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(54) Title: SYNTHESIS OF A BIARYL SYNTHETIC INTERMEDIATE

(57) Abstract: An efficient process for manufacturing a biphenyl chloride chemical intermediate is disclosed. The biphenyl chloride is a synthetic intermediate for manufacturing a chemical compound which is a CETP inhibitor. The process comprises a CH activation step in which a phenyl bromide is coupled to the phenyl ring of a phenyl oxazoline to make a biphenyl structure.

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TITLE OF THE INVENTION
SYNTHESIS OF A BIARYL SYNTHETIC INTERMEDIATE

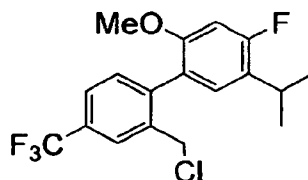
FIELD OF THE INVENTION

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This invention relates to a chemical process for making a pharmaceutically active compound, and specifically to a process for making a biaryl intermediate in the process for making the compound.

10 SUMMARY OF THE INVENTION

Biaryl chloride **10** is one of two penultimate intermediates in a process for making a pharmaceutically active compound. Biaryl chloride **10** is prepared in a seven step sequence starting from available starting materials. One of the intermediates in the 7-step sequence is prepared in one step, so that the overall preparation of biaryl chloride **10** requires 8 process steps starting from commercially available difluorobromobenzene **1** and trifluoromethylbenzonitrile **6**.



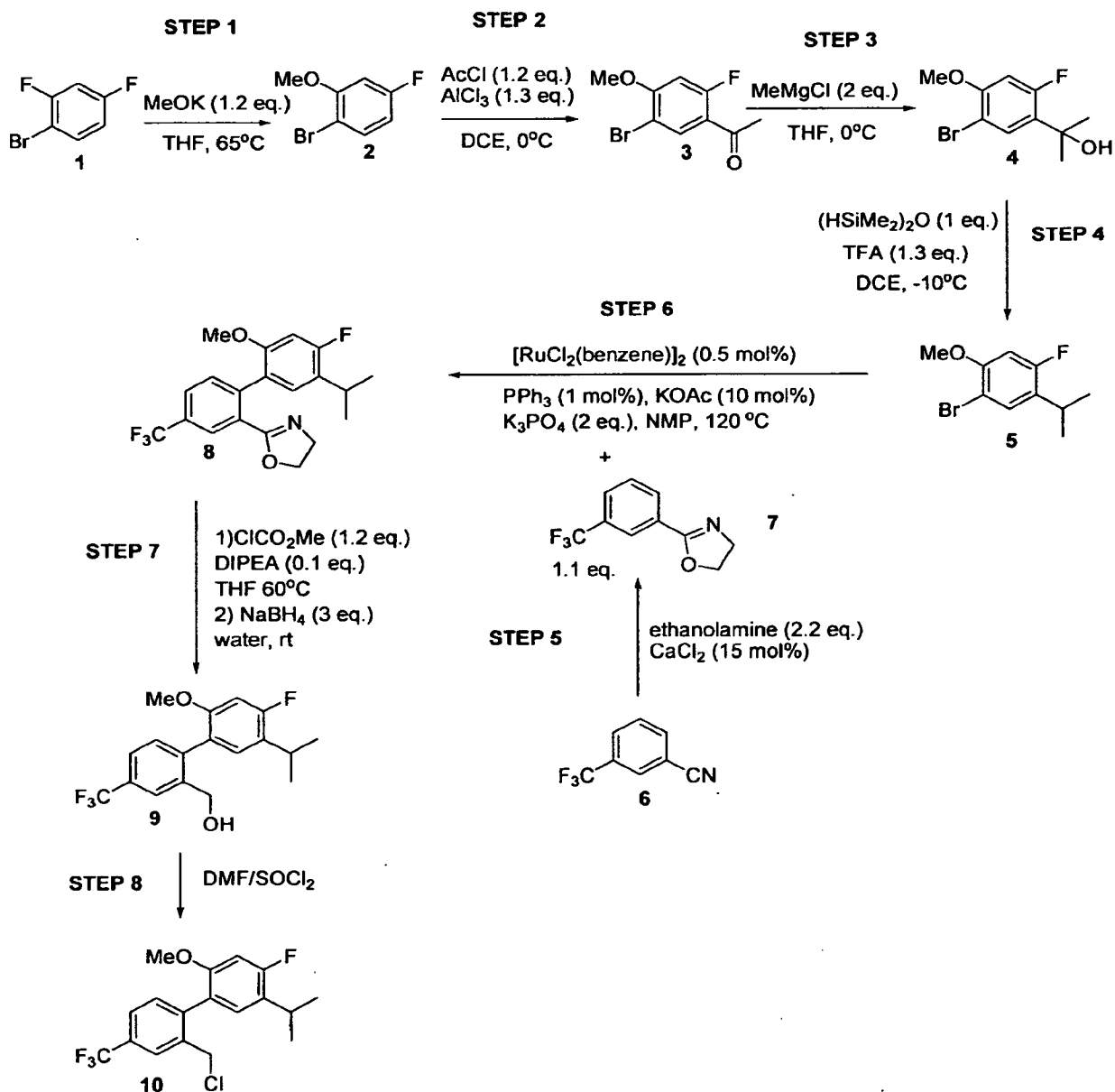
Biaryl chloride **10**

DETAILED DESCRIPTION OF THE INVENTION

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The process for making compound **10** is summarized in Scheme 1 below, and is described in more detail in the subsequent Example. Modifications of this process to obtain similar products, and the products of these process will be readily apparent to one of skill in the art. For example, the process can be modified to produce biaryl halides other than chloride, such as bromide. Similarly, the trifluoromethyl and isopropyl groups can be replaced with other alkyl and fluoroalkyl groups in the synthetic schemes. The methoxyl group can also be replaced with other alkoxy groups in this process by use of a different alkoxy compound in step 1.

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Scheme 1: Synthesis of Biaryl Chloride 10

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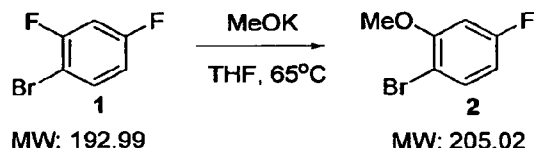
Example

The Example below is provided to illustrate the invention, and should not be construed as limiting the invention. The scope of the invention is defined by the Claims.

The product of this invention is a useful synthetic intermediate for making certain CETP inhibitors, such as those described in PCT patent applications WO2007/005572 (published after the priority date of this application), WO2006/014413, and WO2006/014357.

5 **STEP 1: Methoxylation**

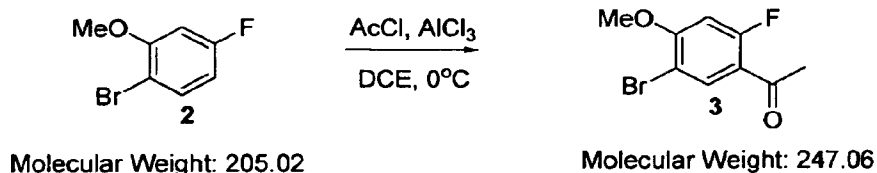
Methoxylation of bromodifluorobenzene **1** is highly regioselective when THF is the solvent. Using the conditions described below, the reaction typically yields an 18/1 ratio of product **2** along with 0.7A% (Assay%) of a dimethoxylated impurity. Other combinations of
10 solvent and temperature and other methoxide salts may also be suitable in this sequence.



A 50L round bottom flask (RBF) equipped with an overhead stirrer, a nitrogen inlet, a temperature probe and a condenser was charged with 1-bromo-2,4-difluorobenzene **1**
15 (3780 g) followed by THF (14 L) and KOMe (95 wt%, 1587.6g), and then rinsed with 1.1 L of THF. The reaction mixture was heated to 65 – 68 °C over 30 minutes and stirred at that temperature for 4 hr. A second portion of KOMe was then added (144.4 g), and the reaction was stirred for an additional 2 hr. The reaction mixture was cooled to 15 °C and was transferred into a 50 L extractor containing 13.1 L of water. The reaction flask was rinsed with water (2 L) and
20 methyl t-butyl ether (MTBE) (15 L). The layers were cut and the organic layer was washed twice with water (2 x 15 L). The organic layer was concentrated under vacuum (10-20 mmHg, 30 °C) followed by azeotropic removal of water with THF (8 L) (10-20 mmHg, 30 °C). The crude residue was distilled under reduced pressure (90 °C, 3 torr) to yield anisole **2** as a colorless oil.

25 ¹H NMR (500 MHz, acetone-*d*₆) δ 7.58 (dd, 1H, *J*₁ = 6.2 Hz, *J*₂ = 8.8 Hz), 6.95 (dd, 1H, *J*₁ = 2.8 Hz, *J*₂ = 10.9 Hz), 6.72 (td, 1H, *J*₁ = 2.8 Hz, *J*₂ = 8.4 Hz), 3.94 (s, 3H).

STEP 2: Acylation



A 50L round bottom flask (RBF) equipped with an overhead stirrer, a nitrogen inlet and a temperature probe was charged with anisole **2** (1748.4g) followed by 1,2-dichloroethane (DCE) (19 L). The solution was then cooled to 0 °C and AlCl₃ (3216.9 g) was added in increments such that the internal temperature did not rise above 6 °C. Acetyl chloride (1748.4 g) was then added dropwise over the course of 40 minutes with cooling to maintain the internal temperature below 10 °C. The reaction mixture was aged for 0.5 hour at 0 °C. At this time HPLC showed no more starting material.

The batch was transferred into a 100 L extractor containing H₂O (25 L) and EtOAc (40 L) at 0 °C at a rate such that the internal temperature remained below 20 °C. The batch was stirred for 10 min and the *bottom* aqueous layer was cut away. The organic layer was washed with 1N HCl (20 L) and the layers were cut (*note: the organic layer is at the bottom at this stage*). The organic layer was then washed with saturated NaHCO₃ (20 L) and the layers were cut. The organic layer was finally washed with half saturated brine (5 L brine + 5 L H₂O), and the *top* aqueous layer was cut away.

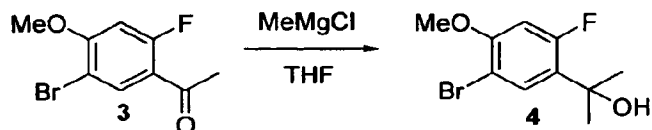
The organic layer was then transferred through an inline filter (Polycap™ 75 HD, Whatman Inc.) into a 50 L RBF and concentrated under vacuum (30 mmHg, 30 °C) to a final volume of ~11L, and the solvent was switched to hexanes (74 L) at this volume. The resulting suspension was stirred ~30 min at room temperature and 45 min at 0 °C.

The slurry was filtered through a filter pot, and the solid obtained was washed with cold hexanes (0 °C, 10 L). The solid was dried overnight under vacuum and a nitrogen sweep to give acetophenone **3** as white needles.

¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 12.5 Hz, 1H), 3.96 (s, 3H), 2.60 (d, *J* = 5.2 Hz, 3H); HRMS ESI (*m/z*): [M+H]⁺ calcd for C₉H₉O₂FBr, 246.9762; found 246.9764.

STEP 3: Grignard addition

Carbinol 4 is obtained by addition of methylmagnesium chloride (bromide and iodide can also be used). The reaction also proceeds with trimethylaluminum (AlMe_3) in DCE/heptane.



Molecular Weight: 247.06

Molecular Weight: 263.1

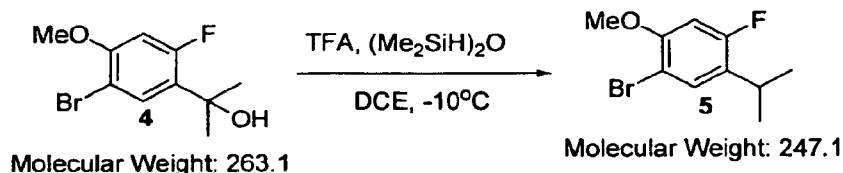
A 100L RBF equipped with an overhead stirrer, a nitrogen inlet and a temperature probe was charged with MeMgCl (3.13M in THF, 10.5 L) and cooled to -10°C . Then, a solution of acetophenone 3 (4112.7 g) in THF (23.5 L) was added over the course of 3 hours so that the internal temperature did not rise above 4°C . The reaction mixture was aged for 0.5 hour at 0°C . At this time HPLC showed no more starting material.

2N HCl (24 L) was added *dropwise* via a dropping funnel into the reaction mixture (batch was cooled to -10°C) so that the internal temperature would stay $<20^\circ\text{C}$ (*caution: very exothermic*). The mixture was then transferred into a 100 L extractor containing EtOAc (30 L). The batch was stirred ~ 10 min and the bottom aqueous layer was cut away. The organic layer was then successively washed with brine (10 L) and a solution of half saturated brine (5 L brine + 5 L H_2O). The organic layer was transferred into a 100 L RBF and concentrated under vacuum (10-30 mmHg, 30°C) to a final volume of ~ 17 L, then solvent switched to hexanes (75 L) at this volume.

The resulting slurry was cooled to 0°C and filtered through a filter pot. The solid obtained was washed with cold hexanes (4 L) and dried overnight under vacuum with nitrogen sweep to give carbinol 4 as a white solid.

^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, $J = 8.7$ Hz, 1H), 6.64 (d, $J = 13.2$ Hz, 1H), 3.89 (s, 3H), 1.99 (s, 1H), 1.63 (s, 6H); HRMS ESI (m/z): $[\text{M}-\text{H}_2\text{O}]^+$ calcd for $\text{C}_{10}\text{H}_{11}\text{OFBr}$, 244.9968; found 244.9972.

STEP 4: Silane reduction

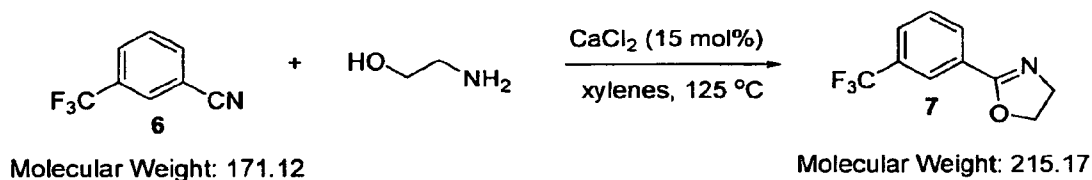


A 50L RBF equipped with an overhead stirrer, a nitrogen inlet and a temperature probe was charged with tetramethyl disiloxane (2.7 L, 15.50 mole) and DCE (10 L), cooled to -20°C , and then TFA (1.5 L, 20.19 mole) was added. Then, a solution of carbinol 4 (4074 g, 15.48 mole) in DCE (14 L) was added dropwise over the course of 2-3 hours so that the internal temperature stayed below -5°C . Temperatures above 5°C caused increases in impurities. The reaction mixture was aged for 15 min. at -10°C . At this time HPLC showed no more starting material.

The batch was transferred into a 100 L extractor containing 16.8 Kg of saturated NaHCO_3 , stirred for 5 min, and the layers were cut. The *bottom* organic layer was washed twice with saturated NaHCO_3 (12.1 Kg and 8.8 Kg) and finally with brine (17 Kg). The *bottom* organic layer was then transferred to a 50 L RBF and concentrated under vacuum (5 mmHg, 40°C). The residue was then distilled at $90\text{--}100^{\circ}\text{C}$ under full vacuum (1 torr) to give bromoanisole 5 as a colorless liquid which is contaminated with 5-10% of residual siloxanes. The siloxanes are carried to the next step.

^1H NMR (400 MHz, CDCl_3) δ 7.40 (d, $J = 7.9$ Hz, 1H), 6.63 (d, $J = 11.8$ Hz, 1H), 3.89 (s, 3H), 3.17 (sept, $J = 6.9$ Hz, 1H), 1.25 (d, $J = 6.9$ Hz, 6H).

STEP 5: Oxazoline formation



A 20L RBF equipped with an overhead stirrer, a nitrogen inlet, a temperature probe and a condenser was charged with the benzonitrile 6 (3930 g), followed by ethanolamine (3041 mL), CaCl_2 (382.4 g) and xylenes (1965 mL). The reaction mixture was heated to 125°C over 45 min and stirred at this temperature for 17 hr. Then the reaction mixture was allowed to cool to about 80°C , and toluene (1965 mL) was added before cooling the reaction mixture to room temperature. The crude reaction mixture was then transferred into a 100 L extractor containing 39 L of 0.1 M KH_2PO_4 . The reaction flask was rinsed with MTBE (8 L) and water (4 L).

Heptane (28 L) was added to the extractor and the layers were cut. The aqueous layer was back extracted with a mixture of MTBE (10 L) and heptane (10 L), and then the combined organic layers were washed twice with water (2 x 20 L). The organic was concentrated under vacuum (35 °C to 70 °C, 30-5 mmHg). The crude residue was distilled under reduced pressure (110 °C at 1 - 3 torr) to yield oxazoline 7 as a colorless oil.

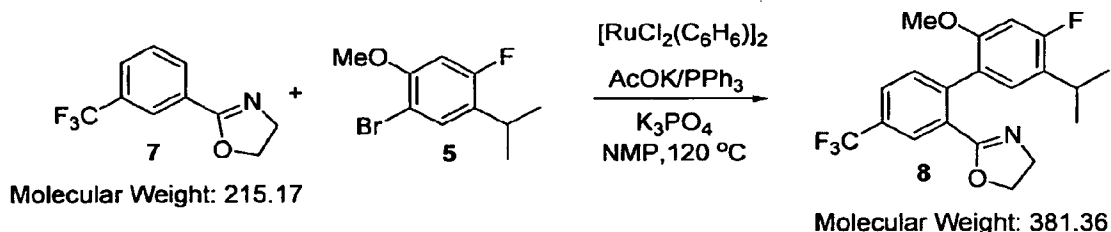
¹H NMR (500 MHz, acetone-*d*₆) δ 8.21 (bs, 2H), 7.90 (d, 1H, *J* = 7.8 Hz), 7.75 (t, 1H, *J* = 7.9 Hz), 4.51 (t, 2H, *J* = 9.6 Hz), 4.06 (t, 2H, *J* = 9.5 Hz).

STEP 6 : Ru CH-activation coupling

Ruthenium-catalyzed cross coupling reactions of aryl oxazolines with aryl bomides were first described in a publication by Shuichi Oi et al, J. Org. Chem., **2005**, *70*, 3113-3119.

The ruthenium-catalyzed CH-activation cross-coupling reaction described below gives a good yield of product using NMP (N-methyl pyrrolidinone) as solvent. It has been observed that as the amount of catalyst is reduced to less than 1 mole%, the reaction proceeds reproducibly only with NMP that contains greater than 0.5 volume% of gamma-butyrolactone impurity.

The use of 10 mol% of potassium acetate (AcOK) allows Ru catalyst loading to be reduced to 0.5 mol%, regardless of the amount of gamma-butyrolactone in the NMP, giving complete conversion in a reproducible fashion. The reaction appears to go to completion at 0.25 mol% of Ru dimer. Either "RuCl₂ benzene" or "RuCl₂ cymene" dimer can be used. Other Ru (II) complexes may also be suitable. All solvents and reagents have to be thoroughly degassed with nitrogen prior to catalyst addition.



A 50L RBF equipped with an overhead stirrer, a nitrogen inlet and a temperature probe was charged with oxazoline 7 (2755.5 g) followed by anisole 5 (3065.7 g) and NMP (10 L pre-degassed by bubbling nitrogen for 60 min). The reaction after mixing was degassed by bubbling nitrogen for an additional 30 minutes. Then K₃PO₄ (4842.1 g) and KOAc (112.5 g) were

charged, followed by 2 L of degassed NMP (rinse). This suspension was degassed for an additional 60 minutes. The reaction mixture was then heated to 130 °C.

A 5L RBF was charged with degassed NMP (2 L) and triphenylphosphine (29.92 g), and then was degassed by bubbling nitrogen for 30 minutes at rt. The ruthenium complex dimer (28.5 g) was then added, and this solution was degassed for an additional 30 minutes at rt.

When the 50L RBF reaction mixture reached 130 °C, half of the ruthenium solution (1 L) was transferred. The reaction temperature was lowered to 110 °C, and the reaction was stirred at this temperature for 2 hr before the addition of the second half of the ruthenium catalyst. The reaction mixture was then stirred at this temperature for 7 hr, and was then cooled to room temperature.

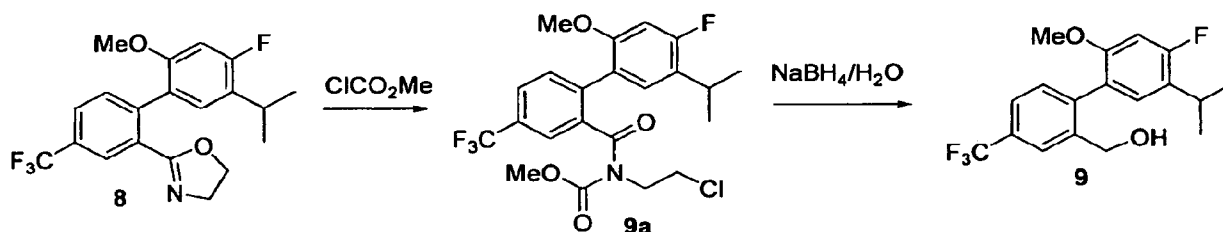
The product was precipitated by adding water (17 L) slowly over 2.5 hr while maintaining the temperature below 25 °C. The resulting slurry was filtered through a filter pot, and the reaction flask and the resulting solid were rinsed with NMP:water (1:1.5, 15 L), followed by a water rinse (40 L). The solid was then dried under vacuum with a flow of nitrogen. Biaryl oxazoline **8** was obtained as a dark brown solid.

¹H NMR (500 MHz, acetone-*d*₆) δ 8.13 (d, 1H, *J* = 1.4 Hz), 7.87 (dd, 1H, *J*₁ = 1.5 Hz, *J*₂ = 8.1 Hz), 7.61 (d, 1H, *J* = 8.1 Hz), 7.18 (d, 1H, *J* = 8.7 Hz), 6.81 (d, 1H, *J* = 12.5 Hz), 4.22 (t, 2H, *J* = 9.6 Hz), 3.88 (t, 2H, *J* = 9.5 Hz), 3.77 (s, 3H), 3.22 (sept, 1H, *J* = 6.9 Hz), 1.27 (d, 6H, *J* = 6.9 Hz).

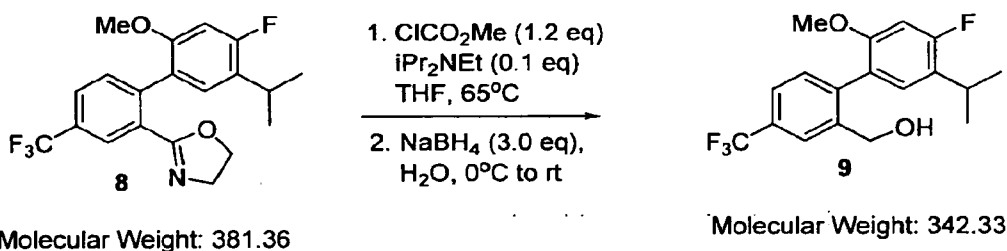
STEP 7 : Oxazoline activation/reduction

Oxazoline activation/reduction is a 2-step one-pot process. Activation of biaryl oxazoline **8** with methyl chloroformate leads to the activated intermediate **9a**, which is subsequently reduced to alcohol **9** by using sodium borohydride in water (Scheme 2). The reduction can also be done with lithium borohydride with MeOH as solvent, and also with other borohydride reducing agents.

Scheme 2: Activation/reduction path



For the activation step, the amount of residual KF from earlier steps has to be below 500ppm before addition of methyl chloroformate.



A 100L RBF equipped with an overhead stirrer, a nitrogen inlet, a temperature probe and a condenser was charged with biaryl oxazoline **8** (4163 g) and THF (11.6 L). Then, diisopropyl ethyl amine (DIPEA, 180 mL) followed by methyl chloroformate (940 mL) were added at rt, and the resulting mixture was heated to 62°C for 45 minutes. HPLC showed complete conversion of **8** to the activated intermediate. The reaction mixture was then cooled to 0°C , and NaBH_4 (1152 g) was added in one portion followed by slow addition of water (3.9 L) over 55 minutes while maintaining the internal temperature below 22°C . The reaction mixture was aged at rt for 17h. HPLC showed complete conversion to biaryl alcohol **9**.

The reaction mixture was cooled to 0°C , and 3.1N HCl (9.8 L) was added dropwise over 1h while maintaining the temperature between 0 and 4°C . The reaction mixture was warmed to rt, and MeOH (7.8 L) was added. The mixture was batch concentrated under reduced pressure (20 mmHg, 25°C) to a volume of 24 L. Then MeOH (15.5 L) was added, and the batch was seeded with crystalline product from earlier batches (97 g). The product crystallizes spontaneously, if seed crystals are not available. The slurry was aged at rt for 1h, and water (20 L) was added slowly over 1h.

The slurry was filtered through a filter pot, and the cake was rinsed with MeOH/water (1:1, 8 L) followed by water (16 L). The cake was dried under vacuum at rt with nitrogen sweep over 2 days to give crude biaryl alcohol.

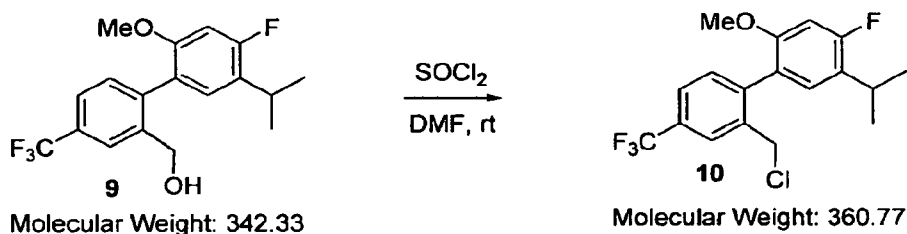
5 DARCO treatment

A 100L RBF equipped with an overhead stirrer, a nitrogen inlet and a temperature probe was charged with crude 92 wt% biaryl alcohol **9** (3637.23g), MTBE (23.4 L), heptane (10 L) and finally DARCO KB-G (1673 g). The slurry was stirred at rt for 2h. DARCO was then removed by filtration on a pad of solka-floc and rinsed with MTBE/heptane (70:30, 39 L). The combined
10 filtrates were batch concentrated into a 100L RBF under reduced pressure (20 mmHg, 40°C) to a final volume of 30L, and solvent was switched to heptane (66 L).

The resulting slurry was aged overnight at rt and was then cooled to -15°C for 2h. The slurry was filtered through a filter pot and the cake was washed with cold heptane (-15°C, 20L). The cake was dried under vacuum with nitrogen overnight at rt to give pure biaryl alcohol **9** as a white powder with a residual Ru content of 25 ppm.

¹H NMR (500 MHz, acetone-*d*₆) δ 7.96 (s, 1H), 7.60 (d, 1H, *J* = 7.0 Hz), 7.33 (d, 1H, *J* = 7.9 Hz), 7.10 (d, 1H, *J* = 8.7 Hz), 6.87 (d, 1H, *J* = 12.5 Hz), 4.47 (bs, 2H), 4.31 (t, 1H, *J* = 5.6 Hz), 3.76 (s, 3H), 3.19 (sept, 1H, *J* = 6.9 Hz), 1.24 (d, 6H, *J* = 6.9 Hz).

STEP 8: chlorination



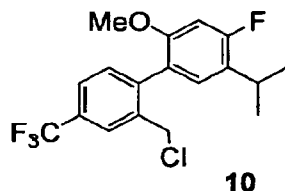
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Thionyl chloride (940ml) was added to a solution of biaryl compound **9** (3.4 kg) in DMF (17L) which was maintained at 10°C. The mixture was warmed to room temperature. The mixture was aged until >99.8% conversion was measured by HPLC. Water (3.4 L) was then added. Seed crystals (1wt%) were added, and the mixture was aged for 30 min more before slowly adding 5.1 L of additional water over ~1hr. The solid was filtered and washed first with 20 L 1:1 DMF:water and then 3x 20L water. The solid product **10** was dried at 20°C until <0.1wt% water remained.

¹H NMR (400 MHz, CDCl₃) δ 7.86 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 6.70 (d, *J* = 12 Hz, 1H), 4.52 (d, *J* = 11.0 Hz, 1H), 4.40 (d, *J* = 11.0 Hz, 1H), 3.76 (s, 3H), 3.25 (sept, *J* = 6.9 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 6H).

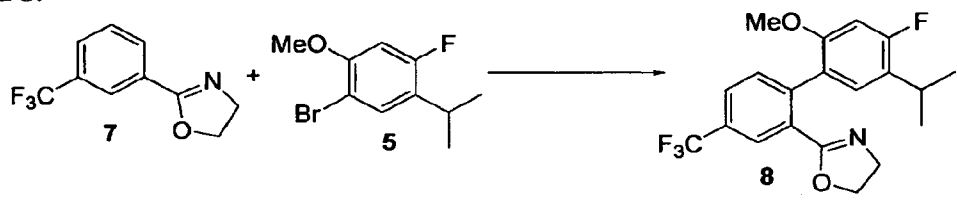
WHAT IS CLAIMED IS:

1. A method of synthesizing compound 10:



comprising the steps of:

- (1) coupling compounds 5 and 7 using a transition metal catalyst to yield compound 8:



and (2) subsequently converting compound 8 to compound 10.

2. A method of synthesizing compound 8, comprising the step of coupling compounds 5 and 7 using a transition metal catalyst.

3. The method of Claim 1 or Claim 2, wherein said transition metal catalyst comprises Ru.

4. The method of Claim 3, wherein said transition metal catalyst comprises a soluble Ru(II) catalyst.

5. The method of Claim 3, wherein said transition metal catalyst is selected from $[\text{RuCl}_2(\text{benzene})]_2$ and $[\text{RuCl}_2(\text{cymene})]_2$.