene]-2,2'-diamine **5** is obtained as a white solid (26.3 g). It can be stored at room temperature under air for > 1 year. **? TROUBLESHOOTING**

Table 4: Chromatographic purification of (*S*)-**5** over silica gel: R_fs (TLC) of product and common impurities.

Compound	**Eluent**	**R_f**	**Visualization: UV light λ= 254 nm and 365 nm**

bis-alkylated aniline (side product)	*n*-Pentane: EtOAc = 97:3 vol/vol	0.22	Blue spot (254 nm)
bis-alkylated aniline (side product)	*n*-Pentane: EtOAc = 90:10 vol/vol	0.79	Blue spot (254 nm)
(*S*)-**5** (product)	*n*-Pentane: EtOAc = 90:10 vol/vol	0.31	Blue spot (254 nm)
(*S*)-BINAM (starting material)	*n*-Pentane: EtOAc = 90:10 vol/vol	0.10	Blue spot (254 nm)
(*S*)-BINAM (starting material)	*n*-Pentane: EtOAc = 80:20 vol/vol	0.29	Blue spot (254 nm)

Stage E: Synthesis of 3,3'',5,5''-tetrakis(trifluoromethyl)-[1,1':3',1''-terphenyl]-5'-amine 6
TIMING: 58 h

CRITICAL: Stage E of this procedure uses 30 g of 3,5-dibromoaniline to produce 53 g of **6**.

84) Assemble the glassware as depicted in 8. Insert a 60 mm oval shaped stirring bar in a 1 L three-neck round bottom flask. Fit a water condenser in the central neck, a thermometer in the second and a glass stopper in the third. Place a Quickfit® right angled adapter on the top of the condenser and connect it to the Schlenk line. Place the stirring plate on a LabJack.

85) Add 30 g of 3,5-dibromoaniline (0.12 mol, 1 equiv.) to the flask.
86) Add 108 g of 3,5-*bis*(trifluoromethyl)phenyl)boronic acid (0.42 mol, 3.5 equiv.) to the flask.
87) Add 490 mg of 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos, 0.012 mol, 1 mol%) to the flask.
88) Evacuate the flask (1 min).
89) Backfill the flask with nitrogen (1 min).
90) Repeat steps 88–89 twice.
91) Under a positive flow of nitrogen, add 480 mL of degassed THF (measured with a cylinder).
92) Stir the solution at room temperature (~21 °C) until complete dissolution of the solids (~5–10 min). A yellow solution is obtained.
93) Under a positive flow of nitrogen, add 120 mL of degassed H_2O (measured with a cylinder).
94) Cool the reaction mixture to 0 °C.
95) Bubble nitrogen through the reaction mixture for 20 min.
96) At 0°C, under a positive flow of nitrogen, add K_2CO_3 portion-wise (5x 18 g = 90 g in total, 0.48 mol, 4 equiv.). **! CAUTION** Exothermic. Monitor the temperature of the reaction mixture to avoid it increasing above room temperature. Ensure efficient stirring is maintained.
97) Replace the ice-bath with a mineral oil bath. **! CAUTION** Wipe the exterior of the flask with some tissue to remove the water prior to immersing it into the oil bath.
98) Set the bath temperature to 60 °C.
99) When the temperature in the flask has reached 60 °C, add 134 mg of $Pd(OAc)_2$ (6 mmol, 0.5 mol%) under a positive flow of nitrogen. **CRITICAL STEP:** If the catalyst sticks on the glass walls during the addition, rinse it with degassed THF. The reaction turns immediately bright orange, then, after few minutes, uniformly dark brown (Figure 9A) **? TROUBLESHOOTING**
100) Stir the reaction mixture at 60 °C for 48 h leaving the connection to the Schlenk line open and the flow of nitrogen at minimum, to not create a closed system. At the end of the reaction, the organic phase appears pale yellow, and a black precipitate is visible both on the flask walls and on the bottom (Figure 9B).
CRITICAL STEP: We suggest monitoring the reaction after 18 h (overnight) or 24 h *via* TLC (eluent *n*-pentane: AcOEt = 90:10 vol/vol, visualisation: UV light, λ= 254 nm; R_f 3,5-dibromoaniline: 0.33, R_f product **6**: 0.22) as it would likely take less than 48 h. Leaving the reaction for up to 72 h has no adverse consequences. *Sample preparation:* Cool the reaction mixture to 40 °C. Increase the nitrogen flow and replace the glass stopper with a rubber septum. Use a 1 mL syringe to pierce the septum and collect 50-100 μL (approximately the dead volume of the needle) from the stirred reaction mixture and transfer it in a vial containing 1 mL of CH_2Cl_2.

101) When the reaction is complete, remove the oil bath and cool the reaction mixture to room temperature.
102) Dilute the reaction mixture with 300 mL of water and 300 mL of CH_2Cl_2.
103) Transfer the reaction mixture into a 2 L separating funnel, rinsing the reaction flask with CH_2Cl_2 (3 x 100 mL).
104) Collect the organic phase (bottom) in an Erlenmeyer flask.
105) Extract the aqueous phase (top) twice with CH_2Cl_2 (2 x 100 mL).
106) Wash the combined organic phases with brine (500 mL).
107) Filter the organic phase trough a $MgSO_4$ pad (diameter: ~ 15 cm, height: ~ 5cm) under vacuum filtration. Collect the filtrate in a 2 L round bottom flask.
108) Reduce the solution to dryness using a rotary evaporator (water bath temperature: 40 °C, pressure: 600 to 5 mbar, gradient).
PAUSE POINT: crude **6** is obtained as a brown waxy solid. It can be kept at room temperature under air until further purification (normally done within 72 h).
109) Pack a chromatographic column with a slurry of silica gel and *n*-pentane (column diameter = ~7 cm, height of silica ~6 cm).
110) Dissolve the crude in the minimum amount of CH_2Cl_2 (~20 mL) and transfer it on top of the silica pad. Wash the flask with 3 x 5 mL of CH_2Cl_2 and transfer it on top of the silica pad.
111) Add ~2 cm of sand on top of the pad.
112) Elute the column with a gradient of *n*-pentane: CH_2Cl_2 = 95:5 to 70:30 vol/vol (700 mL 95:5, then 1.5 L 70:30).
113) Collect the eluate in 500 mL Erlenmeyer flask. Discard the first 700 mL (confirm the absence of product by TLC – *n*-pentane: EtOAc = 90:10 vol/vol, visualisation: UV light, λ= 254 nm; R_f product: 0.22), then collect further 1.5 L (confirm the presence of product by TLC).
114) Combine the fractions containing the pure product and reduce the solution to dryness using a rotary evaporator (water bath temperature: 40 °C, pressure: 800 to 5 mbar, gradient).
PAUSE POINT: 3,3",5,5"-tetrakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-amine **6** is obtained as a white solid (53 g). It can be stored at room temperature under air for > 1 year. **? TROUBLESHOOTING**

Stage F: Synthesis of 5'-isocyanato-3,3'',5,5''-tetrakis(trifluoromethyl)-1,1':3',1''-terphenyl 7
TIMING: 28 h

CRITICAL: Stage F of this procedure uses 54 g of aniline **6** to produce about 40 g of isocyanate **7**.

115) Fix the stirrer motor to a long stand at about 60 cm from the bottom of the fume hood. **! CAUTION** The motor is very heavy. Ensure it is properly fixed, so that the vibration caused by the stirring will not make it loose and cause it to fall.
116) Place a plastic bowl large enough to comfortably contain a 3 L flask below the motor.
117) Place the 3 L, three-neck round bottom flask inside the bowl and hold it upright with a clamp to the central neck.
118) Insert the PTFE stirrer in the central neck, through a Quickfit® cone/screw thread adapter and Quickfit® side arm adapter (Figures 10A and 10B). Use further adaptors to match the sizes of the joint if required but aim to minimise the number of adaptors. Secure each joint with a plastic clip. **CRITICAL POINT:** Efficient stirring of the reaction is critical and made difficult by formation of a slurry (see Step 137). Ensure that the blades of the stirrer are large enough to cover at least half of the diameter of the flask.

119) Secure the stirrer to the motor so that the blades are at about 0.3 cm from the bottom of the flask.
120) Verify the alignment of the joints and that the stirrer works efficiently. **CRITICAL POINT:** Efficient stirring of the reaction is critical and made difficult by formation of a slurry (see Step 137). We recommend checking the set-up carefully prior to starting the reaction to avoid problems at a later stage.
121) Connect the Quickfit® side arm adapter on the central neck to the nitrogen line. Turn on the nitrogen.
122) Put a stopper on one of the side necks, and a Quickfit® right angled adapter on the other.
123) Connect the Quickfit® right angled adapter to a trap containing a saturated aqueous solution of $NaHCO_3$ (Figure 10C)
124) Weigh 11.4 g of triphosgene (0.39 mol, 0.37 equiv.) into a capped vial. If the balance is outside of a fumehood:
- Weigh a capped vial (~20 mL) on the balance and record the tare.
- In the fume hood, transfer the triphosgene in the vial and cap it.
- Weigh the vial.
- Repeat until the required amount (11.4 g) has been weighed.

! CAUTION Triphosgene is very toxic. Moreover, it hydrolyses slowly with the humidity in the air liberating phosgene, recognisable from the cut-grass-like smell. All manipulations MUST be performed in a ventilated fume hood. Ideally the balance used for the weighing should be placed in the same fume hood used for running the reaction. After handling triphosgene, put all the material that was in contact with triphosgene (*e.g*. the spatula used for weighing, the vial, paper used to collect spillages, gloves, etc.) in a bowl containing a mixture of methanol and an aqueous solution of $NaHCO_3$. Leave it in the fume hood overnight before disposing according to local regulations.

125) Transfer the triphosgene into the 3 L flask.
126) Add 600 mL of CH_2Cl_2 to the flask.
127) Under a positive flow of nitrogen, stir gently to dissolve the triphosgene (~5–10 min).
128) Add a mixture of ice and water to the bowl underneath the flask to cool the solution to 0 °C. Wait at least 10 min.
129) Meanwhile weigh 54 g of 3,3",5,5"-tetrakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-amine **6** (0.10 mol, 1 equiv.) in a 500 mL round bottom flask equipped with a magnetic stirring bar.
130) Add 300 mL of CH_2Cl_2 to the 500 mL round bottom flask.
131) Stir at room temperature until complete dissolution of aniline **6**.
132) Replace the stopper on one of the side-neck of the 3 L flask with a 500 mL dropping funnel, sealed with a stopper.
133) Ensure that the tap of the dropping funnel is closed. Transfer the solution of aniline **6** (from Step 131) into the dropping funnel. Rinse the 500 mL flask with CH_2Cl_2 (2 x 20 mL).
134) At 0 °C, add the solution of aniline **6** to the 3 L flask *via* the dropping funnel over 15 min. The reaction gets hazy, but this does not prevent stirring of the reaction mixture. **CRITICAL STEP:** Adjust the stirring speed to maintain efficient stirring and avoid splashing of the solution on the flask walls.
135) Rinse the dropping funnel with further 100 mL of CH_2Cl_2 and add it to the reaction vessel. **CRITICAL STEP:** Ensure the flask walls are washed as the aniline might precipitate during the addition. It might be useful removing the dropping funnel and rinsing the flask with a Pasteur pipette. Do not breath the vapours.
136) Transfer into the dropping funnel 2 x 500 mL of a saturated aqueous solution of $NaHCO_3$.
137) At 0 °C, add the solution to the 3 L flask *via* the dropping funnel over ~30 min. The addition causes the immediate precipitation of a thick white solid. **CRITICAL STEP:** Initial slow addition is necessary to ensure homogeneous stirring and thus reproducible results. Gradually increase the stirring speed to cope with the increased viscosity of the reaction mixture. After the first 500 mL have been added, the feed rate can be increased.
138) Under a positive flow of nitrogen, stir the reaction at 0 °C for 45 min. **CRITICAL STEP:** We recommend monitoring the reaction *via* ^{1}H-NMR. *Sample preparation:* stop the stirring and with a syringe collect a sample from the organic layer (bottom). Transfer it in a vial and remove the solvent in a rotary evaporator under a fume hood. Dissolve the sample in 400 µL of $CDCl_3$ and record the NMR spectrum. The signals of the starting material and of the product are reported in the *analytical data* section and in Figure 11).
139) Meanwhile, prepare the material needed for the work-up: a 2 L separating funnel, 1 L Erlenmeyer flasks, a 10 cm diameter Büchner fritted funnel, a 1 L 1-neck round bottom flask and a Quickfit® side arm adapter. Assemble the frit on top of the round bottom flask *via* the Quickfit® side arm adapter and connect it to the vacuum aspirator. Fill the funnel with a ~4 cm high $MgSO_4$ pad (Figure 10 D).

140) After 45 min, transfer the reaction mixture into the separating funnel. **! CAUTION** Unreacted triphosgene or other toxic side products might still be present in the reaction mixture.
141) Let it decant and separate the layers. Collect the organic one (bottom) in an Erlenmeyer flask.
142) Filter the organic layer through the $MgSO_4$ pad (diameter ~10 cm, height ~ 4 cm) under light vacuum.
143) Concentrate the solution to dryness with a rotary evaporator located in a fume hood (water bath temperature: 30 °C, pressure: 600 to 5 mbar, gradient). **! CAUTION** Phosgene is formed during the reaction and might still contaminate the product.

PAUSE POINT: The crude product is a white solid, which is better stored in the fridge until further purification (normally done within 72 h). **CRITICAL STEP:** ^{1}H and ^{19}F NMR of the crude product in $CDCl_3$ appear deceptively clean and they are not a sign of sufficient purity for the subsequent step. We strongly suggest recrystallising the product prior to attempting the urea coupling. Note that some of the impurities that contaminate the crude isocyanate are not soluble in CH_2Cl_2 or $CHCl_3$, thus an NMR

sample of the crude product might appear hazy. Use of deuterated THF is suggested to assess the product purity, as this solvent can solubilise both the product and the impurities.

144) Purify the crude product by recrystallisation:
- Transfer the crude product into a round bottom flask equipped with a stirring bar.
- Add 20 mL/g product of *n*-hexane.
- Add a water condenser on the top of the flask and immerse it in an oil bath.
- Set the temperature of the oil bath to 70 °C and bring the mixture to reflux while stirring.
- Add THF until full dissolution of the solid (~0.5–0.75 mL/g product). A yellow solution is obtained. The water present in the THF could hydrolyse the product. To maximise yield, ensure that the time the product is in contact with THF at high temperature is the minimum required for its full dissolution (< 30 min).
- Remove the flask from the oil bath and let it cool to room temperature. The pure product will start to precipitate within 60 min. Wait 3–5 h.
- Filter the precipitate on a Büchner funnel covered with filter paper using a water aspirator.
- Use the mother liquor to resuspend residual solid in the flask and collect it.
- Wash the crystals with cold (0 °C) THF (2 x 5 mL). Crush the solid with the flat part of a glass stopper.
- Let it dry on the filter in the fume hood for 18 h (overnight).

CRITICAL STEP: for maximum yield, collect the mother liquor and remove the solvent. Repeat step 144. **CAUTION:** in the absence of further safety data, treat this compound as hazardous and always wear appropriate PPE during its manipulation.

PAUSE POINT: Pure **7** is obtained as a white solid (40 g). The compound is fully soluble in CH_2Cl_2 and $CHCl_3$, unlike the crude reaction mixture. We recommend storing the isocyanate in the fridge (+4 °C) to prolong its shelf life (stable for > six months at +4 °C).

? TROUBLESHOOTING

Stage G: Synthesis of catalyst (*S*)-2 TIMING: 90 h

CRITICAL: Stage G uses 13 g of (*S*)-5 to produce about 52 g of (*S*)-**2**.

CRITICAL: Anhydrous conditions required. The presence of water results in the formation of achiral Schreiner-type urea **14** (1,3-bis(3,3",5,5"-tetrakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)urea) as a by-product (Figure 12). This compound is difficult to remove and is catalytically active as a phase-transfer catalyst.

See the Equipment setup section for instructions on how to dry the glassware.

145) Insert a 40 mm oval shaped stirring bar into a 500 mL two-neck round bottom flask. Connect the flask to the Schlenk line *via* a Quickfit® right angled adapter (Figure4B).

146) Follow the procedure in Equipment setup for drying glassware (Figure 4B).

147) Under a positive flow of nitrogen, transfer 2.3 g of 3Å powdered molecular sieves into the flask.

148) Under a positive flow of nitrogen, transfer 45.22 g of isocyanate **7** (83.2 mmol, 2 equiv.) into the flask.

149) Replace the glass stopper on the side neck with a rubber septum.

150) Transfer ~280 mL of anhydrous THF into the flask *via* a cannula (see Equipment setup, Figure 4C). Isocyanate **7** is soluble in CH_2Cl_2 and a pale-yellow suspension (due to the sieves) is obtained.

151) Cool the reaction mixture to 0 °C using an ice bath while stirring.

152) Transfer ~60 mL of anhydrous pyridine into the reaction mixture at 0 °C. No changes are observed.

153) Follow the procedure in Equipment setup to dry a 100 mL two-neck round bottom flask equipped with a 20 mm oval shaped stirring bar.

154) Add 13 g of (*S*)-N^2-ethyl-[1,1'-binaphthalene]-2,2'-diamine **5** to the 100 mL two-neck round bottom flask under a positive flow of nitrogen.

155) Add 40 mL of anhydrous THF to the 100 mL 2-necks round bottom flask.

156) Stir the mixture at room temperature until full dissolution of the solid (~5-10 min). The solution should be brown.

157) At 0 °C, cannulate the solution of (*S*)-N^2-ethyl-[1,1'-binaphthalene]-2,2'-diamine **5** (from step 156) into the stirred solution of isocyanate **7** (from step 152) over 20 min.

158) Remove the ice-bath and let the reaction mixture warm to room temperature.

! CAUTION Place an empty bowl under the reaction flask and let it sit on a cork ring to reduce the weight held by the clamp.

159) Stir for 36 h at room temperature (~21 °C) under a flow of nitrogen. No changes should be observed over this period.
CRITICAL STEP: We suggest monitoring the reaction *via* TLC. *Sample preparation*: Increase the nitrogen flow and replace the glass stopper with a rubber septum. Use a 1 mL syringe to pierce the septum and collect 50–100 μL (approximately the dead volume of the needle) from the stirred reaction mixture. Transfer the sample into a vial containing 500 μL of CH_2Cl_2 and a drop of MeOH to quench eventual residual isocyanate. TLC eluent: *n*-pentane:AcOEt = 80:20, R_f product (*S*)-**2**: 0.74, R_f Starting material (*S*)-**4**: 0.54).

160) Upon completion of the reaction, add 5 mL of MeOH to the reaction mixture to quench eventual residual isocyanate. No changes should be observed.

161) Stir at room temperature (~21 °C) for 15 min.

162) Filter the reaction mixture on a frit with a 2 cm celite filter aid pad, to remove the powdered molecular sieves. Use a water vacuum pump to speed up the filtration and collect the filtrate in a 1 L round bottom flask.

163) Rinse the reaction flask three times with 20 mL of CH_2Cl_2.

164) Concentrate the solution to dryness with a rotary evaporator located in a fume hood.**! CAUTION** Pyridine is still in the flask.
PAUSE POINT: crude (*S*)-**2** is obtained as an off white solid (57.9 g). It can be kept at room temperature under air until further purification (normally done within 72 h).**? TROUBLESHOOTING**

165) Purify the crude product by crystallisation:
- Transfer the crude product into a round bottom flask equipped with a stirring bar.
- Suspend the solid in *n*-heptane (5 mL/g product).
- Add a water condenser on the top of the flask and immerse it in an oil bath.
- Set the temperature of the oil bath to 100 °C and bring the mixture to reflux while stirring.
- Add EtOH until complete dissolution of the solid (~ 6 mL/g product).
- Cool the mixture to room temperature (~21 °C), then further to 0 °C with an ice bath and finally to –20 °C, moving the flask into a freezer.
- Let the product precipitate at – 20 °C for 24 h.
- Filter the precipitate on a Buchner funnel covered with filter paper.
- Use the mother liquor to resuspend residual solid in the flask and collect it.
- Wash the crystals with cold (0 °C) EtOH (2 x 10 mL). Crush the solid with the flat part of a glass stopper.
- Let it dry on the filter in the fume hood for 18 h (overnight), then in an oven at 80 °C for further 24 h.

? TROUBLESHOOTING

CRITICAL STEP: for maximum yield, collect the mother liquor and remove the solvent. Repeat step 165. **PAUSE POINT**: Catalyst (*S*)-**2** is obtained as a white solid (52 g). It can be stored at room temperature on the bench for > 1 year.

166) Determine purity by reverse-phase HPLC using the following method (For further details, see equipment set-up). Retention times of (*S*)-**2** and expected impurities are reported in table 5.
- *HPLC conditions:* Column Luna C-18 (analytical); eluent: H_2O:CH_3CN = 15:85 to 2:98 over 3 min, then hold at 2:98 for 15 min. 1 mL/min. Detection at 254 nm.

Table 5: Retention times for reverse-phase HPLC analysis of (*S*)-**2** and expected impurities generated in the urea formation step.

Methyl (3,3",5,5"-tetrakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)carbamate **14**	6.5 min
1,3-Bis(3,3",5,5"-tetrakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)urea (Schreiner-type urea) **15**	12.5 min
1-(2'-(Ethylamino)-[1,1'-binaphthalen]-2-yl)-3-(3,3",5,5"-tetrakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)urea **16**	10.5 min
(*S*)-**2**	13.9 min

? TROUBLESHOOTING

Timing
Timing based on large scale reactions (> 10 g); reagent additions, work up and purification times are expected to be shorter for smaller scale reaction (1–5 g)

Stage A (Steps 1–22): 8 h. Set-up: 10 min; reaction time (total): 2.5–3 h (including 45 min of portion-wise addition); work up: 1–1.5 h; purification ~ 3 h for each column (total 6 h).
Stage B (Steps 23–38): 55 h. Set-up= 30 min; reaction time = 36–48 h; work up = 1 h; purification ~ 3 h for each column (total 6 h).
Stage C (Steps 39–51): 20 h. Set-up= 30 min; reaction time = 18 h (presumably faster, but it can be conveniently left overnight); work up = 1 h (solvent evaporation).
Stage D (Steps 52–83): 34 h. Part 1: set-up= 30–60 min; reaction time = 18 h; work up = 1 h; Part 2: set-up= 30 min; reaction time = 18 h; work up = 2–3 h; purification ~ 3 h for each column (total 12 h).
Stage E (Steps 84–114): 58 h. Set-up= 1 h; reaction time= 24–48 h; work up = 1–2 h purification= 2 h
Stage F (Steps 115–144): 28 h. Set-up= 2–3 h; reaction time = 1 h; work up= 1 h; purification = 25 h.
Stage G (Steps 145–166): 90 h. Set-up= 1 h; reaction time= 36; work up = 1–2 h; purification = 50 h.

TROUBLESHOOTING
Troubleshooting advice is included in Table 6.

Table 6: Troubleshooting advice

Step	Problem	Possible Reason	Solution
A			
9	Stirring bar blockage	Addition of $NaBH_4$ was too fast.	Remove the flask from the clamp and gently shake it to unblock the stirring bar. If this does not work, use a glass rod to stir the reaction mixture and unblock the stirring bar. Add the remaining $NaBH_4$ at a slower rate.
9	No gas evolution.	$NaBH_4$ is inactive (old batch)	Check if this is the case by throwing a few milligrams (<5 mg) of $NaBH_4$ into a vial containing ^{i}PrOH. If no gas evolution is observed the $NaBH_4$ is inactive: use a different batch. If gas evolution is observed see below.
9	No gas evolution.	The solid is stuck in the funnel. This is due to $NaBH_4$ adsorbing the humidity from the flask and sticking on the funnel.	Remove the funnel from the flask and empty it on a weighing boat. To prevent further clogging, scrape the side of the funnel with a spatula after every addition.
14	An emulsion is formed during the work-up.	Not enough EtOAc.	Wait 5–10 min. The emulsion should break spontaneously. If this does not happen, add more EtOAc and some brine. This should help disperse the THF and increase the density difference of the phases.
21	The solid is reddish.	The aniline is contaminated by small amounts of oxidation product.	Check the ^{1}H NMR purity of a sample of 5 mg of **3** in 400 μL of $CDCl_3$. If the purity is > 95% the aniline can be used in the subsequent step. Otherwise repeat the purification (Step 21)
21	Low yield (see expected yield)	Losses during chromatographic purification.	Check the presence of product in the discarded fractions from the column by TLC (Product R_f = 0.56; *n*-pentane:EtOAc = 90:10 vol/vol visualisation: UV light λ= 254 nm and 365 nm, blue spot). Flush the column with *n*-pentane:AcOEt = 50:50. This allows the collection of unreacted starting material and an estimate of the complete mass balance.
B			
29	Stirring bar blockage	Addition of isocyanate was too fast.	Remove the flask from the clamp and gently shake it to unblock the stirring bar. This will also help mass transfer and ultimately the solid will react further and dissolve. Add the remaining isocyanate at a slower rate.

37	Low yield (see expected yield)	Losses during the column due to mixed fraction.	Purify the mixed fractions according to step 36
37	(*S*)-**1** contains EtOAc	The solvent is coordinated to the catalyst	Recrystallise the catalyst (see below, troubleshooting information for step 38: "(*S*)-**1** is not pure". .
38	(*S*)-**1** is not pure	Reaction conditions were not fully anhydrous. Incomplete reaction.	Assess whether it is possible to repeat the chromatographic purification. If not possible, dissolve (*S*)-1 in the minimum amount of Et_2O (~ 1.2 mL/g (*S*)-**1**). Gently layer *n*-hexane (~ 6 mL/ g (*S*)-**1**) on top of the Et_2O solution and let it diffuse at room temperature. After 24 h, filter the solid, washing it with the minimum amount of cold *n*-hexane (kept in a dry ice box). Note the yield of crystallisation should be ~ 94%.
38	Purity is low: contaminated by Schreiner's urea catalyst	Reaction conditions were not fully anhydrous.	Preventive action: Use new bottles of anhydrous solvents/freshly distil the solvents.
38	Purity is low: contaminated by Schreiner's urea catalyst	Schreiner's urea catalyst formed in the reaction is difficult to remove by chromatography over silica gel using the conditions reported in the PROCEDURE. (Poor solubility causes tailing)	Corrective action: Repurify by chromatography using a short silica plug and eluting with pure $CHCl_3$. (Schreiner's urea catalyst is not soluble in $CHCl_3$).
38	Purity is low: contaminated by *mono*urea intermediate **13**	Incomplete reaction.	Preventive action: Accurately measure the reagents. On a small scale, ensure that no isocyanate is lost on the flask walls during the addition. Gently swirl the solvent to collect any reagent left on the flask walls.
38	Purity is low: contaminated by *mono*urea intermediate **13**	Mixed fractions during purifications have been collected.	Corrective action: Either repeat the chromatographic purification or proceed to the crystallisation (see above, troubleshooting information for step 38: "(*S*)-**1** is not pure".).
C			
51	The solid is not white	The crude contains impurities from the starting material.	This does not affect the next step. No action is needed.
51	The solid is sticky and smells acetic acid-like	The solid contains trifluoroacetic acid.	Leave it under vacuum until all trifluoroacetic acid has been removed. It might be useful scrape the solid from the walls of the flask to increase the surface area.
D			
58	Stirring bar blockage	The flask was not correctly placed to guarantee good stirring.	Use a glass rod to stir the reaction mixture and unblock the stirring bar. Adjust the position of the flask to ensure uniform continuous stirring.
77	An emulsion is formed during the work-up.	Not enough EtOAc.	Add more EtOAc and some brine. If this becomes impractical due to the volumes involved, filter the mixture through a celite pad and concentrate it *in vacuo* to remove the EtOAc and EtOH. Be careful as the aqueous phase is very basic. When all the organic solvents have been evaporated, transfer the aqueous solution

			in a separatory funnel and extract it three times with 300 mL of EtOAc.
83	The solid is not white.	The aniline is contaminated by small amounts of air oxidation product.	Check the ^{1}H-NMR purity of a sample of 5 mg of **5** in 400 μL of $CDCl_3$. If the purity is >95% the aniline can be used in the subsequent step. Otherwise repeat the purification.
83	Low yield (see expected yield)	Losses during chromatographic purification.	Check the presence of product in the discarded fractions from the column by TLC (Product R_f = 0.56; *n*-pentane:EtOAc = 90:10 vol/vol visualisation: UV light λ= 254 nm and 365 nm, blue spot). Flush the column with *n*-pentane:AcOEt = 50:50. This allows the collection of unreacted starting material and an estimate of the complete mass balance.
E			
99	A black precipitate is immediately formed, and the reaction is very pale.	Catalyst deactivation, possibly because of inadequate degassing.	Check the reaction after 2 h and 5 h *via* TLC (eluent *n*-pentane: EtOAc = 90:10 vol/vol, visualisation: UV light, λ= 254 nm R_f dibromoaniline: 0.33, R_f **6**: 0.22). If no substantial difference is observed between the two TLC and unreacted starting material is still present, bubble nitrogen into the stirred solution for further 30 min. Then add 134 mg (0.5 mol%) of fresh $Pd(OAc)_2$
99	Poor conversion.	Catalyst deactivation - Was the flask evacuated and backfilled three times? - Were the solvents degassed for at least 30 min? - Were the additions done under inert atmosphere? - Was SPhos added?	If you answer yes to all the questions in the "Possible reasons" column, check the vacuum of the Schlenk line.
114	Solid is not white	Pad was too short or too much CH_2Cl_2 was used to charge the crude. The product is contaminated by a compound more polar than the target material (yellow band on silica)	Check the ^{1}H-NMR purity of a sample of 5 mg of **6** in 400 μL of $CDCl_3$. If the purity is > 90% the aniline can be used in the subsequent step. Otherwise repeat the chromatographic purification reducing the amount of CH_2Cl_2 used to charge the product or increasing the amount of silica employed. Watch out for a yellow band which is eluted before the target material.
F			
144	Yield is low	Loss of product in the mother liquor.	Repeat the crystallisation.
G			
164	The crude is not solid.	Pyridine is still contained in the crude.	Dissolve the residue in CH_2Cl_2 and wash the solution three times with an aqueous solution of HCl (1M)
165	A large excess of EtOH compared to	An insoluble residue contaminates the product	1) Use the heat-gun to warm up a round bottom flask and a glass funnel.

	the quantity reported has been added, but a small amount of solid does not get dissolved.	(possibly molecular sieves)	2) Place a paper filter on top of the hot funnel. 3) Filter the hot solution to remove the insoluble residue.
165	Yield is low (see anticipated results)	Loss of product in the mother liquor.	For maximum yield, recover the mother liquor and repeat the crystallisation. More EtOH is likely to be necessary this time
167	Purity is low: the product is contaminated by Schreiner type urea **14**	No anhydrous conditions	Preventive action: Use new bottles of anhydrous solvents/freshly distil the solvents; activate the molecular sieves immediately prior to performing the reaction.
167	Purity is low: the product is contaminated by carbamate **15**	Excess of isocyanate	Preventive action: Weigh the reagents accurately. Consider washing the container of aniline **5** with anhydrous CH_2Cl_2 to guarantee quantitative transfer.
167	Product is low: the product is contaminated by monourea **16**	Defect of isocyanate.	Preventive action: Weigh the reagents accurately.
167	Purity is low after recrystallisation (see anticipated results)	Recrystallisation was too quick (cooling was too fast)	Corrective action: Repeat the crystallisation applying a slower cooling.

ANTICIPATED RESULTS

Both catalyst (*S*)-**1** and (*S*)-**2** and all intermediates reported in this protocol have been previously isolated and characterised, [8, 9] except for isocyanate **7**. For convenience, analytical data of all compounds described in the PROCEDURE are listed in this section. Typical yields for each stage of the procedure are listed in Table 7. The small-scale yields reported in Table 7 refer to previously published results,[8-10] while the large-scale synthesis has not been previously reported. Yields are usually good for this reaction and no major changes are observed upon scale-up.

Table 7 Typical yields

Stage	Yield (1–2.5 g scale)	Yield (≥ 10 g scale)	Aspect
A	51-57%[8]	60%	White solid
B	91%[8]	80%	White solid
C	> 99%[8] (no purification required)	> 99% (no purification required)	Greyish solid
D	62–72%[8]	60%	White solid
E	81%[9]	86%	White solid
F	-	71%	White solid
G	80% (purified by chromatography over silica gel)	87% (purified by recrystallisation)	White solid

Stage A:

(*S*)-N^2-isopropyl-[1,1'-binaphthalene]-2,2'-diamine (*S*)-**3** [8]

White solid. mp 165–166 °C

[α]D = –170.6 (c 1.0 in $CHCl_3$ at 25 °C)

TLC (*n*-Pentane:EtOAc = 95:5 vol/vol, visualisation: UV light, 254 nm) R_f = 0.26

^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.90 (d, *J* = 9.0 Hz, 1H), 7.75–782 (m, 3H), 7.34 (d, *J* = 9.0 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.17–7.07 (m, 4H), 6.76 (dd, *J* = 8.2, 0.8 Hz, 1H), 6.73 (dd, *J* = 8.1, 0.8 Hz , 1H), 4.67 (s, 2H), 3.84– 3.75 (m, 1H), 3.40 (s, 1H), 1.01 (d, *J* = 6.3 Hz, 3H), 0.91 (d, *J* = 6.3 Hz, 3H)

^{13}C NMR (126 MHz, DMSO-d_6) δ = 144.8, 144.2, 134.1, 133.8, 129.5, 129.4, 128.6, 128.5, 127.7, 127.7, 126.7, 123.9, 123.4, 121.9, 121.7, 118.9, 115.9, 113.2, 109.8, 44.4, 23.6, 23.5

IR (thin layer film) ν (cm^{-1}) = 3462, 3368, 2969, 1611, 1591, 1508, 1490, 1461, 1424, 1382, 1349, 1316, 1287, 1245, 1212, 1168, 1145, 1123, 1029, 958, 909, 821, 809, 772, 747, 687, 621
HRMS ($APCI^+$) *m/z* calculated for $C_{23}H_{23}N_2^+$ $[M+H]^+$ 327.1855, found 327.1847

Stage B
(*S*)-3-(3,5-*bis*(trifluoromethyl)phenyl)-1-(2'-(3-(3,5-*bis*(trifluoromethyl)phenyl)ureido)-[1,1'-binaphthalen]-2-yl)-1-isopropylurea (*S*)-**1**[8]
White solid. mp 139–140 °C
[α]$_D$ = –49.9 (c 1.0 in $CHCl_3$ at 25 °C)
TLC (*n*-Pentane:EtOAc = 80:20 vol/vol, visualisation: UV light, 254 nm) R_f = 0.49
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.53 (d, *J* = 8.9 Hz, 1H), 8.15 (d, *J* = 8.9 Hz, 1H), 8.01 (d, *J* = 9.1 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.80 (s, 2H), 7.60 (s, 2H), 7.56–7.48 (m, 4H), 7.42–7.38 (m, 2H), 7.32–7.28 (m, 1H), 7.26–7.21 (m, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.12 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.79 (s br, 1H), 3.65 (sept, *J* = 7.0 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.67 (s br, 3H)
^{19}F NMR (470 MHz, $CDCl_3$) [overlapping signals] δ = –63.2 (s, 12F)
^{13}C NMR (126 MHz, $CDCl_3$) [overlapping signals] δ = 155.9, 151.8, 139.9, 139.8, 139.3, 135.6, 133.7, 133.2, 133.1, 132.3 (q, $J_{C–F}$ = 33.5 Hz), 131.9 (q, $J_{C–F}$ = 33.5 Hz), 131.8, 130.7, 130.3, 129.9, 128.5, 128.2, 127.9, 127.5, 127.3, 127.2, 127.1, 126.9, 125.2, 124.6, 123.1 (q, $J_{C–F}$ = 273.0 Hz), 122.9 (q, $J_{C–F}$ = 273.0 Hz), 120.2, 119.9, 118.1, 117.4, 115.8, 53.2, 20.9, 20.6.
IR (thin layer film) ν (cm^{-1}) = 3328, 3064, 2929, 1687, 1637, 1621, 1602, 1540, 1506, 1473, 1439, 1385, 1338, 1276, 1175, 1127, 1060, 1035, 948, 930, 882, 843, 820, 785, 775, 749, 725, 700, 683, 634
HRMS ($APCI^+$) *m/z* calculated for $C_{41}H_{29}O_2N_4F_{12}^+$ $[M+H]^+$ 837.2093, found 837.2077

Stage C
(*S*)-*N*-*N'*-([1,1′-binaphthalene]-2,2′-diyl)*bis*(2,2,2-trifluoroacetamide) (*S*)-**4**[8]
Greyish solid. mp not determined (crude reaction mixture)
TLC (*n*-Pentane:AcOEt = 90:10 vol/vol, visualisation: UV light, 254 nm) R_f = 0.13
^{1}H NMR (500 MHz, CDCl3) δ 8.24 – 8.12 (m, 4H), 8.04 (d, *J* = 8.2 Hz, 2H), 7.80 (br s, 2H), 7.58 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 2H), 7.40 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H)
^{19}F NMR (470 MHz, CDCl3) δ -76.34
^{13}C NMR (126 MHz, CDCl3) δ 155.7 (q, J_{C-F} = 37.6 Hz), 132.3, 131.8, 131.7, 130.9, 128.7, 128.2, 127.0, 124.7, 124.1, 121.9, 115.3 (q, J_{C-F} = 288.6 Hz)

Stage D
(*S*)-N^2-Ethyl-[1,1'-binaphthalene]-2,2'-diamine (*S*)-**5**[8]
White solid. mp 159–160 °C
[α]$_D$ = –170.4 (c 1.0 in $CHCl_3$ at 25 °C)
TLC (*n*-Pentane:EtOAc = 90:10 vol/vol, visualisation: UV light, 254 nm) R_f = 0.31
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 9.1 Hz, 1H), 7.67–7.74 (m, 3H), 7.20–7.03 (m, 6H), 6.98–6.94 (m, 1H), 6.93–6.80 (m, 1H), 6.56 (s br, 3H), 3.16 (q, *J* = 7.1 Hz, 2H), 0.95 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, CDCl3) δ = 144.4, 143.0, 134.0, 133.6, 129.6, 129.5, 128.5, 128.2, 128.1, 127.7, 126.8, 126.7, 124.0, 123.8, 122.4, 121.9, 118.3, 114.3, 112.5, 112.4, 38.7, 15.2
IR (thin layer film) ν (cm^{-1}) = 3435, 3370, 3348, 2964, 1614, 1596, 1567, 1508, 1494, 1470, 1427, 1378, 1349, 1334, 1304, 1280, 1259, 1246, 1213, 1166, 1144, 1066, 1023, 964, 928, 860, 821, 810, 773, 755, 748, 683
HRMS (ESI^+) *m/z* calculated for $C_{22}H_{21}N_2^+$ $[M+H]^+$ 313.1699, found 313.1699

Stage E
3,3'',5,5''-tetrakis(trifluoromethyl)-[1,1':3',1''-terphenyl]-5'-amine **6**[9]
White solid. mp 123 – 124 °C
TLC (*n*-Pentane: AcOEt = 90:10 vol/vol, visualisation: UV light, λ= 254 nm) R_f = 0.22
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03 (s, 4H), 7.90 (s, 2H), 7.12 (br t, *J* = 1.7 Hz, 1H), 6.96 (d, *J* = 1.6 Hz, 2H), 4.03 (br s, 2H)
^{19}F NMR (377 MHz, $CDCl_3$) δ = –62.82 (s, 12F)
^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.1, 143.2, 140.9, 132.3 (q, $J_{C–F}$ = 33.3 Hz), 127.5, 123.5 (q, $J_{C–F}$ = 273.0), 121.5, 116.5, 114.1
IR (thin layer film) ν (cm^{-1}) = 3407, 1624, 1602, 1400, 1309, 1170, 1124, 899, 842, 753, 705
HRMS (ESI^+) *m/z* calculated for $C_{22}H_{12}F_{12}N^+$ $[M+H]^+$ 518.07726, found 518.07727

Stage F

5'-isocyanato-3,3",5,5"-tetrakis(trifluoromethyl)-1,1':3',1"-terphenyl **7**
White crystalline solid. mp 145–146 °C
^{1}H NMR (400 MHz, CDCl3) δ 8.02 (br s, 4H), 7.95(br s, 2H), 7.58 (t, *J* = 1.6 Hz, 1H), 7.40 (d, *J* = 1.6 Hz, 2H)
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.81
^{13}C NMR (101 MHz, CDCl3) δ 141.7, 141.3, 135.8, 132.8 (q, $J_{C–F}$ = 33.5 Hz), 127.7 – 127.5 (m), 125.5, 124.1, 123.3 (q, $J_{C–F}$ = 273.6 Hz), 123.8, 122.41 – 122.07 (m)
IR (thin layer film) ν (cm^{-1}) = 2298, 1831, 1601, 1372, 1279, 1176, 1133, 1114, 1077, 943, 907, 872, 845, 819, 735, 705, 683
HRMS (APCI$^-$) m/z calculated for $C_{23}H_8ONF_{12}^-$ $(M-H)^-$ 542.0420, found 542.0207

Stage G
(*S*)-1-ethyl-3-(3,3",5,5"-tetrakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)-1-(2'-(3-(3,3",5,5"-tetrakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)ureido)-[1,1'-binaphthalen]-2-yl)urea (*S*)-**2**[9]
White solid. mp 228-230 °C (followed by decomposition)
$[\alpha]_D$ = –116.1 (c 0.5 in $CHCl_3$ at 25 °C)
TLC (*n*-Pentane:AcOEt = 80:20, visualisation: UV light, λ= 254 nm) R_f = 0.74
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.49 (br s, 1H), 8.15 (d, *J* = 8.9 Hz, 1H), 8.08 (d, *J* = 9.3 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.84 (s, 4H), 7.77 (s, 2H), 7.74 (s, 2H), 7.72 (s, 4H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.59 (s, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.1 Hz, 1H), 7.33 (t, *J* = 7.1 Hz, 1H), 7.30 (s, 3H), 7.21 (s, 3H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.05 (s, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.72 (s, 1H), 3.44 – 3.33 (m, 1H), 3.07 (br s, 1H), 1.05 (t, *J* = 7.0 Hz, 3H)
^{19}F NMR (470 MHz, $CDCl_3$) δ = –62.9 (s, 12F), –63.0 (s, 12F)
^{13}C NMR (126 MHz, CDCl3) [overlapping signals] δ = 156.1, 152.7, 142.2, 141.6, 140.1, 139.9, 139.8, 139.7, 138.6, 135.3, 133.9, 133.4, 133.3, 132.3 (q, $J_{C–F}$ = 33.0 Hz), 132.0 (q, $J_{C–F}$ = 33.0 Hz), 131.9, 130.8, 130.3, 128.7, 128.5, 128.1, 127.8, 127.4, 127.1, 127.0, 126.7, 125.3, 123.2 (q, $J_{C–F}$ = 273.0 Hz), 123.1 (q, $J_{C–F}$ = 272.9 Hz), 121.6 (m), 121.5 (m), 121.3, 120.7, 120.3, 120.0 119.9, 118.2, 44.4, 13.6
IR (thin layer film) ν (cm^{-1}) = 3323, 2929, 1600, 1756, 1507, 1469, 1367, 1279, 1179, 1132, 901, 845, 706, 683
HRMS (APCI$^+$) *m/z* calculated for $C_{68}H_{39}O_2N_4F_{24}$ $[M+H]^+$ 1399.2684, found 1399.2690

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AUTHORS CONTRIBUTIONS

All authors have contributed to the design and development of these catalysts. G.P and F.I. developed the first synthesis of this class of catalysts and A.C.V has modified the process for scale up. V.G. conceived and directed the project. All authors contributed to drafting and commenting on the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

DATA AVAILABILITY

The authors declare that additional data related to this protocol is available in the key primary references (DOI: 10.1126/science.aar7941; DOI: 10.1021/jacs.8b12568; DOI 10.1021/jacs.0c05131). Analytical data of all compounds described in the PROCEDURE are included directly within this manuscript.

FIGURES' CAPTIONS:

Figure 1: Hydrogen bonding for electrophile and nucleophile activation. (A) Electrophile activation *via* LUMO lowering and anion binding catalysis. (B) Nucleophile activation *via* hydrogen bonding phase-transfer catalysis (HB-PTC). (C) Asymmetric synthesis of β-fluorosulfides, β- and γ-fluoroamines under HB-PTC. Nu^- = Nucleophile; E^+ = Electrophile; LG = Leaving group (Cl, Br, I), Bzh = Benzhydryl.

Figure 2: Reaction scheme for the synthesis of (*S*)-**1**. The reductive amination was performed on 10 g of (*S*)-BINAM (Stage A) and the urea formation step on 6.8 g of (*S*)-**3** (Stage B). In parenthesis the yield of the small-scale reactions (starting from 1.5 g of (*S*)-BINAM).

Figure 3: Reaction scheme for the synthesis of (*S*)-**2**. The protection-alkylation-deprotection sequence was performed on 40 g of (*S*)-BINAM, affording 26.3 g of (*S*)-5 (Stages C–D). The Suzuki-coupling (Stage E) between 3,5-dibromoaniline (30 g) and 3,5-*bis*(trifluoromethyl)phenyl boronic acid (108 g) yielded 53 g of aniline **6**, which was converted into the corresponding isocyanate **7** (40 g) in Stage F. The urea formation step (Stage G) was conducted on 13 g of (*S*)-**5** using 45.22 g of isocyanate **7**, and yielded 52 g of (*S*)-**2**.

Figure 4: Equipment setup. (A) Solvent degassing. (B) Use of Schlenk line to dry the glassware. (C) Cannulation of dry solvents/solutions: connection of the solution to be transferred to the Schlenk line (I and II); cannulation (III).

Figure 5: HPLC traces of the catalysts. (A) HPLC traces of (*S*)-**1** (≥99% purity). (B) HPLC traces of (*S*)-**2** (≥99% purity).

Figure 6: Step 9, addition of $NaBH_4$ for the second step of the reductive amination to obtain (*S*)-**3**.

Figure 7: Structures of possible by-products obtained in the second step of the synthesis of catalyst (*S*)-**1** (urea formation, Stage B).

Figure 8: Set-up for the Suzuki-Miyaura cross-coupling between 3,5-dibromoaniline and 3,5-*bis*(trifluoromethyl)phenyl)boronic acid (Stage E).

Figure 9: Suzuki-Miyaura cross-coupling of 3,5-dibromoaniline and 3,5-*bis(*trifluoromethyl)phenyl)boronic acid. (A) Beginning and (B) end of the Suzuki-Miyaura cross coupling (test reaction to evaluate optimal conditions).

Figure 10: Set-up for the synthesis of isocyanate **7** (stage F). (A) Overview of the reaction set-up. (B) Details of the connections. (C) Detail of the $NaHCO_3$ trap. (D) Overview of the set up for the work-up.

Figure 11: Comparison of the ^{1}H NMR spectra of aniline **6** (top) and isocyanate **7** (bottom).

Figure 12: Structures of possible by-products obtained in the final step of the synthesis of catalyst (*S*)-**2** (urea formation, Stage G).

[1] *Hydrogen Bonding in Organic Synthesis*; Pihko, P. M., Ed.; (Wiley-VCH: Weinheim, Germany, 2009).

[2] Taylor, M. S.; Jacobsen, E. N. Asymmetric catalysis by chiral hydrogen-bond donors. *Angew. Chem. Int. Ed.* **45**, 1520–1543 (2006).

[3] Doyle, A. G.; Jacobsen, E. N. Small-molecule H-bond donors in asymmetric catalysis. *Chem. Rev.* **107**, 5713–5743 (2007).

[4] Brak, K.; Jacobsen, E. N. Asymmetric Ion-Pairing Catalysis. *Angew. Chem. Int. Ed.*, **52**, 534–561 (2013).

[5] Ford, D. D.; Lehnherr, D.; Kennedy, C. R.; Jacobsen, E. N. Anion-abstraction catalysis: The cooperative mechanism of α-chloroether activation by dual hydrogen-bond donors. *ACS Catal.* **6**, 4616–4620 (2016)

[6] Pfeifer, L. *et al.* Hydrogen-Bonded Homolopetic Fluoride-Diarylurea Complexes: Structure, Reactivity and Coordinating *J. Am. Chem. Soc*. **138**, 13314–13325 (2016).

[7] Zhou, Y.; Zhang, J. F.; Yoon, J. Fluorescence and colorimetric chemosensors for fluoride-ion detection. *Chem. Rev.*, **114**, 5511–5571 (2014).

[8] Pupo, G. *et al.* Asymmetric nucleophilic fluorination under hydrogen bonding phase-transfer catalysis. *Science*, **360**, 368–642 (2018).

[9] Pupo, G *et al.* Hydrogen bonding phase-transfer catalysis with potassium fluoride: enantioselective synthesis of β-fluoroamines. *J. Am. Chem. Soc.*, **141**, 2878–2883 (2019).

[10] Roagna, G. *et al.* Hydrogen bonding phase-transfer catalysis with ionic reactants: enantioselective synthesis of γ-fluoroamines. *J. Am. Chem. Soc.* **142**, 14045–14051 (2020).

[11] Harsanyi, A.; Sandford, G. Organofluorine chemistry: applications, sources and sustainability. *Green Chem.* **17**, 2081–2086 (2015).

[12] Ibba F. *et al.* Impact of multiple hydrogen bonds with fluoride on catalysis: insight from NMR spectroscopy. *J. Am. Chem. Soc*. **142**, 19731–19744 (2020).

[13] Kim, K. H.; Lee, D.-W.; Lee, Y.-S.; Ko, D.-H.; Ha, D.-C. Enantioselective oxidative coupling of methyl-3-hydroxy-2-naphthoate using mono-*N*-alkylatedoctahydrobinaphthyl-2,20-diamine ligand. *Tetrahedron*, **60**, 9037–9042 (2004).

[14] Cotarca, L.; Geller, T.; Répási, J. Bis(trichloromethyl)carbonate (BTC, triphosgene): a safer alternative to phosgene? *Org. Process Res. Dev.* **21**, 1439–1436 (2017).