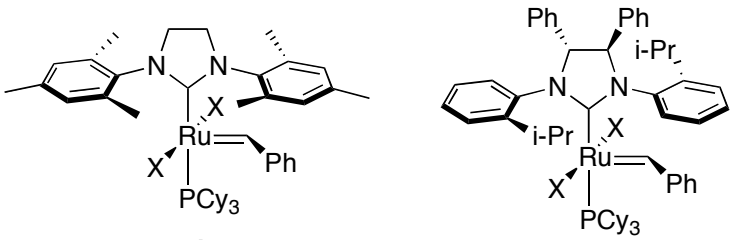
Chapter 2

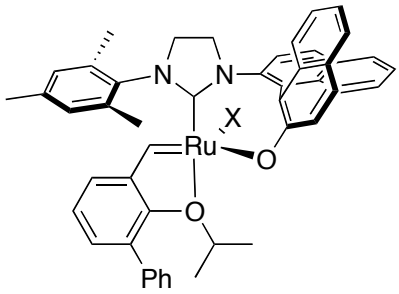
Design and Synthesis of Chiral Ruthenium Olefin Metathesis Catalysts

Since the initial report of asymmetric olefin metathesis for small molecule synthesis,[1] a variety of chiral, ruthenium- and molybdenum-based alkylidene catalysts have been developed.[2-3] The molybdenum catalysts have been shown to give excellent enantioselectivities in asymmetric ring-closing metathesis (ARCM), asymmetric ring-opening ring-closing metathesis (ARORCM), and asymmetric ring-opening cross metathesis (AROCM).[4-5] Our interest in ruthenium-based olefin metathesis catalysts stems from their increased functional-group tolerance compared to the molybdenum systems, as well as their stability to air and moisture.[5b] As I began my work in this field, our laboratory had developed a class of chiral ruthenium catalysts, those containing monodentate N-heterocyclic carbenes (NHCs) with chirality in the backbone of the carbene (**2a** and **2b**).[3c] Shortly thereafter, another class was developed by Hoveyda et al., those containing chiral, bidentate NHC/binaphthyl ligands (**3a** and **3b**).[3a,b]



1a,b

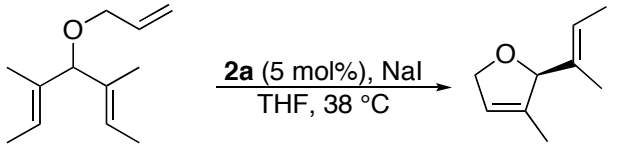
2a,b



3a,b

Figure 2.1. Chiral olefin metathesis catalysts and parent catalysts. **a**: X = Cl, **b**: X = I.

While catalysts of the latter type gave good enantioselectivities and yields for AROCM reaction,[6] they exhibited reduced reactivity and selectivity toward ARCM relative to those of the former class. The ruthenium catalysts containing monodentate, chiral NHCs (**2a** and **2b**) had the same air and moisture stability of the parent catalyst **1a**, as well as a similar level of reactivity.[7] Additionally, we had achieved a single example of 90% enantiomeric excess (*ee*) in RCM using **2b** (Figure 2.2).[3c] Catalyst **2b** was generated *in situ* from **2a** by treatment with 20 equivalents of NaI, which resulted in halide exchange at the metal center.

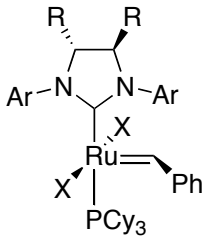


4 **5**

90% ee, 82% yield

Figure 2.2. First highly enantioselective ruthenium-catalyzed olefin metathesis.

In the report on the discovery of this singular example of highly enantioselective ruthenium-catalyzed olefin metathesis, a number of catalyst modifications were examined (Figure 2.3). These changes were essential to the successful ARCM of **4**.



2a,b	R = Ph,	Ar = *o*-isopropylphenyl
6a,b	R = Ph,	Ar = *o*-methylphenyl
7a,b	R = Ph,	Ar = mesityl
8a,b	R = -$(CH_2)_4$-,	Ar = *o*-isopropylphenyl
9a,b	R = -$(CH_2)_4$-,	Ar = *o*-methylphenyl
10a,b	R = -$(CH_2)_4$-,	Ar = mesityl

Figure 2.3. Catalysts used for the first reported Ru-catalyzed ARCM. **a**: X = Cl, **b**: X = I.

Catalysts **8a,b–10a,b** all gave <9% *ee* for the ARCM of **4**, while **2a** and **6a** gave 23% *ee* and **7a** gave only 13% *ee*. Catalyst **2b** proved to be slightly better (90% *ee*) than catalyst **6b** (85% *ee*) for the ARCM of **4**.

It is believed that a gearing effect is behind the trends in catalyst selectivity for **2a,b-10a,b**. A crystal structure was obtained for a related compound (**11**) (Figure 2.4).

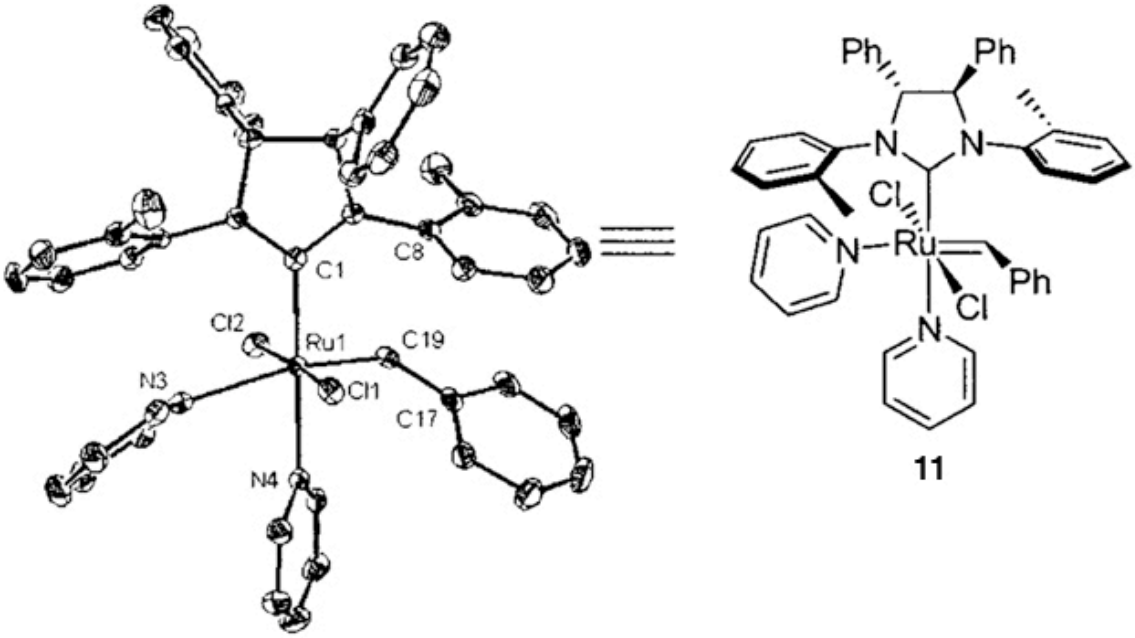


Figure 2.4. X-ray structure illustrating a gearing interaction.

The gearing effect is the interaction between the phenyl groups on the backbone of the N-heterocyclic carbene (NHC) and the differentially substituted N-bound aryl rings on the NHC. This results in the ortho groups on the aryl rings lying on opposite sides of the catalyst to the phenyl rings in the backbone, thus creating a chiral C_2-symmetric environment around the metal center. The gearing effect is limited for catalysts **8a,b–10a,b** because the chiral backbone is the relatively flat cyclohexyl ring. On the other hand, catalysts **2a**–**7a** have a pronounced gearing effect due to the diphenyl backbone. The gearing effect should also increase as the steric difference between the two ortho

positions on each aryl rings becomes more pronounced. Thus, *ortho*-isopropylphenyl rings result in better gearing and hence better *ee* than *ortho*-methylphenyl rings and both are more effective than mesityl rings. As we prepared to expand the scope of ARCM and to attempt other asymmetric transformations, such as AROCM and asymmetric cross metathesis (ACM), we desired a larger series of catalysts to test for these reactions. Since the gearing provided by the diphenyl backbone seemed essential, we decided to examine a variety of substitution patterns on the N-bound aryl rings.

Initial efforts focused on introducing a *tert*-butyl group at the ortho position of the N-bound aryl rings. The successful syntheses of **2a,b–10a,b** had all followed the same synthetic route (Figure 2.5). Palladium catalyzed couplings of enantiopure diamines and aryl bromides afforded enantiopure secondary diamines, which were then treated with NH_4BF_4 and $HC(OEt)_3$ to give the enantiopure NHC salts. Treatment of ruthenium precursor **12** with the chiral NHC salts and $KOC(CF_3)_2CH_3$ afforded the desired catalysts in high purity after column chromatography.

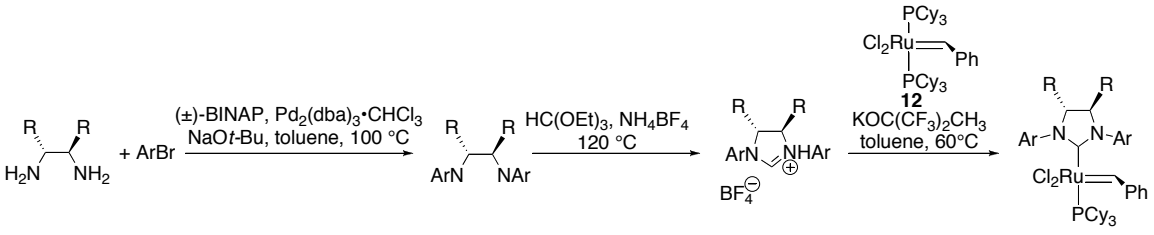


Figure 2.5. General synthetic strategy for catalyst preparation.

Based on this precedent, the first efforts towards catalysts with bulkier groups at both the ortho positions focused on the palladium catalyzed coupling of (1*R,* 2*R*)-(+)-diphenylethylenediamine with 2,5-di-*tert*-butyl-phenylbromide or 2-*tert*-butyl-phenylbromide. However, under a variety of conditions, no coupling was observed. Therefore, other synthetic routes were considered. Three variations of a condensation

approach were tried (Figure 2.6, routes 1-3), as was one reductive coupling route (Figure 2.6, route 4).[8]

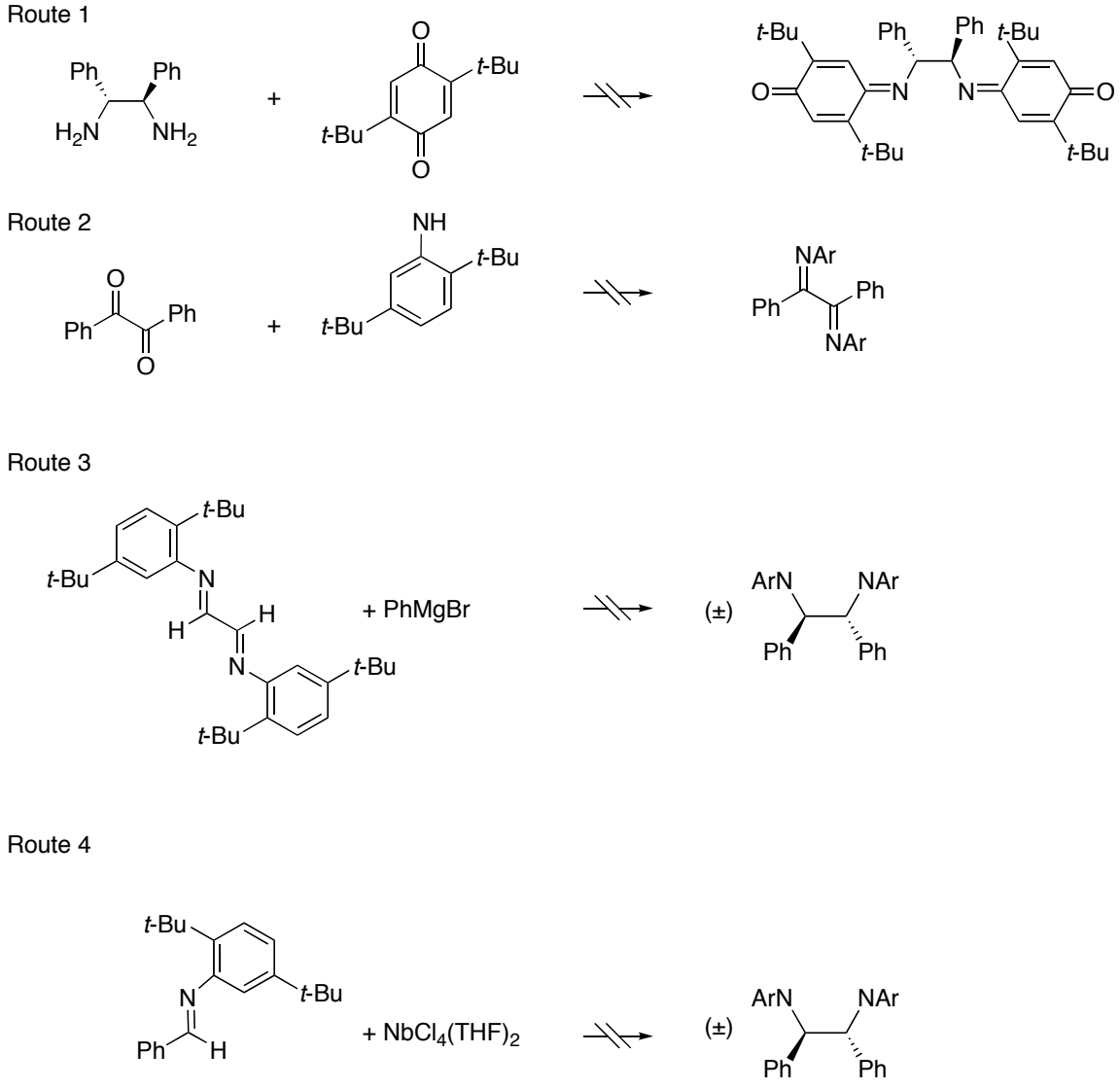


Figure 2.6. Efforts towards catalysts bearing *ortho-tert*-butylphenyl rings.

The difficulty encountered in these routes coincided with the discovery that NHC salts with a ketal (C(-OCH_2CH_2O-)Me) in the ortho position of the aniline ring were unreactive in the preparation of the catalysts from **11**.[9] If a ketal cannot be accommodated in the ortho position, it is unlikely that a *tert*-butyl group could be

accommodated. Hence, efforts were abandoned to prepare catalysts with *tert*-butyl groups in an ortho position of each of the N-bound aryl rings.

Instead, catalysts were designed with an isopropyl group in the 1 position of each N-bound aryl rings and varying substituents in the 4 positions (numbering scheme depicted in Figure 1.7). The return to an isopropyl group in the 1 position allowed the use of palladium catalyzed couplings to prepare the enantiopure secondary diamines. The preparations of the aryl bromides necessary for the coupling were straightforward (Figure 2.7).

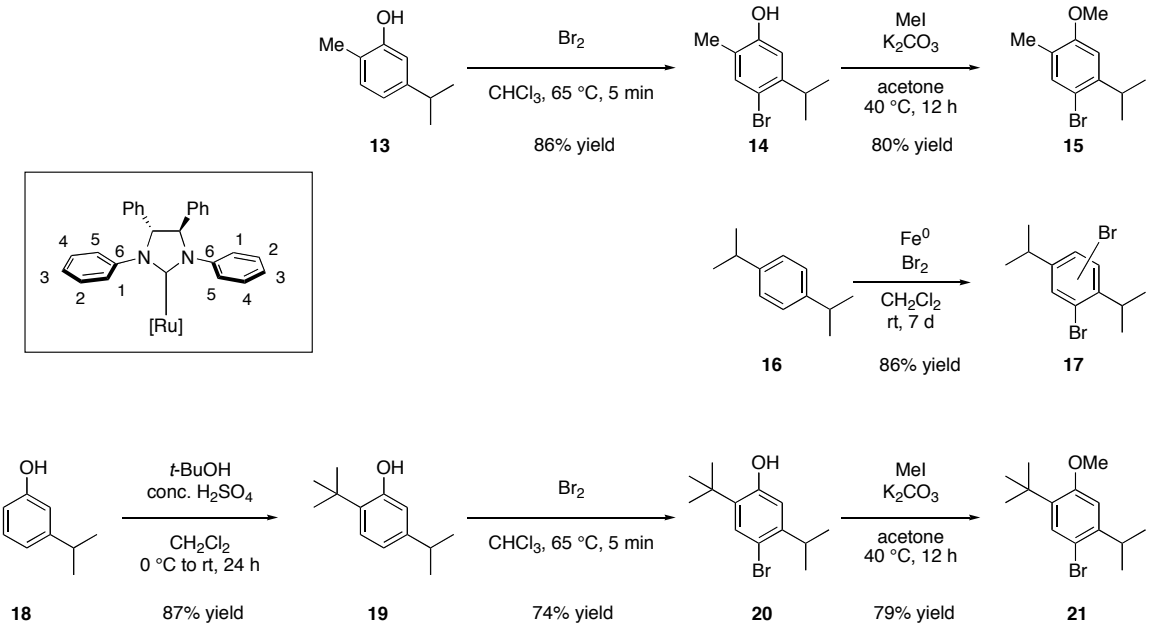


Figure 2.7. Preparation of aryl bromides **15**, **17** and **21**.

With the aryl bromides in hand, catalyst syntheses were also facile (Figure 2.8), although purification of the final catalysts (**28–30**) presented some challenges. Catalyst **28** was only prepared once, but catalysts **29** and **30** were prepared a number of times and the efficiency of their isolation varied. Using identical eluents on identically sized silica gel columns, the purity of the isolated compounds varied, sometimes requiring up to 3

columns to ensure >95% purity of the catalyst. Yields were reduced with repeated column chromatography. Dr. Steven Goldberg performed the initial synthesis of **29** from **16**.

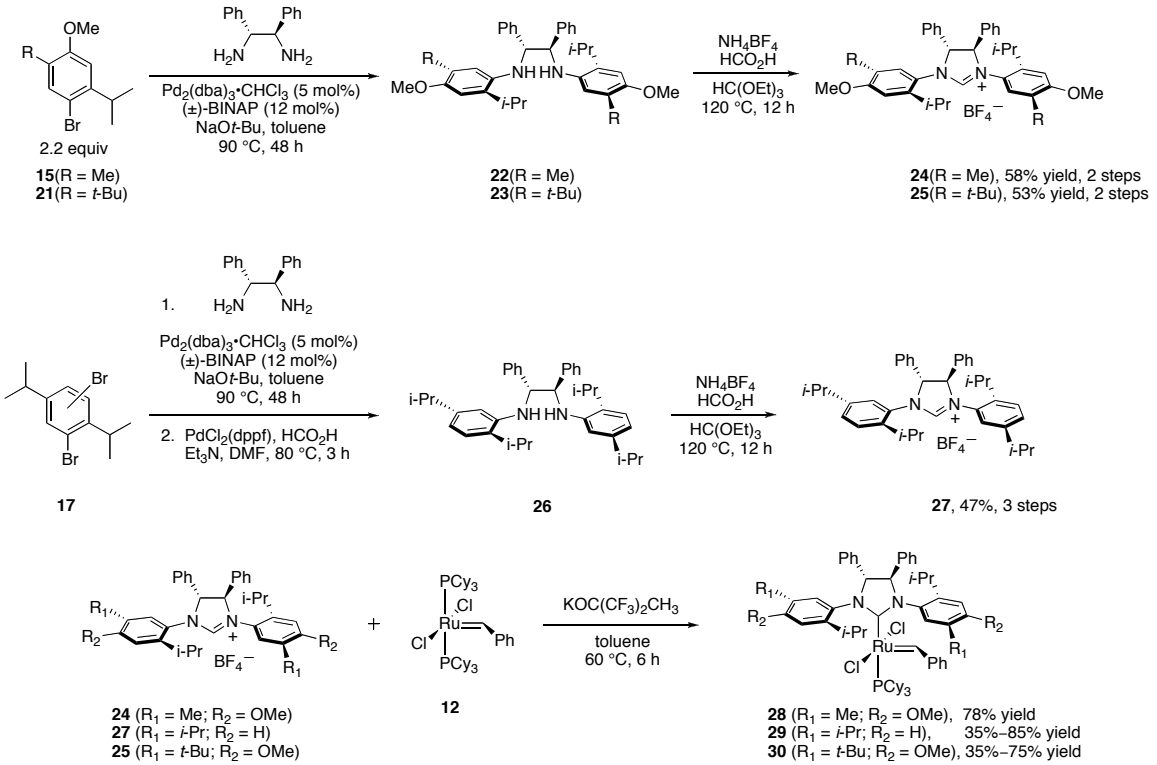


Figure 2.8. Synthesis of chiral ruthenium catalysts for olefin metathesis.

Another desired substitution pattern placed substitution at the 1 and 2 positions. The desired aryl bromide for this substitution pattern (1-bromo-2,3-diisopropylbenzene) proved much more difficult to prepare than the previous aryl bromides (Figure 2.9). There were two steps that proved to be challenging. In order to install the bromine in the desired position, it was necessary to turn to directed lithiation. However, an *ortho*-isopropyl group proved to be a poorer directing group than expected and this reaction proceeded in only 12-25% yield. The variable yields are the result of attempting a variety of different conditions for this reaction. Surprisingly, much more challenging than this step was the hydrogenation of **34**. It is clear that **34** is a conformationally restricted

molecule, as there are three ^{1}H NMR signals for the isopropyl group. It was envisioned that the isopropyl group lies orthogonal to the aryl ring and the isopropenyl group lies in plane with the aryl ring, with the olefin (which is less bulky than a methyl group) oriented towards the isopropyl group. Numerous efforts to hydrogenate this olefin with heterogeneous catalysts proved entirely unsuccessful. Moreover, attempted hydrogenations with tosyl hydrazide and Crabtree's catalyst also failed. Fortunately, using a more stable variant of Crabtree's catalyst — (*R*)-[Ir(Ph_2; ^{i}Pr-PHOX)(COD)]BAr_F[10] — at high catalyst loading (10 mol%) at 500 psi for 24 hours resulted in clean conversion to **35**.

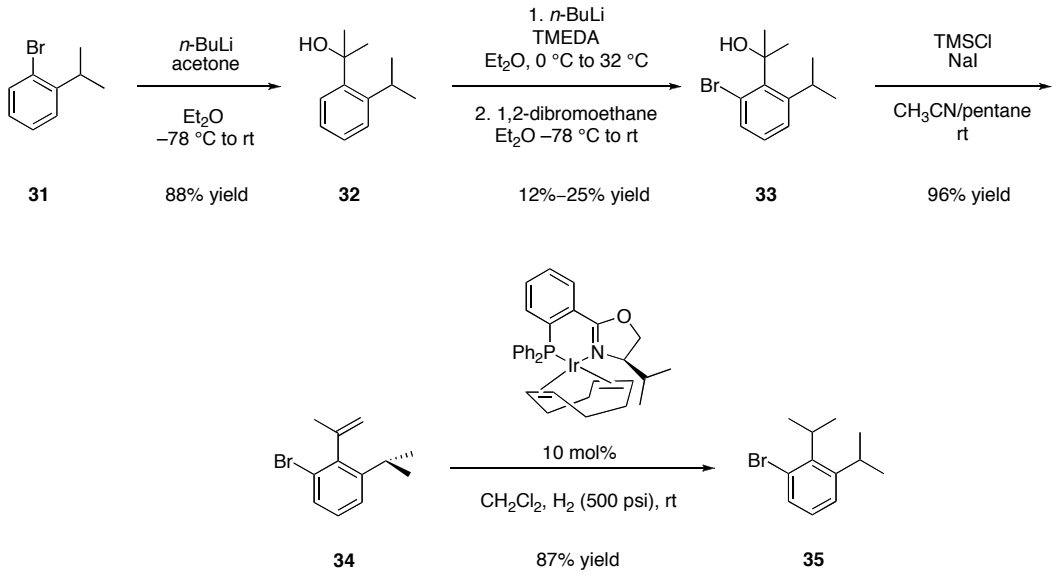


Figure 2.9. Preparation of a aryl bromide **35**.

With aryl bromide **35** in hand, the final catalyst preparation followed the same route as before (Figure 2.10). The yields to prepare the imidazolium salt were lower in this case, and the purification of the final catalyst was challenging again, but the catalyst was obtained in sufficient quantities for further testing.

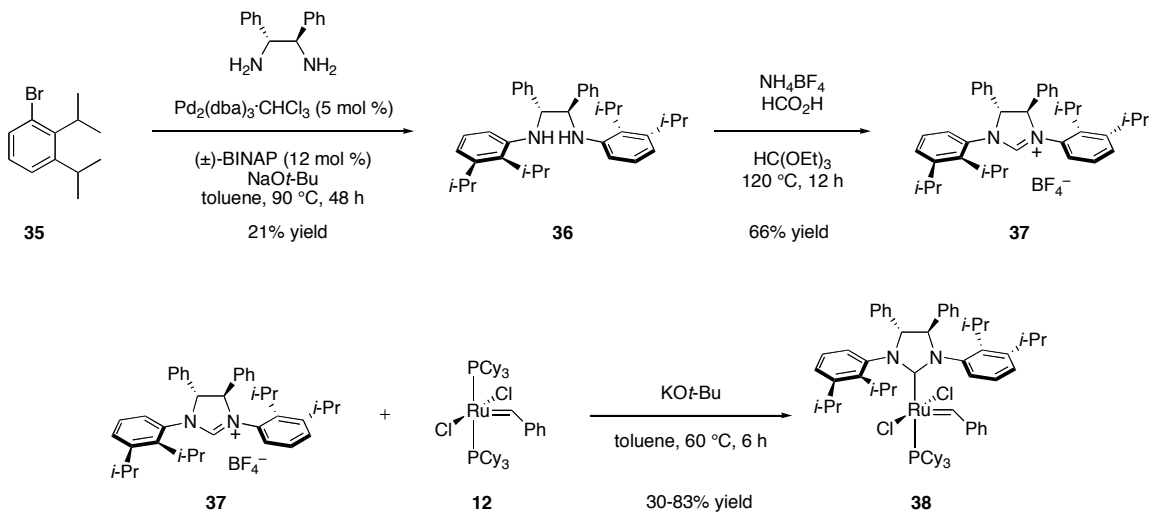
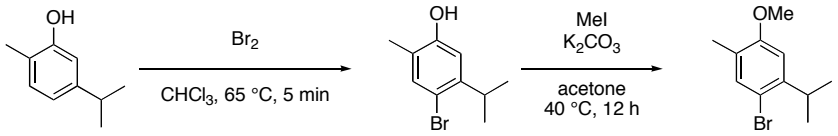


Figure 2.10. Preparation of a chiral ruthenium metathesis catalyst.

Experimentals

General Information. NMR spectra were recorded on an Oxford 300 MHz NMR spectrometer running Varian VNMR software. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent for ^{1}H NMR and ^{13}C NMR spectra. Chemical shifts are reported in parts per million (ppm) downfield from H_3PO_4 for ^{31}P NMR spectra. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet (m), and broad (br). Optical rotations were taken on a Jasco P-1010 polarimeter with a wavelength of 589 nm. The concentration "c" has units of g/100 mL (10 mg/mL) unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was performed with standard potassium permanganate stain or UV light. Flash column chromatography of organic compounds was performed using

silica gel 60 (230-400 mesh), and flash column chromatography of ruthenium compounds was performed using silica gel 60 (230-400 mesh) from TSI Scientific (Cambridge, MA). All glassware was either oven dried or flame dried, and reactions were done under an atmosphere of argon unless otherwise noted. All organic solvents were dried by passage through solvent purification columns containing activated alumina. All commercial chemicals were used as obtained, and $(PCy_3)_2Ru(=CHPh)Cl_2$ (**12**) was generously donated by Materia, Inc.

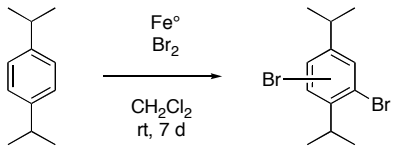


13 **14** **15**

4-Bromo-5-isopropyl-2-methyl-anisole (15). Br_2 (1.7 mL, 33 mmol) in $CHCl_3$ (20 mL) was added dropwise over 20 min from an addition funnel to carvacrol (**13**) (5 g, 33 mmol) in $CHCl_3$ (60 mL) stirring at 65 °C. The solution was stirred for 5 min and then quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic layer was removed; the aqueous layer was extracted 3x with $CHCl_3$ and the combined organic fractions were dried over $MgSO_4$, concentrate, and purified by column chromatography (5% EtOAc/Hex) to yield 6.54 g (86%) of **14**. CAUTION: Be extremely careful if you attempt to scale this reaction up further. Great care must be taken with the addition rate of the bromine solution to prevent the solution from exotherming too greatly and generating bromine gas. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 0.9 Hz, 1H), 6.70 (s, 1H), 4.97 (s, 1H), 3.26 (sept, J = 6.6 Hz, 1H), 2.19 (s, 3H), 1.20 (d, J = 6.9 Hz, 6H); ^{13}C

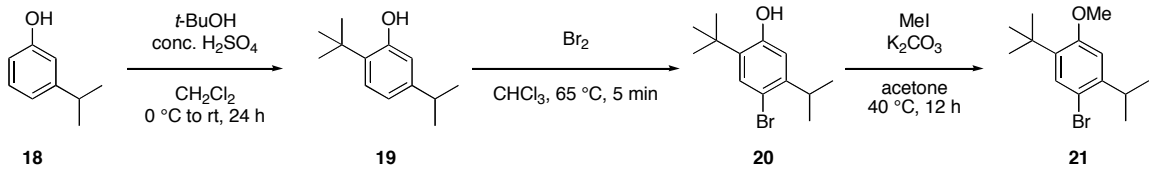
(75 MHz, $CDCl_3$) δ 153.6, 146.3, 134.6, 123.6, 114.5, 113.5, 32.8, 23.0, 15.3; HRMS (EI+) calc for $C_{10}H_{13}OBr$, 228.0150. Found 228.0156.

To a solution of **14** (6.54 g, 29 mmol) and K_2CO_3 (11.9 g, 86 mmol) in acetone (125 mL) was added MeI (5.4 ml, 86 mmol). The solution was heated to 40 °C and stirred for 12 h. Then the solution was cooled to rt and filtered through a glass frit, which was rinsed with acetone. The solution was then concentrated and purified by column chromatography (2% EtOAc/Hex) to yield 5.54 g (80%) of **15**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 0.9 Hz, 1H), 6.73 (s, 1H), 3.83 (s, 3H), 3.33 (sept, J = 6.9 Hz, 1H), 2.16 (d, J = 0.4 Hz, 3H), 1.25 (d, J = 6.9 Hz, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 157.57, 145.65, 134.25, 126.4, 114.1, 108.4, 55.7, 33.2, 23.1, 15.7; HRMS (EI+) calc for $C_{11}H_{15}OBr$, 242.0306. Found 242.0306.



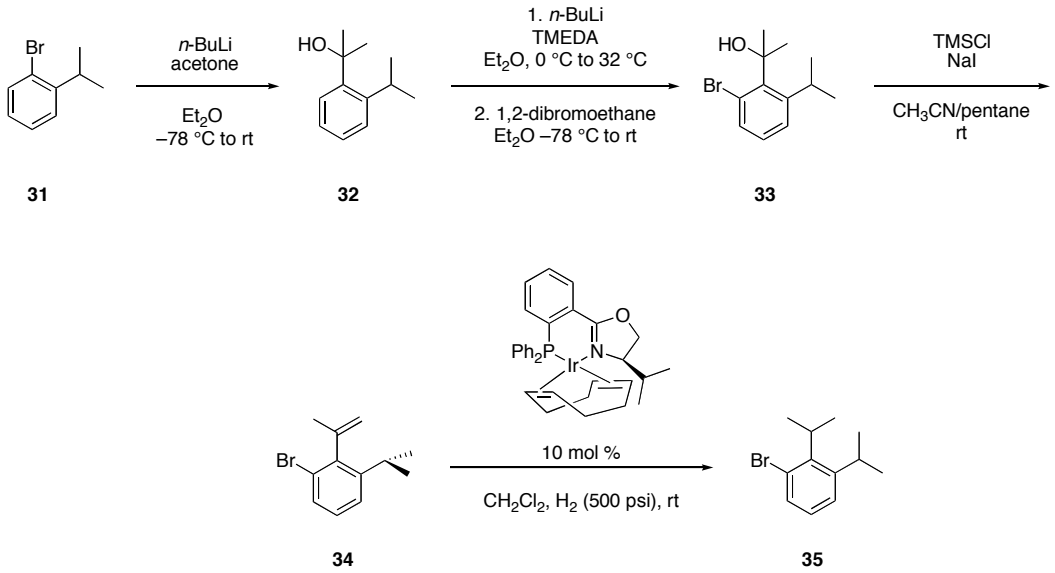
16 **17**

2-Bromo-1,4-diisopropylbenzene as a mixture (17). Following a known procedure,[11] to 1,4-diisopropylbenzene (10 mL, 53 mmol) and Fe (250 mg, 4.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added by syringe over 15 min Br_2 (2.67 mL, 52 mmol) in CH_2Cl_2 (10 mL). The red solution was warmed to rt and stirred for 7 days. The solution was filtered and washed with Na_2SO_3 until it was colorless, and was dried over $MgSO_4$ and concentrated. The oil was purified by column chromatography (100% pentane) to yield 11.35 g (86% yield by weight) of **17**, which was a 4:1 mixture of brominated products and starting material.



1-Bromo-5-*tert*-butyl-2-isopropyl-4-methoxybenzene (21). To a solution of 3-isopropyl phenol (10 g, 73 mmol) in CH_2Cl_2 at 0 °C was added *tert*-butyl alcohol (7.0 mL, 73 mmol) and conc. H_2SO_4 (3.9 mL, 73 mmol). The solution was allowed to warm to rt and stirred for 24 h. It was quenched with $NaHCO_3$ and the organic layer was removed. The aqueous layer was extracted 3× with CH_2Cl_2 and the combined organic fractions were dried over $MgSO_4$, concentrated, and purified by column chromatography (5% EtOAc in hexanes) to yield 12.2 g (87%) of the alkylated phenol **19**. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.20 (d, J = 8.1 Hz, 1H), 6.76 (dd, J = 8.1, 1.8 Hz, 1H), 6.54 (d, J = 1.8 Hz, 1H), 4.71 (s, 1H), 2.83 (sept, J = 6.9 Hz, 1H), 1.41 (s, 9H), 1.24 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 154.2, 148.2, 133.6, 127.1, 118.7, 114.9, 34.4, 33.5, 29.9, 24.1. HRMS (EI+) calc for $C_{13}H_{20}O$, 192.1514. Found 192.1511. Br_2 (980 μL, 19 mmol) in $CHCl_3$ (8 mL) was added dropwise over 20 min from an addition funnel to the alkylated phenol (3.5 g, 19 mmol) in $CHCl_3$ (35 mL) stirring at 65 °C. The solution stirred for 5 min and was quenched with saturated $Na_2S_2O_3$ (aq). The organic layer was removed and the aqueous layer was extracted 3× with $CHCl_3$, and the combined organic fractions were dried over $MgSO_4$, concentrated, and purified by column chromatography (5% EtOAc in hexanes) to yield 3.6 g (74%) of the brominated phenol **20**. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.36 (s, 1H), 6.58 (s, 1H), 4.80 (s, 1H), 3.24 (sept, J = 6.9 Hz, 1H), 1.38 (s, 9H), 1.20 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz,

$CDCl_3$, ppm): δ 153.9, 146.0, 135.9, 131.3, 115.0, 114.8, 34.6, 32.7, 29.7, 23.0. HRMS (EI+) calc for $C_{13}H_{19}OBr$, 270.0619. Found 270.0617. To a suspension of the brominated phenol (3.55 g, 13 mmol) and K_2CO_3 (5.39 g, 39 mmol) in acetone (100 mL) was added MeI (2.45 mL, 39 mmol). The solution was heated to 40 °C and stirred for 12 h. It was cooled to rt, filtered through a glass frit, and washed with acetone. The filtrate was concentrated and purified by column chromatography (5% EtOAc in hexanes) to yield 2.93 g (79%) of **21**. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.36 (s, 1H), 6.76 (s, 1H), 3.83 (s, 3H), 3.30 (sept, J = 6.9 Hz, 1H), 1.34 (s, 9H), 1.24 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 158.3, 145.7, 138.1, 130.8, 114.7, 110.1, 55.4, 34.8, 33.1, 29.8, 23.1. HRMS (EI+) calc for $C_{14}H_{21}OBr$, 284.0776. Found 284.0762.

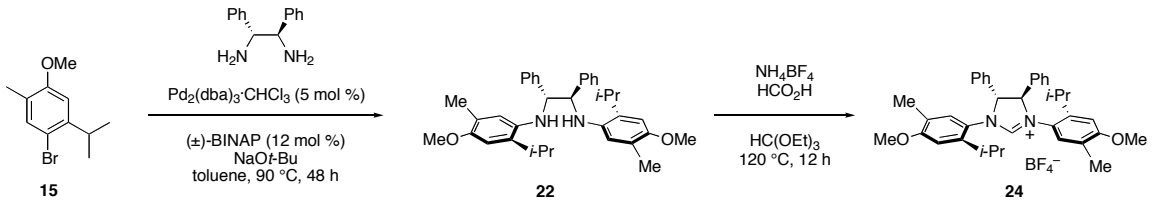


1-Bromo-2,3-diisopropylbenzene (35). To a solution of 2-isopropylbromobenzene (purchased from Lancaster) (8.6 mL, 56 mmol) in Et_2O (100 mL) at 0 °C was added *n*-BuLi (1.4 M in Et_2O, 42 mL, 59 mmol) and the solution stirred for 5 h at 0 °C. The solution was cooled to –78 °C and acetone (41 mL, 560 mmol) was added in one portion.

The solution was allowed to warm to rt as it stirred for 12 h and was quenched with H_2O. The organic layer was removed, washed with saturated NaCl (aq), dried over $MgSO_4$, concentrated, and purified by column chromatography (7% EtOAc in pentane) to give 8.82 g (88%) of the desired aromatic alcohol **32** as a white solid. On a larger scale (25 g of 2-isopropylbromobenzene), instead of purifying by column chromatography, the concentrated solution crystallized upon standing at rt for 48 h, yielding 13.22 g (59%) of **32**. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.45-7.38 (m, 2H), 7.29-7.24 (m, 1H), 7.16-7.11 (m, 1H), 3.91 (sept, J = 6.9 Hz, 1H), 1.79 (br s, 1H), 1.70 (s, 6H), 1.27 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 148.3, 144.5, 128.0, 127.7, 125.5, 125.1, 73.8, 32.0, 29.5, 25.0. HRMS (EI+) calc for $C_{12}H_{18}O$, 178.1350. Found 178.1358. This procedure was based on a literature precedent.[12] This reaction has given variable yields of 12%—25%; what follows is the procedure for the reaction that gave 25% yield. To a solution of the aromatic alcohol **32** (600 mg, 3.4 mmol) and TMEDA (2 mL, 13 mmol) in Et_2O (23 mL) at 0 °C was added *n*-BuLi (1.3 M in Et_2O, 10 mL, 13 mmol). The solution warmed to rt over 15 min and a reflux condenser was attached, and it was heated to 32 °C for 4 h. The solution was cooled to –78 °C, and 1,2-dibromoethane (1.5 mL, 17 mmol) was added. The solution was allowed to warm to rt as it stirred for 12 h. It was quenched with H_2O, washed with NaCl (aq), dried over Na_2SO_4, concentrated, and purified by column chromatography (7% EtOAc in pentane) to give 214 mg (25%) of the brominated aromatic alcohol **33** and 232 mg (39%) of unreacted starting material **32**. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.40 (dd, J = 7.8, 1.5 Hz, 1H), 7.31 (dd, J = 7.8, 1.5 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 4.03 (sept, J = 6.9 Hz, 1H), 1.87 (s, 6H), 1.22 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 151.9, 144.2, 133.2, 127.8, 127.5, 120.2, 76.3, 32.3,

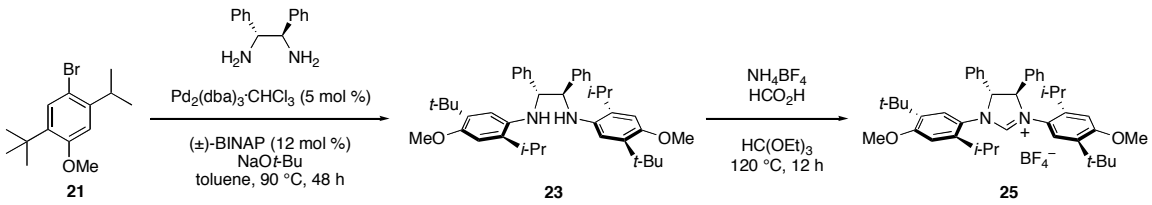
31.4, 25.4. HRMS (EI+) calc for $C_{12}H_{17}OBr$, 256.0470. Found 256.0463. This procedure was based on a literature precedent.[13] TMSCl (1.5 mL, 11 mmol), NaI (1.7 g, 11 mmol), and CH_3CN (300 μL) were prestirred for 30 min at rt, and the brominated aromatic alcohol **33** (500 mg, 1.9 mmol) was added as a solution in pentane (5 mL) and CH_3CN (200 μl). The solution stirred for 5h at rt, and Et_2O and H_2O were added. The organic layer was removed, dried over $MgSO_4$, concentrated, and the residue was passed through a small plug of silica gel with Et_2O to give 439 mg (96%) of the bromostyrene **34** as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.40 (dd, J = 7.8, 1.5 Hz, 1H), 7.24 (dd, J = 7.8, 1.5 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 5.32-5.30 (m, 1H), 4.84-4.83 (m, 1H), 3.13 (sept, J = 6.9 Hz, 1H), 2.02 (t, J = 1.5 Hz, 3H), 1.22 (d, J = 7.2 Hz, 3H), 1.16 (d, J = 5.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 130.0, 128.6, 124.7, 116.4, 31.0, 25.3, 24.4, 24.2. HRMS (EI+) calc for $C_{12}H_{15}Br$, 238.0353. Found 238.0357. A solution of the bromostyrene **34** (2.0 g, 8.4 mmol) and (*R*)-[Ir(Ph_2; ^{i}Pr-PHOX)(COD)]BAr_F[10] (1.3 g, 0.84 mmol) in CH_2Cl_2 (20 mL) was placed in a stainless steel pressure bomb. The bomb was purged with 3 × 500 psi H_2 and was sealed at 500 psi H_2. The solution stirred at rt for 24 h and was vented, concentrated, and passed through a short plug of silica gel (100% pentane) to yield 1.73 g (87%) of **35** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.39 (dd, J = 7.8, 1.5 Hz, 1H), 7.23-7.21 (dd, J = 7.8, 1.5 Hz, 1H), 6.99 (t, J = 7.8 Hz, 1H), 3.93-3.28 (m, 2H), 1.47 (br s, 2H), 1.36 (d, J = 6.9 Hz, 4H), 1.24 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 130.8, 127.6, 127.0, 34.1, 29.8, 24.9, 24.3, 21.9, 20.4. HRMS (EI+) calc for $C_{12}H_{17}Br$, 240.0524. Found 240.0514.

General 2-step procedure for chiral 4,5-dihydroimidazolium salts. A solution of the aryl bromide (2.2 equiv) in toluene in a sealable schlenk tube was degassed by three freeze/pump/thaw cycles. After reaching rt, the positive argon pressure was briefly stopped and to this solution was added (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (1 equiv), $Pd_2(dba)_3$•$CHCl_3$ (0.05 equiv), and (±)-BINAP (0.12 equiv) in one portion. The argon pressure was immediately resumed, and a very brief pump/backfill was performed at rt. NaO*t*-Bu (3 equiv) was added and the solution was heated to 90 °C and sealed. The solution stirred for 48 h at 90 °C, and after cooling to rt was quickly passed through a small silica gel column with 5% EtOAc in hexanes. The eluting was stopped when no more UV active material came off the column. The eluent containing partially purified diaryl diamine was concentrated and $(EtO)_3CH$ was added. To this solution was added NH_4BF_4 (1 equiv) and 2 drops of formic acid. The solution was heated to 120 °C and stirred for 12 h. Upon cooling to rt, Et_2O was added and a white precipitate was briefly observed, but ultimately a thick oil formed. Thus, the solution was concentrated, purified by flash chromatography (MeOH in CH_2Cl_2), and placed under high vacuum for 12 h to yield the desired 4,5-dihydroimidazolium salt as a hard foam.



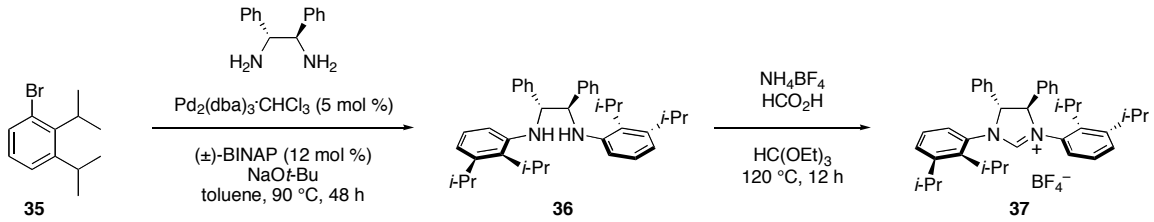
Tetrafluoroborate imidazolium salt 24. Following the above procedure with **15** (2.66 g, 11 mmol), toluene (17 mL), (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (1.1 g, 5 mmol),

$Pd_2(dba)_3$•$CHCl_3$ (260 mg, 0.125 mmol), (±)-BINAP (374 mg, 0.6 mmol) and NaO*t*-Bu (1.44 g, 15 mmol) followed by $(EtO)_3CH$ (8.3 mL, 50 mmol) and NH_4BF_4 (524 mg, 5.2 mmol) with 2 drops of formic acid gave a solution that was concentrated, purified by flash chromatography (10% MeOH/CH_2Cl_2), and placed under high vacuum for 12 h to yield 1.85 g (58%) of **24** as a hard foam. $[\alpha]^{22}_D$ +285.08 (c 0.57, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (1H, s), 7.46-7.33 (10H, m), 7.21 (2H, s), 6.60 (2H, s), 5.68 (2H, s), 3.78 (6H, s), 3.05 (2H, sept, 6.6 Hz), 2.12 (6H, d, 6.6 Hz), 1.29 (6H, d, 6.9 Hz), 1.12 (6H, d, 6.9 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 159.4, 157.9, 143.8, 133.4, 131.0, 130.5, 130.0, 129.9, 128.9, 128.8, 127.1, 123.2, 107.3, 55.6, 29.0, 25.0, 24.1, 15.7; HRMS (FAB+) calc for $C_{37}H_{43}N_2O_2$, 547.3325. Found 547.331.



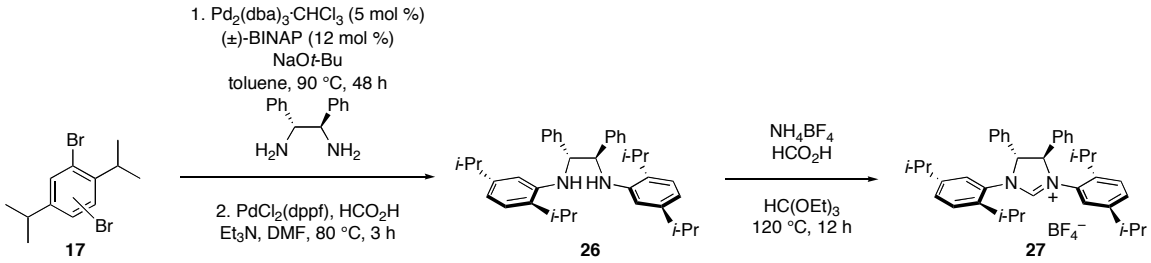
(4*R*,5*R*)-1,3-Bis-(5-*tert*-butyl-2-isopropyl-4-methoxyphenyl)-4,5-diphenyl-4,5-dihydro-3*H*-imidazol-1-ium tetrafluoroborate (25). Using the general procedure above, **21** (1.0 g, 3.5 mmol), (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (351 mg, 1.6 mmol), $Pd_2(dba)_3$•$CHCl_3$ (83 mg, 0.08 mmol), (±)-BINAP (118 mg, 0.19 mmol), and NaO*t*-Bu (461 mg, 4.8 mmol) in 3.5 mL toluene gave crude **23**, which was used directly in the next step. Assuming 100% yield in the coupling, **23**, $(EtO)_3CH$ (2.7 mL, 16 mmol), NH_4BF_4 (168 mg, 1.6 mmol), and 2 drops of formic acid gave crude product that was purified by 10% MeOH in CH_2Cl_2 to yield a viscous yellow oil. This oil is the

desired salt by ^{1}H NMR, but further purification gives better yields in the catalyst preparation step. Further purification consists of dissolving the yellow oil in copious Et_2O (100 mL) and letting the solution sit at rt for 12 h. At this time, a white precipitate was observed, the rest of the ether was decanted off, the precipitate was washed with a minimal amount of ether and dried to yield 614 mg (53% over 2 steps) of **25**. The remaining ether can be concentrated to give additional material that can also be used to make catalyst but in a reduced yield. $[\alpha]_D^{22} = +191.31$ (c 0.53, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.21 (s, 1H), 7.43-7.39 (m, 10H), 7.18 (s, 2H), 6.66 (s, 2H), 5.64 (s, 2H), 3.81 (s, 6H), 3.11 (sept, J = 7.2 Hz, 2H), 1.36 (d, J = 6.6 Hz, 12H), 1.24 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 161.1, 160.0, 157.6, 151.1, 143.7, 138.0, 133.7, 130.6, 129.9, 129.0, 127.0, 123.2, 108.8, 55.3, 34.9, 29.5, 29.0, 25.0, 24.3. HRMS (FAB+) calc for $C_{43}H_{55}N_2O_2$, 631.4264. Found 631.4280.



(4*R*,5*R*)-1,3-Bis-(2,3-diisopropylphenyl)-4,5-diphenyl-4,5-dihydro-3*H*-imidazol-1-ium tetrafluoroborate (37). Using the general procedure above, **35** (788 mg, 3.3 mmol), (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (327 mg, 1.5 mmol), $Pd_2(dba)_3$•$CHCl_3$ (78 mg, 0.075 mmol), (±)-BINAP (112 mg, 0.18 mmol), and NaO*t*-Bu (432 mg, 4.5 mmol) in 4 mL toluene gave 444 mg **36** (21%). **36** (444 mg, 0.83 mmol), $(EtO)_3CH$ (2.0 mL, 12 mmol), NH_4BF_4 (84 mg, 0.83 mmol), and 2 drops of formic acid gave crude product that was purified by 10% MeOH in CH_2Cl_2 to give 333 mg (66%) of **37** as a hard foam.

$[\alpha]_D^{22}$ = +209.3 (c 0.82, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.12 (br s, 1H), 7.41-7.23 (m, 16H), 5.74 (br s, 2H), 3.36-3.33 (m, 4H), 1.63 (s, 6H), 1.47 (br s, 6H), 1.25-1.18 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 150.1, 140.6, 130.6, 130.2, 130.0, 129.0, 128.2, 29.6, 29.0, 24.8, 24.5, 22.9, 22.6. HRMS (FAB+) calc for $C_{39}H_{47}N_2$, 543.3748. Found 543.3739.

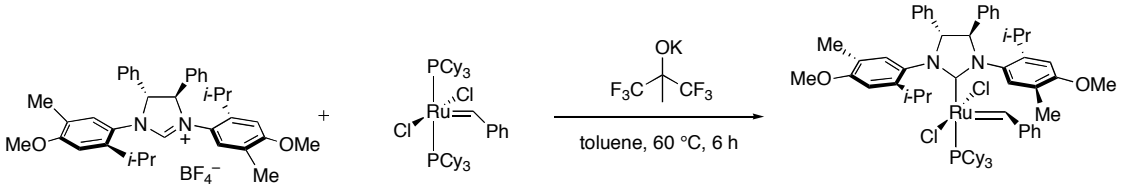


(4*R*,5*R*)-1,3-Bis-(2,5-diisopropylphenyl)-4,5-diphenyl-4,5-dihydro-3*H*-imidazol-1-ium tetrafluoroborate (27). This is a three-step procedure with stable, isolated intermediates. The first and third steps follow the general procedure above. A solution of **17** (1.58 g, 6.6 mmol) in 5 mL toluene in a sealable schlenk tube was subjected to three freeze/pump/thaw cycles and warmed to rt. To this solution was added (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (500 mg, 2.3 mmol), $Pd_2(dba)_3$•$CHCl_3$ (122 mg, 0.12 mmol), and (±)-BINAP (220 mg, 0.36 mmol) in one portion. NaO*t*-Bu (680 mg, 7.1 mmol) was added and the solution was heated to 90 °C and sealed. It stirred for 48 h and after cooling to rt it was quickly passed through a small silica gel column with 5% EtOAc in hexanes. The eluting was stopped when no more UV active material came off of the column. The eluent was concentrated, and 765 mg of the crude product was isolated as a mixture of mono- and dibrominated arenes. $PdCl_2(dppf)$•CH_2Cl_2 (7.7 mg, 0.0094 mmol) was added to the crude product (576 mg), and the flask was flushed with argon. To this

mixture was added degassed DMF (2.5 mL) and Et_3N (394 μl, 2.8 mmol). The solution was heated to 80 °C and formic acid (62 μL, 1.7 mmol) was added. After stirring for 3 h at 80 °C, a 1:1 solution of Hex/Et_2O (10 mL) was added. The solution was washed with 1N HCl (aq), saturated $NaHCO_3$ (aq), and saturated NaCl (aq). The organic layer was dried over Na_2SO_4 and purified by flash chromatography (6:1 pentane in CH_2Cl_2) to give 430 mg of the desired diamine (**26**). To **26** (1.32 g, 2.5 mmol) was added $(EtO)_3CH$ (4.1 mL, 25 mmol), NH_4BF_4 (260 mg, 2.5 mmol) and 2 drops of formic acid. The solution was heated to 120 °C and stirred for 12 h. It was cooled to rt, Et_2O was added, and a yellow solid precipitated. The solid was purified by flash chromatography (10% MeOH in CH_2Cl_2) to yield 1.35 g (86%) of **27**. $[\alpha]^{22}_D$ +270.78 (c 0.51, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.11 (s, 1H), 7.48-7.19 (m, 16H), 5.83 (s, 2H), 3.11 (sept, J = 6.9 Hz, 2H), 2.82 (sept, J = 6.9 Hz, 2H), 1.31 (d, J = 6.9 Hz, 6H), 1.18 (d, J = 6.6 Hz, 6H), 1.13-1.09 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 157.0, 148.9, 142.0, 132.9, 130.9, 130.6, 129.8, 129.1, 126.8, 126.6, 77.1, 33.6, 28.6, 24.9, 24.3, 23.8, 23.5. HRMS (FAB+) *m/z* calc for $C_{39}H_{47}N_2$; 543.3739, found 543.3755.

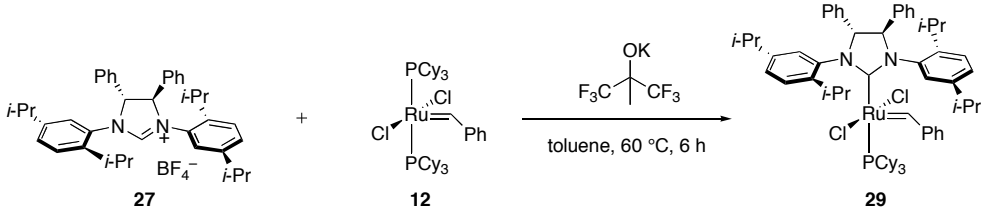
General procedure for the synthesis of chiral ruthenium catalysts 28–30, **39.** In a nitrogen atmosphere drybox, potassium hexafluoro-*t*-butoxide, imidazolium salt, and $(PCy_3)_2Ru(=CHPh)Cl_2$ (**12**) were suspended in toluene. The flask was sealed with a septum and heavy parafilm, removed from the glove box and the solution was stirred at 60 °C for 6 hours. The solution was concentrated and purified by flash chromatography using TSI silica gel (see general information section) to afford the desired ruthenium catalyst, which was lyophilized from benzene to give a brown powder. Further

purification by flash chromatography was occasionally necessary due to difficulties in separating unreacted **12**. This further purification resulted in diminished yields.



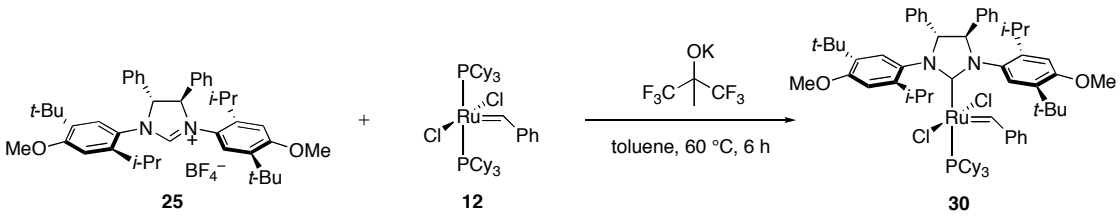
24 **12** **28**

Ruthenium Compound 28. Following the general procedure above, potassium hexafluoro-*tert*-butoxide (308 mg, 1.39 mmol), potassium imidazolium salt **24** (1.07 g, 0.71 mmol), and $(PCy_3)_2Ru(=CHPh)Cl_2$ (**12**) (334 mg, 0.71 mmol) in toluene (25 mL) afforded **28** (600 mg, 78%) after purification by flash chromatography (10% Et_2O/Hexanes). ^1H NMR (300 MHz, C_6D_6) δ 19.88 (s, 1H), 8.83 (s, 1H), 7.64 (d, J = 7.2 Hz, 4H), 7.11-6.88 (m, 14H), 6.62 (s, 1H), 5.40 (d, J = 4.2 Hz, 1H), 5.04 (d, J = 4.2 Hz, 1H), 4.19 (septet, J = 6.6 Hz, 1H), 3.26 (s, 3H), 3.04 (s, 3H), 2.33 (s, 3H), 1.83 (d, J = 6.3 Hz, 6H), 1.75-1.45 (m, 21H), 1.28 (d, J = 7.2 Hz, 6H), 1.15-1.00 (m, 12H); $^{31}P\{^1H\}$ NMR (C_6D_6) δ 25.6 (s); ^{13}C NMR (126 MHz, C_6D_6, ppm) only diagnostic peaks reported: δ 221.0 (d, J = 88.4 Hz). HRMS (FAB+) calc for $C_{62}H_{81}N_2PCl_2RuO_2$, 1088.446. Found 1088.449.



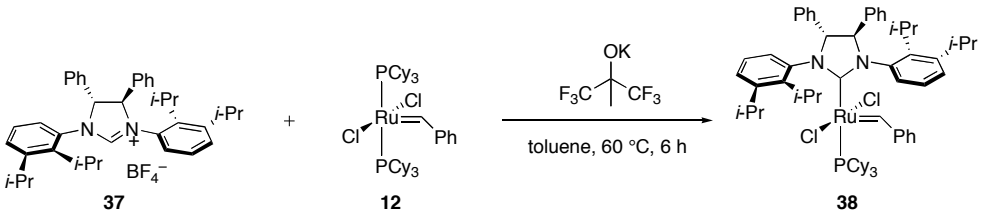
27 **12** **29**

Ruthenium Compound 29. Following the general procedure above, potassium hexafluoro-*t*-butoxide (140 mg, 0.64 mmol), **27** (400 mg, 0.64 mmol), and $(PCy_3)_2Ru(=CHPh)Cl_2$ (**12**) (261 mg, 0.32 mmol) in 8 mL toluene afforded 294 mg (85%) of **29** (10% Et_2O in pentane), which was lyophilized from benzene to give a brown powder. ^1H NMR (300 MHz, C_6D_6, ppm): δ 19.83 (s, 1H), 8.50 (s, 1H), 7.53-7.48 (m, 5H), 7.05-6.89 (m, 15H), 6.67 (d, J = 8.1 Hz, 1H), 6.48 (d, J = 8.4 Hz, 1H), 5.34 (d, J = 4.8 Hz, 1H), 5.10 (d, J = 4.5 Hz, 1H), 4.25 (sept, J = 6.6 Hz, 1H), 3.96 (br s, 1H), 2.87 (sept, J = 6.6 Hz, 1H), 2.36 (sept, J = 6.6 Hz, 1H), 2.06 (q, J = 10.8 Hz, 5H), 1.80-0.85 (m, 52H). $^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6, ppm): δ 25.5 (s). ^{13}C NMR (126 MHz, C_6D_6, ppm) only diagnostic peaks reported: δ 297.7 (br s), 219.1 (d, J = 78.7 Hz). HRMS (FAB+) calc for $C_{64}H_{85}N_2PCl_2Ru$, 1084.487. Found 1084.483.



Ruthenium compound 30. Following the general procedure above, potassium hexafluoro-*t*-butoxide (60 mg, 0.27 mmol), **25** (197 mg, 0.27 mmol), and $(PCy_3)_2Ru(=CHPh)Cl_2$ (**12**) (150 mg, 0.18 mmol) in 6 mL toluene afforded 159 mg (75%) of **30** (10% Et_2O in pentane), which was lyophilized from benzene to give a brown powder. ^1H NMR (300 MHz, C_6D_6, ppm): δ 19.80 (s, 1H), 8.28 (s, 1H), 7.65 (d, J = 7.2 Hz, 2H), 7.57 (d, J = 7.2 Hz, 2H), 7.38 (s, 2H), 7.16-7.00 (m, 10H), 6.74 (s, 1H), 6.09 (s, 1H), 5.35 (d, J = 4.8 Hz, 1H), 5.19 (d, J = 4.8 Hz, 1H), 4.49 (sept, J = 6.6 Hz, 1H), 3.83

(sept, J = 6.9 Hz, 1H), 3.32 (s, 3H), 3.16 (s, 3H), 2.24-1.11 (m, 63H). $^{31}P\{^{1}H\}$ NMR (121 MHz, C_6D_6, ppm): δ 25.4 (s). ^{13}C NMR (126 MHz, C_6D_6, ppm) only diagnostic peaks reported: δ 296.3 (d, J = 351.0 Hz), 219.9 (d, J = 79.6 Hz). HRMS (FAB+) calc for $C_{68}H_{93}N_2PCl_2RuO_2$, 1172.540. Found 1172.546.



Ruthenium compound 38. Following the general procedure above, potassium hexafluoro-*t*-butoxide (109 mg, 0.50 mmol), **37** (313 mg, 0.50 mmol), and $(PCy_3)_2Ru(=CHPh)Cl_2$ (**12**) (273 mg, 0.33 mmol) in 6 mL toluene afforded a brown solid (5% Et_2O in pentane), which was a 9:1 ratio of **38**:**12**. Purification by a second flash column (5% Et_2O in pentane) using TSI silica gel followed by lyophilization from benzene afforded 160 mg (30%) of **38** as a brown powder. ^{1}H NMR (300 MHz, C_6D_6, ppm): δ 19.87 (s, 1H), 9.26 (d, J = 6.6 Hz, 1H), 7.75 (d, J = 7.5 Hz, 2H), 7.17-6.89 (m, 16H), 6.39 (d, J = 7.2 Hz, 1H), 6.14 (br s, 1H), 5.28 (d, J = 3.3 Hz, 1H), 4.98 (d, J = 3.3 Hz, 1H), 4.35 (quint, J = 7.2 Hz, 1H), 4.04 (br s, 1H), 3.41 (quint, J = 6.9 Hz, 1H), 3.11 (br s, 1H), 2.21-0.39 (m, 57H). $^{31}P\{^{1}H\}$ NMR (121 MHz, C_6D_6, ppm): δ 26.2 (s); HRMS (FAB+) calc for $C_{64}H_{85}N_2PCl_2Ru$, 1084.487. Found 1084.489.

[1] (a) Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499. (b) Fujimura, O.; de la Mata, F. J.; Grubbs, R. H. *Organometallics* **1996**, *15*, 1865.

[2] Ruthenium catalysts: (a) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502. (b) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954. (c) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225.

[3] Molybdenum catalysts: (a) Totland, K. M.; Boyd, T. J.; Lavoie, G. G.; Davis, W. M.; Schrock, R. R. *Macromolecules* **1996**, *29*, 6114. (b) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041. (c) Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251. (d) Alexander, J. B.; Schrock, R. R.; Davis, W. M.; Hultzsch, K. C.; Hoveyda, A. H.; Houser, J. H. *Organometallics* **2000**, *19*, 3700. (e) Aeilts, S. L.; Cefalo, D. R.; Bonitatebus, Jr., P. J.; Houser, J. H.; Hoveyda, A. H.; Schrock, R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1452. (f) Tsang, W. C. P.; Schrock, R. R.; Hoveyda, A. H. *Organometallics* **2001**, *20*, 5658. (g) Hultzsch, K. C.; Bonitatebus, P. J.; Jernelius, J.; Schrock, R. R.; Hoveyda, A. H. *Organometallics* **2001**, *20*, 4705. (h) Schrock, R. R.; Jamieson, J. Y.; Dolman, S. J.; Miller, S. A.; Bonitatebus, P. J.; Hoveyda, A. H. *Organometallics* **2002**, *21*, 409. (i) Tsang, W. C. P.; Jernelius, J. A.; Cortez, G. A.; Weatherhead, G. S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 2591.

[4] (a) Sattely, E. S.; Cortez, G. A.; Moebius, D. C.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 8526. (b) Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron* **2004**, *60*, 7345.

[5] For reviews of asymmetric olefin metathesis reactions, see: (a) Hoveyda, A. H. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2, Chapter 2.3. (b) Schrock. R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (c) Hoveyda, A. H.; Schrock. R. R. *Chem. Eur. J.* **2001**, *7*, 945.

[6] Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288.

[7] Scholl, M.; Ding, S.; Less, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

[8] Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152.

[9] Ward, D. W. personal communication, 2002.

[10] (a) Pfaltz, P.; Blankenstein, J.; Hörmann, E.; McIntyre, S.; Menges, F.; Hilgraf, R.; Schönleber, M.; Smidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33. (b) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2897.

[11] Patel, B. A.; Ziegler, C. B.; Cortese, N. A.; Plevyak, J. E.; Zebovitz, T. C.; Terpko, M.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3903.

[12] Taber, D. F.; Dunn, B. S.; Mack, J. F.; Saleh, S. A. *J. Org. Chem.* **1985**, *50*, 1987.

[13] Sakai, T.; Miyata, K.; Utaka, M.; Takeda, A. *Tet. Lett.* **1987**, *28*, 3817.