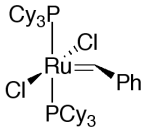
CHAPTER 3

Initial Efforts to Develop a Small-Molecule Water-Soluble Olefin Metathesis Catalyst Containing an *N*-Heterocyclic Carbene Ligand

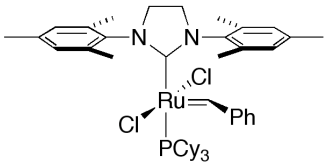
Abstract

Early research pursuing a discrete, water-soluble olefin metathesis catalyst containing an *N*-heterocyclic carbene (NHC) ligand is reported. Two general strategies for generating the desired catalyst are outlined. The first strategy incorporates water-soluble groups into the NHC ligand. The second strategy incorporates water-soluble groups onto phosphine, pyridine, and isopropoxybenzylidene ligands, which are ligands that dissociate during metathesis reactions. The syntheses of ligands and ruthenium complexes inspired by these two strategies are described.

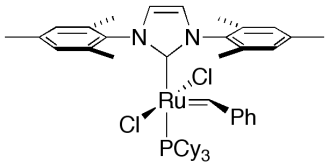
Introduction



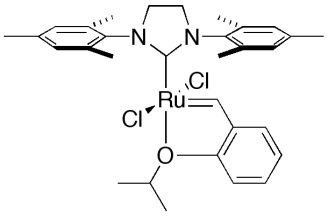
1



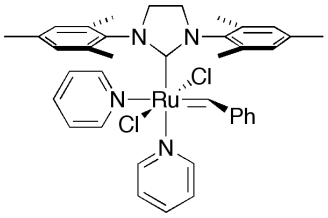
2



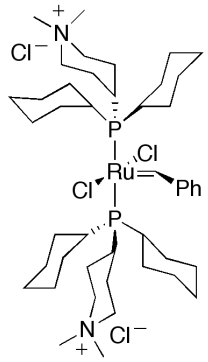
3



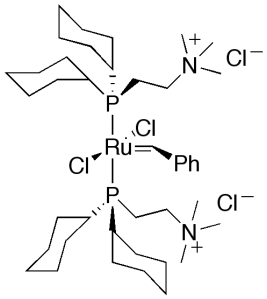
4



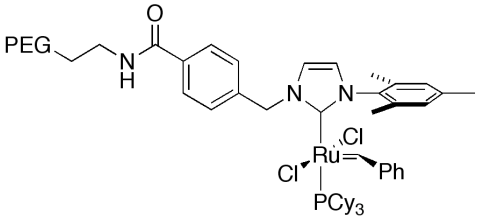
5



6



7



8

Earlier chapters describe the development and utility of catalysts **1**–**8** and their impact on olefin metathesis.[1-14] Of particular interest to this chapter are catalysts **6**–**8**, which are soluble and operate in polar protic solvents, including water.[9-14] The first homogenous, well-defined water-soluble catalysts, complexes **6** and **7**, are capable of performing ring-opening metathesis polymerization (ROMP) in water and show limited ring-closing metathesis activity in polar protic solvents.[9-13] The development of catalyst **8**

is described in Chapter 2. This catalyst also shows metathesis activity in polar protic solvents.[14]

The increased stability and activity of *N*-heterocyclic carbene (NHC)-containing olefin metathesis catalysts over their bis(phosphine) analogs inspires the production of water-soluble catalysts like **8**.[15-17] The hypothesis is that the benefits that NHC ligands impart on ruthenium-based olefin metathesis catalysts used in aprotic solvents will also be observed in their water-soluble analogs. Consistent with this hypothesis, catalyst **8** does show increased ROMP activity in water over the water-soluble bis(phosphine) catalyst **7**.[14] However, as described in Chapter 2, complex **8** is unable to mediate the metathesis of acyclic substrates in water and is less active than parent catalyst **3** in aprotic solvents.

Three augmentations of catalyst **8** may yield a water-soluble catalyst with improved stability and activity. First, one of the nitrogen substituents of the NHC ligand of complex **8** positions two benzyl protons close to the ruthenium center. One of the decomposition pathways of metathesis catalysts is ruthenium insertion into a carbon-hydrogen bond presented by a nitrogen substituent of the NHC ligand.[18] Therefore, avoiding the amino-benzyl protons of catalyst **8** should produce a catalyst with greater stability. Second, the NHC ligand of catalyst **8** has an unsaturated backbone. As NHC ligands with saturated backbones yield metathesis catalysts with higher activities,[1,19] trading the unsaturated NHC ligand of catalyst **8** with a saturated analog should increase the catalyst's metathesis activity. Finally, the long, polydisperse poly(ethylene oxide) (PEG) chain of catalyst **8** complicates its characterization and possibly inhibits the approach of substrate molecules to the catalyst's ruthenium center. Thus, catalysts that

replace PEG with water-soluble ionic groups, such as quaternary amines, can be better characterized and may show improved activity over catalysts displaying PEG.

Figure 3.1 illustrates various strategies to generate water-soluble olefin metathesis catalysts, which contain saturated NHC ligands and avoid the amino-benzyl protons of catalyst **8**. As shown in Figure 3.1, water-soluble groups can be incorporated onto the NHC ligand or onto pyridine, phosphine or isopropoxybenzylidene ligands to produce water-soluble analogs of catalysts **3**–**5**. This chapter describes early efforts to synthesize such NHC-containing, water-soluble olefin metathesis catalysts. Although these efforts did not produce a water-soluble catalyst, they did lay the groundwork for future success in aqueous metathesis as described in Chapter 5.

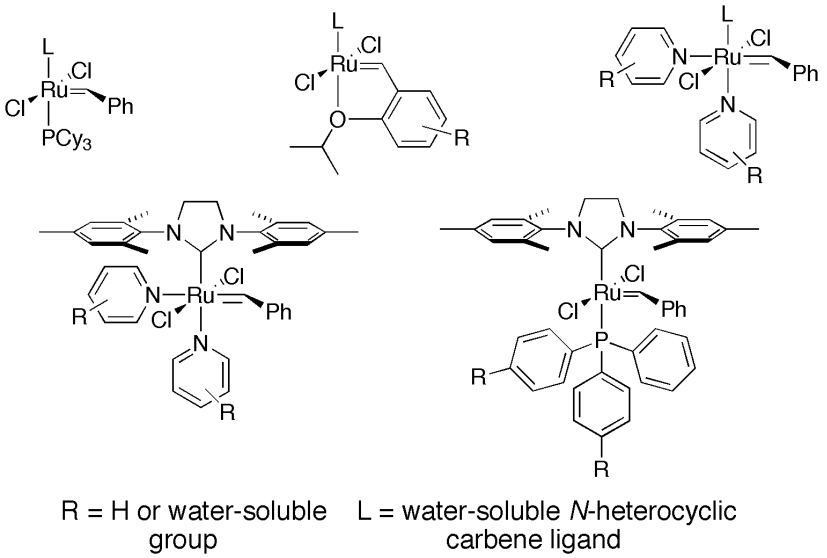


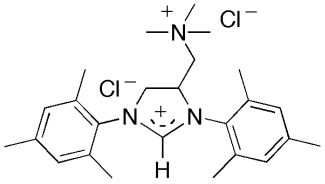
Figure 3.1. Water-soluble groups can be incorporated onto NHC ligands or ligands that dissociate during metathesis reactions to produce NHC-containing olefin metathesis catalysts that are soluble in water.

Results and Discussion

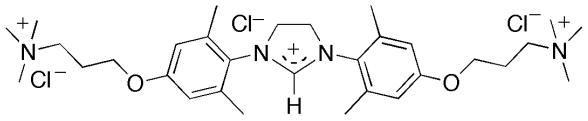
Strategies involving water-soluble NHC ligands. Early efforts to synthesize catalysts with improved stability and activity in water focused on incorporating water-soluble groups onto NHC ligands. The driving force for this direction of research is the persistent coordination of the NHC ligand to the ruthenium center. In contrast, as part of the mechanism of olefin metathesis, water-soluble phosphine, pyridine or isopropoxybenzylidene ligands will dissociate from the metal center to yield a fourteen-electron complex.[20-22] The solubility of the fourteen-electron complex in water is unknown though there is evidence that it prefers a nonpolar environment.[23] Therefore, the solubility of catalysts containing water-soluble groups only on their dissociating ligands may change during a metathesis reaction with possible deleterious effects.[24] In contrast, catalysts that incorporate water-soluble groups onto their NHC ligands should remain dissolved in water throughout the catalytic cycle of olefin metathesis.

NHC ligands containing ammonium salts. Imidazolium salts **9** and **10** were the NHC ligand precursors initially targeted. These salts contain tetraalkylamines as the water-soluble functional group. Ammonium salts were chosen because they are noncoordinating, readily made, and were the functional group employed by catalysts **6** and **7** to achieve solubility in water.[9,11,12] However, care must be taken with the choice of counter-ion for these NHC ligands as anions such as iodide, bromide, carboxylates, and sulfonates are known to replace the chloride ligands of metathesis catalysts to yield ruthenium complexes with lower activities.[20,25-27] The chloride anion was chosen because of its successful use in water-soluble catalysts **6** and **7**. While ruthenium complexes

incorporating **9** and **10** were not produced, precursors **9** and **10** are representative of this strategy of incorporating water-soluble groups onto NHC ligands.



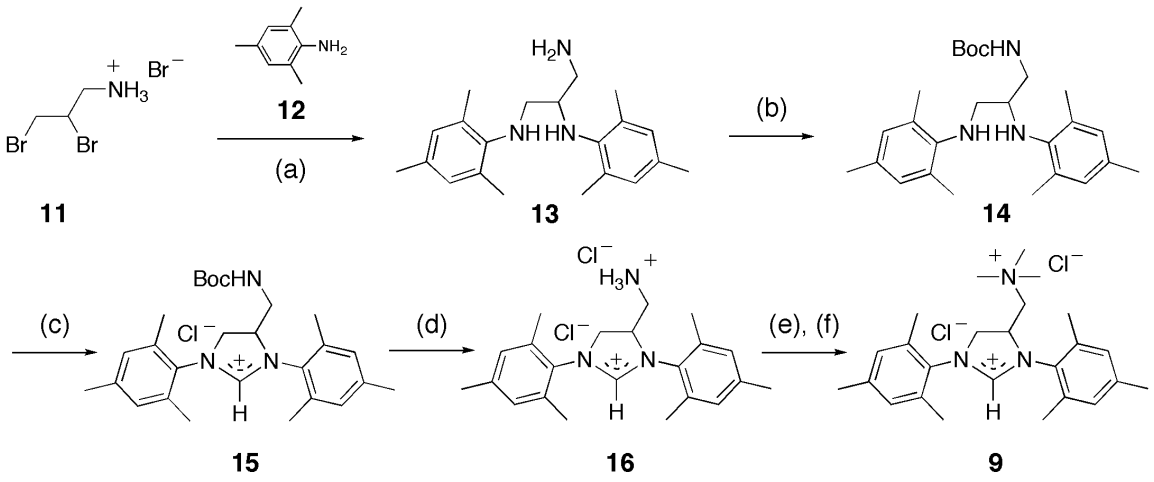
9



10

The synthesis of NHC precursor **9** is presented in Scheme 3.1. The nucleophilic displacement of the bromides of readily-made 2,3-dibromopropane-1-amine hydrobromide (**11**)[28] by 2,4,6-trimethylaniline (**12**) provides triamine **13**. The selective protection of the primary amine of **13** with a *tert*-butyloxycarbonyl (Boc) group provides diamine **14**, which can be readily cyclized with triethylorthoformate to produce Boc-protected imidazolium salt **15**. The Boc deprotection of **15** with hydrochloric acid followed by methylation with iodomethane then yields **9** after anion exchange and desalination.

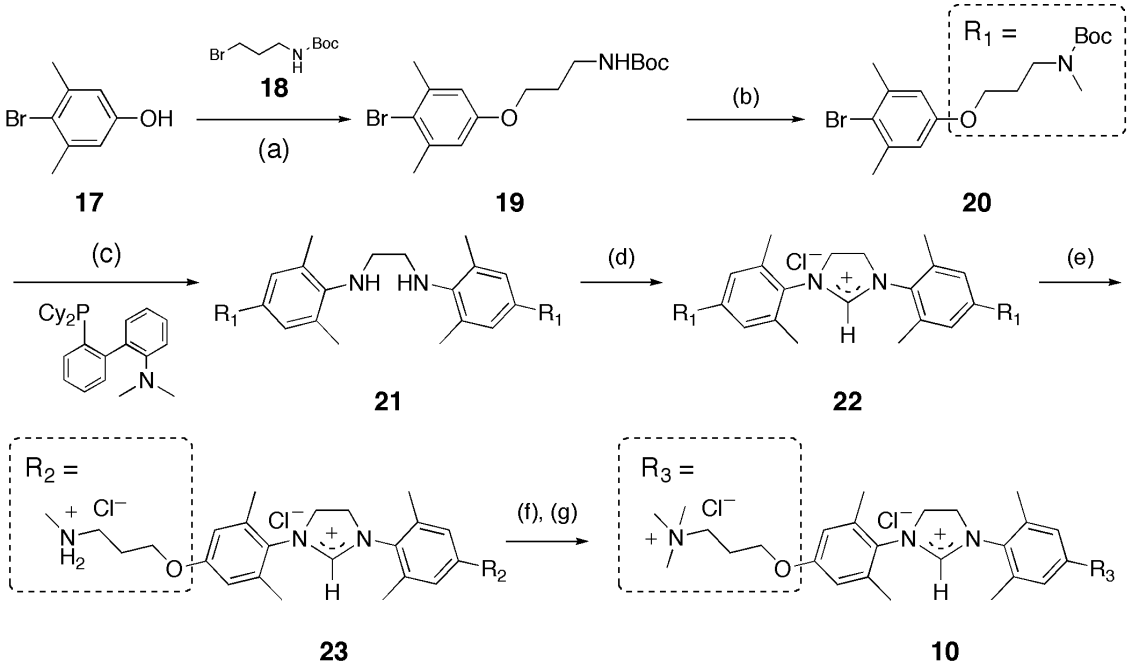
Scheme 3.1.



Reagents and conditions: (a) 120 °C, 19 h (39%), (b) Boc_2O, CH_2Cl_2, rt, 13 h (86%), (c) $HC(OEt)_3$, 120 °C, 16 h (90%), (d) HCl (aq), MeOH, rt, 30 min (88%), (e) MeI, K_2CO_3, MeOH, 70 °C, 32 h, (f) HCl (aq), MeOH, rt, 2 h (64%, 2 steps).

The synthesis of NHC precursor **10** is more involved than the synthesis of **9** (Scheme 3.2). The alkylation of commercially available 4-bromo-3,5-dimethylphenol (**17**) with readily made *tert*-butyl 3-bromopropylcarbamate (**18**)[29] provides aryl ether **19**. As palladium will couple aryl bromides to carbamate nitrogens,[30-32] **19**'s carbamate nitrogen must be methylated with iodomethane prior to the challenging palladium-mediated coupling reaction with ethylene diamine to yield product diamine **21**.[33] Cyclization with triethylorthoformate followed by Boc deprotection with hydrochloric acid provides imidazolium salt **23**, which can be methylated with iodomethane to produce **10** after ion exchange and desalination.

Scheme 3.2.



Reagents and conditions: (a) K_2CO_3, MeCN, 90 °C, 72 h (56%), (b) MeI, NaH, THF, reflux, 6 h (79%), (c) ethylene diamine, $Pd_2(dba)_3$, NaO^{t}Bu, toluene, 100 °C, 24 h (31%), (d) $HC(OEt)_3$, NH_4Cl, 120 °C, 16 h (68%), (e) HCl (aq), MeOH 25 °C, 14 h (94%), (f) MeI, K_2CO_3, MeOH, 70 °C, 32 h, (g) HCl (aq), MeOH, rt, 3 h (72%, 2 steps).

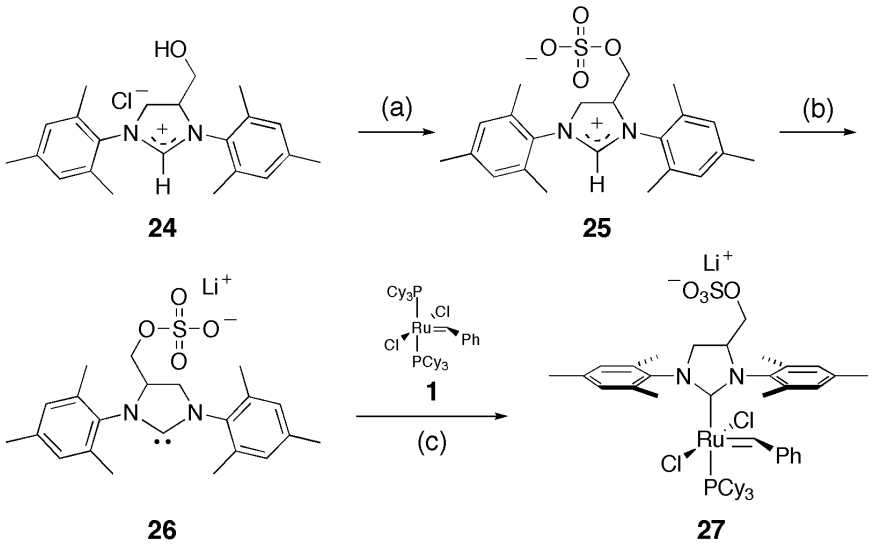
As previously mentioned, neither compound **9** nor **10** were ever used to generate a water-soluble olefin metathesis catalyst. The formation of the free carbene from precursor **9** failed due to the decomposition of **9** upon treatment with base, and the low-yielding, expensive multi-step synthesis of **10** limited its production. A new synthetic route to **10** was required for it to provide useful amounts of an NHC ligand. However, this was abandoned in favor of other projects and more promising leads. While neither **9** nor **10** led to water-soluble metathesis catalysts, Boc-protected imidazolium salt **15**, which was produced during the synthesis of **9**, was utilized in future research and was ultimately used to produce a new water-soluble metathesis catalyst (Chapter 5).[34,35]

NHC ligand and metathesis catalyst containing a sulfate group. Imidazolium salt **24**, which presents an alcohol from its backbone, can be readily made following literature procedures.[36] This alcohol provides a synthetic handle for the incorporation of water-soluble functional groups. However, reactions with this alcohol and various acid chlorides, including PEG-acid chloride, met with limited success**.** Pleasingly, the alcohol of **24** reacts smoothly with the sulfur trioxide pyridine complex to provide the zwitterionic NHC precursor **25** (Scheme 3.3), which displays the water-soluble sulfate group.[37]

Complex **25** is a very crystalline solid with a limited solubility in most solvents. Even so, it is readily deprotonated by potassium hexamethyldisilazane in THF to form the soluble carbene. However, the free carbene, **26**, readily accepts a proton from undetermined sources to reform compound **25**, which precipitates from solution. This complicates the synthesis and isolation of ruthenium complex **27**. Fortunately, the use of

the irreversible base, *tert*-butyl lithium and a mild excess of ruthenium complex **1** allow for the isolation of catalyst **27** in a reasonable yield and good purity (Scheme 3.3).

Scheme 3.3.

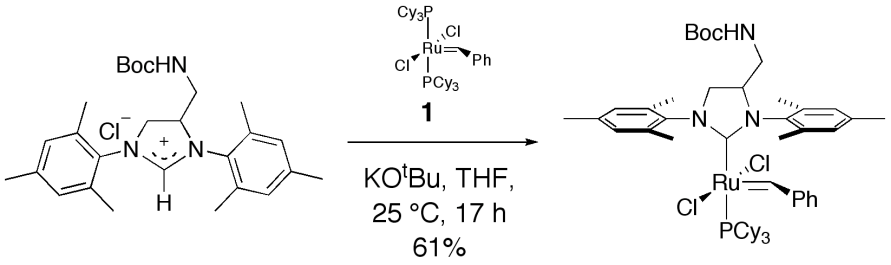


Reagents and conditions: (a) SO_3•Pyr, $CHCl_3$, 25 °C, 6 h (75%), (b) ^{t}BuLi, THF, –78 °C, 25 min, (c) 0 °C – rt, 16 h (69%, 2 steps).

Observation of rotational isomers by NMR spectroscopy. NMR spectroscopy reveals some interesting structural behavior of catalyst **27**. At room temperature, the ^{1}H NMR spectrum of catalyst **27** contains one broad benzylidene proton resonance. This resonance corresponds to two broad phosphorus resonances in the ^{31}P NMR spectrum. The benzylidene proton and phosphorus resonances both separate and sharpen into two distinct peaks when the NMR sample of **27** is heated to 75 °C. Furthermore, three benzylidene resonances are visible in the ^{1}H NMR spectrum of compound **27** when the sample is cooled to –72 °C. Finally, the original NMR spectra are again observed when a heated or cooled sample is returned to room temperature.

This NMR behavior is believed to be a property of ruthenium complexes containing an NHC ligand with an unsymmetrical backbone. To further examine this

hypothesis, imidazolium salt **15** was deprotonated with potassium *tert*-butoxide followed by ligand exchange with ruthenium complex **1** to form complex **28**, which also contains an NHC ligand with an unsymmetrical backbone. As anticipated, the NMR behavior of ruthenium complex **28** is similar to that of complex **27**. This NMR behavior is illustrated in Figure 3.2. For clarity, only the variable temperature spectra of complex **28** are shown.



The NMR behavior of complexes **27** and **28** can be understood by considering the rotation around two different ruthenium-carbon bonds, the NHC carbon-ruthenium bond and the benzylidene carbon-ruthenium bond. If rotation around the NHC carbon-ruthenium bond is slower than the chemical-shift NMR time scale, the ruthenium complex will appear as a mixture of two different rotational isomers by NMR spectroscopy (**A** and **B**, Figure 3.3). In the same way, restricted rotation around the benzylidene carbon-ruthenium bond can also yield a mixture of two different rotational isomers (**A** and **C**, Figure 3.3). Cumulatively, restricted rotation around both bonds produces four different rotational isomers (**A**–**D**, Figure 3.3). At room temperature, rotation around the NHC carbon-ruthenium bond of ruthenium complexes **27** and **28** is slow, which allows isomers **A** and **B** to be observed by NMR spectroscopy. Furthermore, rotation around the benzylidene carbon-ruthenium bond is sufficiently retarded at room temperature to broaden the observed phosphorus and benzylidene proton resonances.

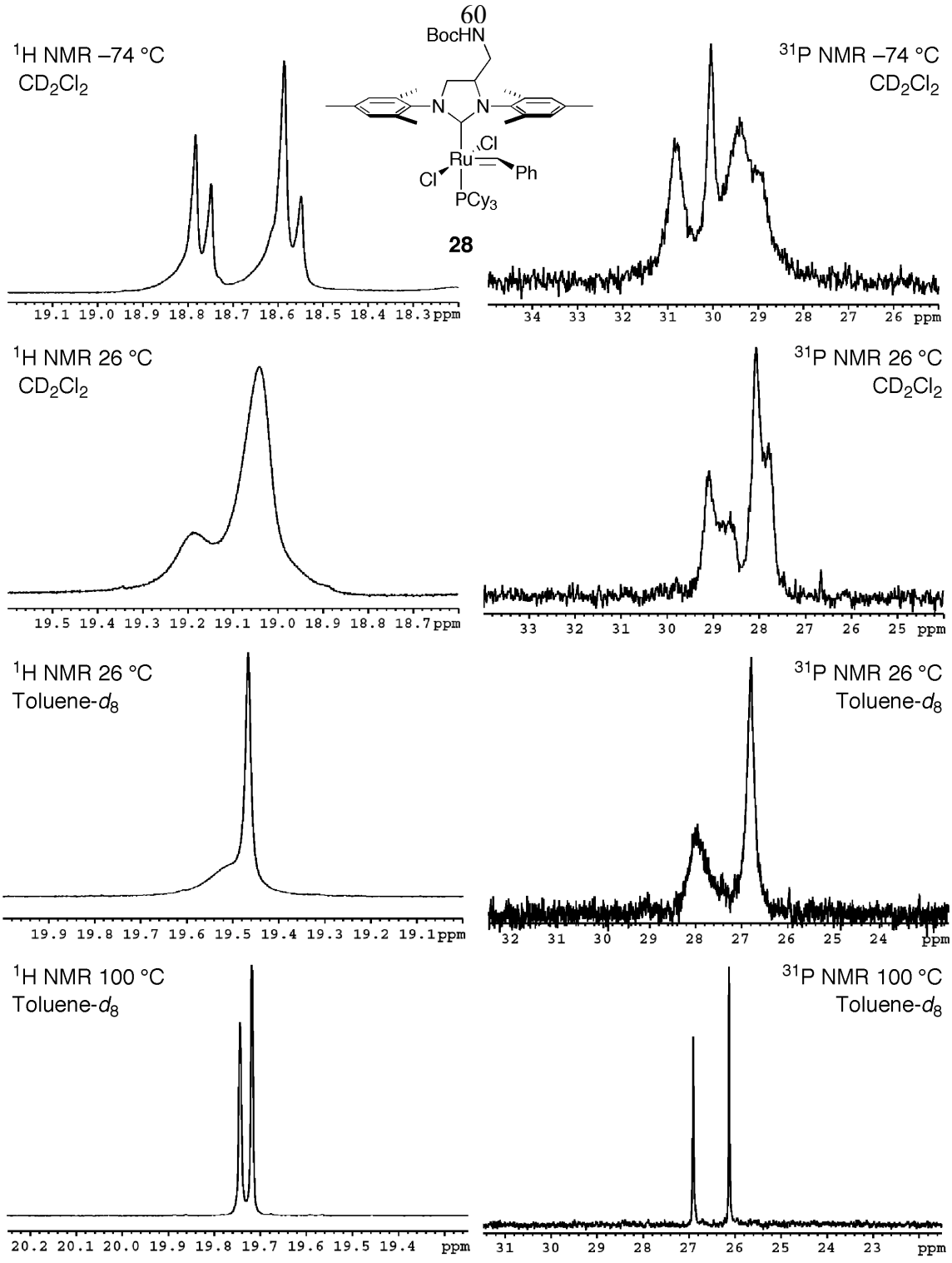


Figure 3.2. The NMR spectra of ruthenium complex **28** show fully reversible, temperature-dependent behavior. For clarity, only the benzylidene proton resonances of the ^{1}H NMR spectra are shown.

Heating the samples allows for free rotation around the benzylidene carbon-ruthenium bond, which causes the benzylidene proton and phosphorus resonances to sharpen. Finally, at low temperatures, rotation around the NHC carbon-ruthenium and benzylidene carbon-ruthenium bonds is sufficiently slow to allow all four rotational isomers of complex **28** to be observed, though only three isomers are observed for complex **27**. Interestingly, free rotation around the NHC carbon-ruthenium bond is not observed even at temperatures as high as 100 °C. This is consistent with earlier results, which show that the half-life for rotation around the NHC carbon-ruthenium bond of parent catalyst **2** is approximately 1.2 seconds at 85 °C.[38]

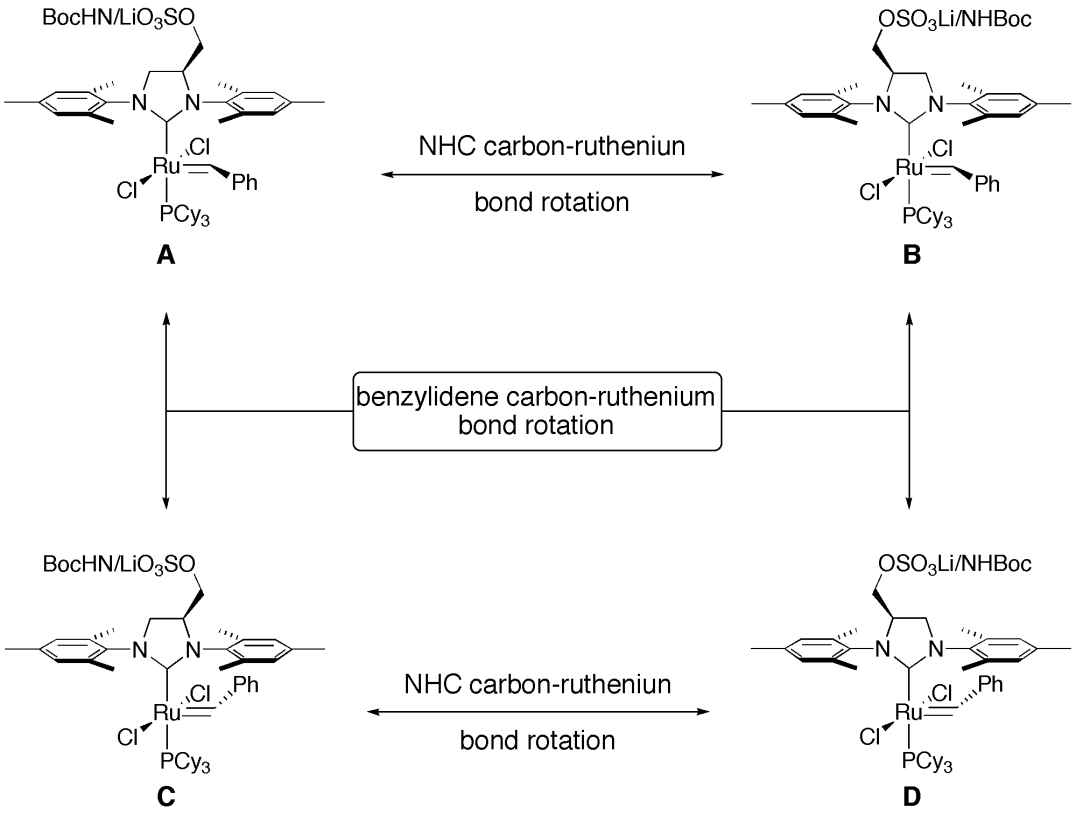


Figure 3.3. Because of the unsymmetrical backbone of their NHC ligands, ruthenium complexes **27** and **28** can exist as four different rotational isomers **A**–**D**.

Solubility and activity of catalyst 27. Catalyst **27** is soluble in such common organic solvents as dichloromethane and THF. While soluble in benzene and toluene, **27** forms aggregates in aromatic solvents as revealed by its ^{1}H NMR spectrum in toluene.[39] While not soluble in water, compound **27** is soluble in the polar protic solvent methanol. This is an improvement over parent catalyst **2**, which is insoluble in polar protic solvents.

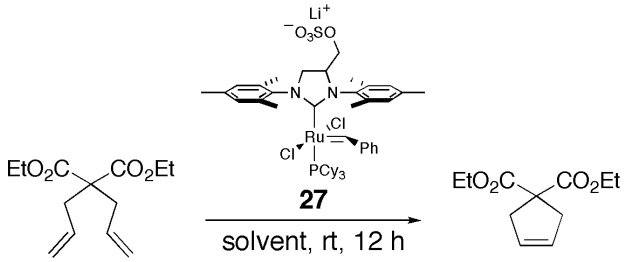


Table 3.1. Ring-closing metathesis of DEDAM in various solvents with catalyst **27**[a]

Solvent[b]	**Conversion (%)**[c]
Dichloromethane	92
Benzene	100
Toluene	94
Methanol	31

[a]Reactions were performed with 5 mol% of **27** and an initial DEDAM concentration of 0.2 M. All conversions represent the average of two trials. [b]All solvents were deuterated, anhydrous and degassed. [c]Conversions were determined by ^{1}H NMR spectroscopy.

The ring-closing metathesis of diethyl diallylmalonate (DEDAM) was used to examine the metathesis activity of catalyst **27** (Table 3.1). Catalyst **27** readily mediates the cyclization of DEDAM in organic solvents to high conversion. Unfortunately, these conversions are typically lower than with parent catalyst **2**.[40,41] Furthermore, the 31% conversion observed for the ring-closing of DEDAM in methanol is mildly less than the 40% conversion observed with catalyst **8** for the same reaction.[14] Interestingly, while initially a heterogenous reaction due to poor catalyst solubility, five mol% of parent catalyst **2** quantitatively ring-closes DEDAM in methanol at 50 °C in 4 hours.

Attempts were made to produce a water-soluble catalyst using complex **27**. Complexes **29**–**31** were all targeted as potentially providing a water-soluble catalyst (Figure 3.4). Unfortunately, complexes **29**–**31** were not produced cleanly. For example, attempts to produce complex **29** gave a mixture of three new benzylidenes complexes, of which none were soluble in water. Also, endeavors to synthesize compounds **30** and **31** yielded product mixtures that were both difficult to purify and insoluble in water.

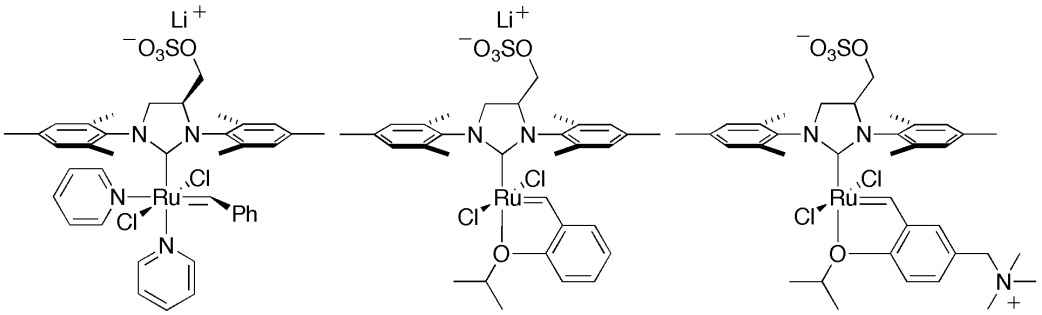
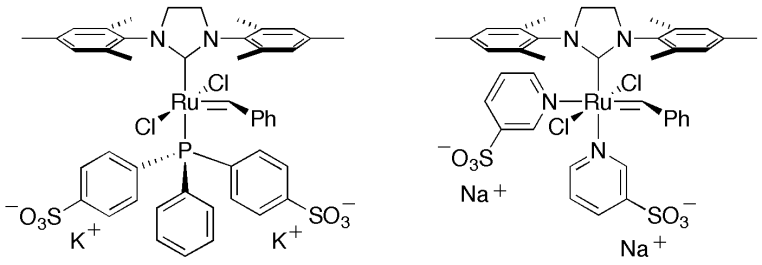


Figure 3.4. Ruthenium complexes **29**–**31** were targeted as potential water-soluble derivatives of catalyst **27**. None of these complexes were ever fully isolated, and the products of their attempted syntheses were not soluble in water.

Strategies involving sulfate-displaying NHC ligand **26** were eventually abandoned. The reasons include the relatively poor metathesis activity of sulfate catalyst **27** and the difficulty in forming water-soluble catalysts from **27**. However, 1-(4-isopropoxy-3-vinylphenyl)-*N*,*N*,*N*-trimethanaminium chloride (**32**), which was originally synthesized for the production complex **31**, was eventually used to produce an active, water-soluble metathesis catalyst (Chapter 5).[34,35]

Strategies involving water-soluble dissociating ligands. Water-soluble functional groups can also be incorporated onto ligands that dissociate during the catalytic cycle of olefin metathesis. Such ligands include phosphine, pyridine, and isopropoxystyrene

ligands. The initial complexes targeted as part of this strategy were compounds **33** and **34**, which contain a water-soluble phosphine and pyridine ligands respectively (Figure 3.5).



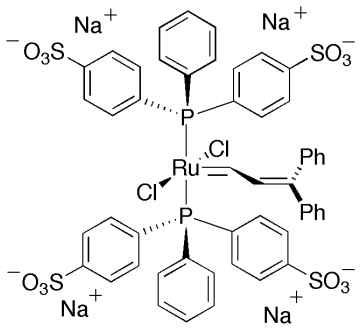
33 **34**

Figure 3.5. Though never isolated, ruthenium complexes **33** and **34** were initial targets for the strategy to incorporate water-soluble groups onto dissociating ligands.

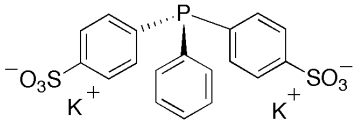
In 1995, Grubbs and co-workers report the synthesis of complex **35** whose triaryl-phosphine ligands display sulfonate groups on the phenyl rings *para* to the phosphorus atom.[42] While complex **35** is not metathesis active, it is soluble in water and prompts the generation of complex **33**. Unfortunately, mixing bis(pyridine) catalyst **5** with commercially available phosphine **36** produces a diverse mixture of products.

Employing water-soluble pyridine ligands to generate an analog of catalyst **5** is a potentially simple manner to produce a water-soluble metathesis catalyst. Bis(pyridine) catalysts are usually readily synthesized by simply mixing catalyst **2** with a heavy excess of the pyridine ligand.[21] Indeed, mixing **2** with an excess of commercially available sodium pyridine-3-sulfonate (**37**) does produce a new benzylidene. However, isolating the product benzylidene from residual pyridine **37** is difficult. This, in combination with the generally lower stability of bis(pyridine) catalysts[21] and the known instability of

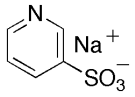
catalysts containing an NHC ligand to the presence of protic solvents and base,[43] led to the pursuit of other strategies to produce a water-soluble metathesis catalyst.



35

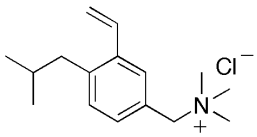


36

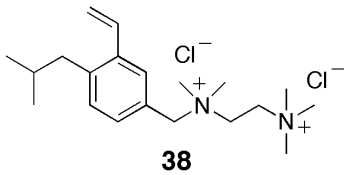


37

The final strategy for incorporating water-soluble groups onto dissociating ligands utilizes isopropoxybenzylidene ligands. Isopropoxystyrene **32**, which contains a single tetraalkyl ammonium chloride salt, is mentioned earlier during the pursuit of complex **31**. Styrene **38**, which displays two tetraalkyl ammonium chloride salts, is the second compound examined as part of this strategy. Pleasingly, both isopropoxystyrenes **32** and **38** can be used to produce water-soluble metathesis catalysts containing an NHC ligand.[34,35] The synthesis of these styrenes and the water-soluble catalysts that they produce are described in Chapter 5.



32



38

Summary

This chapter described initial efforts to synthesize a discrete, water-soluble metathesis catalyst that contains an NHC ligand and displays improved activity over catalyst **8**. Two general strategies pursued to achieve this goal were outlined.

Initial efforts focused on the strategy of including water-soluble functional groups onto the NHC ligand. Research in this area produced NHC precursors **9**, **10**, and **25**, which contain one tetraalkyl ammonium chloride, two tetraalkyl ammonium chloride and a single sulfate group(s) respectively. Though neither compound **9** nor **10** led to a water-soluble catalyst, compound **15** produced during the synthesis of **9** was used in ruthenium complex **28** and in water-soluble catalysts (Chapter 5).[34,35] Ruthenium catalyst **27** was synthesized using NHC precursor **25**. While this catalyst, along with complex **28**, produces interesting NMR spectra, **27** is not soluble in water and shows a lower catalytic activity relative to catalysts **2** and **8** in organic solvents and methanol.

The second strategy to produce the desired metathesis catalyst involved displaying water-soluble groups from phosphine, pyridine and isopropoxystyrene ligands, which are ligands that dissociate during a metathesis reaction. Unfortunately, water-soluble metathesis catalysts incorporating phosphine **36** or pyridine **37**, which display sulfonate salts, were not isolated. However, research into isopropoxystyrenes containing ammonium chloride salts produced isopropoxystyrenes **32** and **38**, which were later used to synthesize active, water-soluble olefin metathesis catalysts (Chapter 5).[34,35]

The work described in this chapter amply demonstrates a common phenomenon in chemical research. Research that fails to deliver the desired result (Chapter 3) can often provide the components for future success (Chapter 5).

Acknowledgements

The author would like to thank Professor Brian Connell for his extensive help and advice during the course of this research. Drs. Dan Sanders, Sebastian Smidt, Jacob Berlin, and Andrew Hejl are also acknowledged for helpful discussions. The author is also grateful to Dr. Scott Ross for his aid with variable temperature NMR spectroscopy and Dr. Mona Shahgholi for mass spectroscopic analysis. The National Institutes of Health (5R01GM068647) is acknowledged for funding.

Experimental

General considerations. All glove-box manipulations were performed in a N_2-filled Vacuum Atmospheres glove box (O_2 < 2.5 ppm). Otherwise reactions run under dry, degassed conditions were performed using standard Schlenk techniques under an atmosphere of dry argon using flame or oven-dried glassware. The variable temperature NMR spectroscopy of compounds **27** and **28** were performed on a Varian Inova 500 (499.85 MHz for ^{1}H; 202.34 MHz for ^{31}P; 125.69 MHz for ^{13}C). All other NMR spectra were recorded on a Varian Mercury 300 (299.817 MHz for ^{1}H, 75.4 MHz for ^{13}C, and 121 MHz for ^{31}P) and reported in parts per millon (ppm) downfield from trimethylsilane as referenced to residual protio solvent peaks. Multiplicity abbreviations used when reporting ^{1}H NMR spectra are: s = singlet, d = doublet, ψt = pseudo-triplet, dd = doublet of doublets, dt = doublet of triplets, q = quartet, p = pentad, m = multiplet, br = broad. All thin-layer chromatography (TLC) of organic compounds was accomplished on silica-gel 60 F254 percoated plates with a fluorescent indicator and visualized by UV light and/or by standard potassium permanganate stains. All flash chromatography of organic compounds was performed with silica-gel 60 (230-400 mesh). Neutral Brockman grade

III alumina was generated by mixing 6% water (by mass) with neutral Brockman grade I alumina (~150 mesh). For anaerobic chromatography, columns are first purged with argon, and all eluant is degassed with a generous argon sparge (at least 30 minutes). Product is then eluted under argon and collected in a round-bottom flask already purged with argon and equipped with a magnetic stir bar while under a stream of argon. Eluant is then removed *in vacuo* (not by rotary evaporation). Desalination was performed on Waters' Sep-Pak Vac 35cc (10g) C18 cartridges.

Materials. All deuterated solvents were purchased from Cambridge Isotope Laboratories. Deuterated dichloromethane, deuterated THF and deuterated DMF were dried over 4 Å molecular sieves, and deuterated methanol was dried over calcium sulfate. Deuterated methanol, deuterated methylene chloride and deuterated THF were degassed by three freeze, pump and thaw cycles while deuterium oxide and deuterated DMF were degassed by a generous argon sparge. Anhydrous methanol was purchased from Aldrich and degassed with a generous argon sparge. All other solvents were purchased from Fischer Scientific. Solvents were dried by passage through purification columns packed with alumina and degassed by a generous argon sparge. All commericial materials were used as obtained. Ruthenium complexes **1** and **2** were gifts from Materia. 2,4,6-trimethylaniline (**12**), di-*tert*-butyl dicarbonate, 4-dimethylamino pyridine (DMAP), triethylorthoformate, 4-bromo-3,5-dimethylphenol (**17**), iodomethane, 60% sodium hydride (suspended in mineral oil), sodium *tert*-butoxide, ethylene diamine, diethyl diallylmalonate, and potassium hexamethyldisilazane were purchased from Aldrich. Tris(dibenzylideneacetone)dipalladium(0), 2-(dicyclohexylphosphino)-2'-(*N*,*N*-

dimethylamino)biphenyl, and bis(*p*-sulfonatophenyl)phenylphosphine dihydrate dipotassium salt were purchased from Strem. Potassium *tert*-butoxide and 1.7 M *tert*-butyl lithium in *n*-pentane were purchased from Alfa Aesar. Potassium carbonate was purchased from JT Baker. Sodium pyridine-3-sulfonate (**37**) was purchased from TCI Americal. Sodium hydroxide, ammonium chloride, concentrated hydrochloric acid, sodium bicarbonate, and sodium chloride were purchased from Malinkrodt, and sodium and magnesium sulfate were purchased from EMS. Compounds **5**,[21] **11**,[28] **18**,[29] 2,3-bis(mesitylamino)propan-1-ol,[36] and $Cl_2Ru(=CH\text{-}o\text{-}O\text{-}i\text{-}PrC_6H_4)PPh_3$[44] were made following literature procedures. The synthesis of isopropoxystyrenes **32** and **38** are described in Chapter 5.[34]

N,N'-Dimesitylpropane-1,2,3-triamine (13). A round-bottom flask, equipped with a stir bar, was charged with 2,3-dibromopropane-1-amminium bromide (**11**) (5.00 g, 17 mmol) and 2,4,6-trimethylaniline (**12**) (30.5 mL, 217 mmol, 12.9 equiv) and equipped with a condenser. After purging with argon, the flask was heated to 120 °C. The reaction was allowed to continue for 19 hours at 120 °C under a positive argon pressure. Upon reaction completion, this mixture was cooled to room temperature, fully dissolved with diethyl ether and 15% aqueous sodium hydroxide and transferred to a separatory funnel. The organic and aqueous layers were separated, and the organic layer was rinsed with water (1×) and with brine (1×) prior to drying over sodium sulfate. Diethyl ether was removed by rotary evaporation to obtain a brown oil. Short-path distillation for 1.5 hours at 100 °C and 0.1 mmHg was used to remove much of the excess 2,4,6-trimethylaniline. The material was further purified chromatographically on silica-gel 60 (10% methanol in

dichloromethane) to obtain 2.15 g (39%) of product as a brown oil. (Note: Unpurified material is a ~1:1 mixture of product and a fully symmetrical side-product resulting from aziridination followed by ring-opening with 2,4,6-trimethylaniline at the less-hindered carbon.) ^{1}H NMR ($CDCl_3$, ppm): δ 6.81 (s, 4H), 3.45 (p, J = 5.7 Hz, 1H), 3.16 (dd, J = 12 Hz, 5.4 Hz, 1H), 2.92 (dd, J = 4.5 Hz, 1.2 Hz, 2H), 2.88 (dd, J = 12 Hz, 5.7 Hz, 1H), 2.82–2.46 (br, 4H), 2.30 (s, 6H), 2.23 (s, 6H), 2.21 (s, 6H). ^{13}C NMR ($CDCl_3$, ppm): δ 143.8, 142.0, 131.5, 130.9, 130.0, 129.9, 129.6, 129.0, 58.7, 51.6, 45.0, 20.7, 20.7, 19.4, 18.5. HRMS (EI+) *m*/*z* calc for $C_{21}H_{32}N_3$: 326.2596, found 326.2595.

***tert*-Butyl 2,3-bis(mesitylamino)propylcarbamate (14).** A round-bottom flask, equipped with a stir bar and purged with argon, was charged with **13** (4.93 g, 15 mmol), di-*tert*-butyl dicarbonate (3.31 g, 15 mmol, 1 equiv) and degassed (argon sparge), reagent grade dichloromethane (30 mL). The flask was cooled to 0 °C prior to the addition of DMAP (185 mg, 1.5 mmol, 0.1 equiv). The reaction was allowed to continue at 0 °C for 30 minutes prior to warming to room temperature and stirring for an additional 2 hours, all while under a positive argon pressure. The product mixture was transferred to a separatory funnel and rinsed with water (2×) and with brine (2×). The organic layer was dried over sodium sulfate, and the dichloromethane was removed by rotary evaporation. Purification by chromatography on silica-gel 60 (15% ethyl acetate in hexanes) yields 5.57 g (86%) of product as a white powder. ^{1}H NMR ($CDCl_3$, ppm): δ 6.85 (s, 2H), 6.83 (s, 2H), 5.04 (s, 1H), 3.53–3.23 (br m, 5H), 3.14 (dd, J = 12 Hz, 5.7 Hz, 1H), 2.90 (dd, J = 12 Hz, 4.5 Hz, 1H), 2.29 (s, 6H), 2.26 (s, 3H), 2.25 (s, 3H), 2.24 (s, 6H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$, ppm): δ 156.6, 143.7, 141.5, 131.5, 131.2, 130.1, 130.0, 129.6, 129.0,

79.6, 57.2, 50.9, 43.4, 28.6, 20.7, 20.7, 19.2, 18.5. HRMS (FAB+) *m*/*z* calc for $C_{26}H_{40}N_3O_2$: 426.3121, found 426.3107.

5-((*tert*-Butoxycarbonylamino)methyl)-1,3-dimesityl-4,5-dihydro-1*H*-imidazol-3-ium chloride (15). A flame-dried round-bottom flask, equipped with a stir bar, was charged with **14** (5.57g, 13 mmol), ammonium chloride (739 mg, 14 mmol, 1.0 equiv), and triethylorthoformate (33 mL, 199 mmol, 15 equiv). The flask was equipped with a condenser and purged with argon prior to heating to 120 °C. The reaction was allowed to continue at 120 °C for 16 hours under a positive argon pressure. After 16 hours, the reaction mixture was cooled to room temperature, and the product precipitated from diethyl ether. The white solid precipitate was isolated by vacuum filtration and rinsed generously with diethyl ether to yield 5.59 g (90%) of product as a white powder. ^{1}H NMR ($CDCl_3$, ppm) : δ 9.34 (s, 1H), 6.82 (s, 4H), 5.29–5.14 (m, 1H), 4.51 (dd, *J* = 12 Hz, 8.3 Hz, 1H), 4.23 (ψt, *J* = 12 Hz, 1H), 3.59–3.44 (m, 1H), 3.17–3.06 (m, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.26 (s, 3H), 2.19 (s, 9H), 1.29 (s, 9H). ^{13}C NMR ($CDCl_3$, ppm): δ 159.6, 156.6, 140.3, 140.0, 135.1, 135.0, 130.5, 130.2, 130.1, 129.8, 129.0, 79.3, 62.5, 55.3, 41.4, 28.4, 21.1, 21.0, 18.9, 18.5, 18.2, 17.8. HRMS (FAB+) *m*/*z* calc for $C_{27}H_{38}N_3O_2$: 436.2964, found 436.2977.

5-(ammoniomethyl)-1,3-dimesityl-4,5-dihydro-1*H*-imidazol-3-ium chloride (16). A solution of compound **15** (440 mg, 0.93 mmole) in methanol (3.6 mL) was cooled to 0 °C. To this solution was added concentrated hydrochloric acid (1.2 mL). The reaction was stirred at 0 °C for 10 minutes prior to warming to warm to room temperature. The

reaction was allowed to continue an additional 20 minutes at room temperature before removing the volatiles by rotary evaporation. The product was dried extensively under high vacuum to obtain 336 mg (88%) of an off-white solid. ^{1}H NMR (DMSO-d_6, ppm): δ 9.29 (s, 1H), 9.00 (s, 3H), 7.13 (s, 2H), 7.10 (s, 2H), 5.51–5.37 (m, 1H), 4.90–4.83 (m, 1H), 4.69 (ψt, J = 12 Hz, 1H), 3.58–3.51 (m, 1H), (ψd, J = 10 Hz, 1H), 2.43–2.22 (m, 18H). ^{13}C NMR (DMSO-d_6, ppm): δ 160.6, 139.9, 136.0, 135.7, 135.4, 130.5, 130.2, 129.7, 129.6, 128.6, 60.0, 55.0, 20.6, 20.6, 18.1, 17.9, 17.6, 17.2. HRMS (FAB+): m/z calc for $C_{22}H_{30}N_3$: 336.2440, found 336.2452.

1,3-dimesityl-5-((trimethylammonio)methyl)-4,5-dihydro-1*H*-imidazol-3-ium chloride (9). A flame-dried round-bottom flask, purged with argon and equipped with a stir bar and a condenser, was charged with compound **16** (188 mg, 0.46 mmol), potassium carbonate (128 mg, 0.92 mmol, 2.0 equiv), iodomethane (0.16 mL, 2.6 mmol, 5.0 equiv), and of dry, degassed methanol (2.3 mL). The reaction was heated to 70 °C and allowed to continue under an atmosphere of argon. After 22 hours, additional potassium carbonate (129 mg, 0.93 mmol, 2.0 equiv) and iodomethane (0.16 mL, 2.6 mmol, 5.0 equiv) were added. The reaction was stirred for an additional 10 hours prior to cooling to room temperature and removing the volatiles by rotary evaporation. Methanol (23 mL) was added to the crude material, and the solution was cooled to 0 °C before adding concentrated hydrochloric acid (7.6 mL, 92 mmol, 200 equiv). The solution was stirred at 0 °C for 20 minutes then at room temperature for 1 hour. The product mixture was passed through a plug of celite, and the volatiles were removed by rotary evaporation. The product was again dissolved in methanol and passed through a plug of

celite. After removing the volatiles by rotary evaporation, the product was dissolved in minimal methanol and precipitated into dietyl ether (~200 mL), and the solid product was collected by vacuum filtration. Desalination was accomplished by loading the product onto a Waters' Sep-Pak Vac 35 cc (10g) C18 cartridge with water (using minimal methanol as required), repeatedly flushing the column with water (4×) and eluting the product with acetonitrile. Removing the volatiles by rotary evaporation yields 133 mg (64%) of a slightly yellow, solid product. ^{1}H NMR (DMSO-d_6, ppm): δ 9.15 (s, 1H), 7.16 (d, J = 3.0 Hz, 2H), 7.12 (s, 2H), 5.71 (q, J = 10 Hz, 1 H), 4.99 (ψt, J = 12 Hz, 1H), 4.75–4.53 (m, 3H), 3.17 (s, 9H), 2.41 (s, 8H), 2.34–2.26 (m, 10H). ^{13}C NMR (DMSO-d_6, ppm): δ 160.9, 140.2, 140.1, 136.6, 135.8, 135.7, 135.1, 130.2, 130,1, 129.5, 127.9, 63.4, 57.9, 56.7, 52.8, 20.7, 20.6, 18.3, 18.2, 17.7, 17.6. Compound decomposes (eliminates trimethylamine) during mass-spectral analysis.

***tert*-Butyl 3-(4-bromo-3,5-dimethylphenoxy)propylcarbamate (19).** A round-bottom flask, equipped with a stir bar and a condenser, was charged with compound **17** (754 mg, 3.8 mmol), compound **18** (1.07 g, 4.5 mmol, 1.2 equiv), potassium carbonate (543 mg, 3.9 mmol, 1.0 equiv), and acetonitrile (7.5 mL). The reaction was allowed to continue for 3 days at 95 °C. After cooling to room temperature, the product mixture was diluted with diethyl ether and rinsed with a saturated solution of sodium bicarbonate in water (1×), water (1×), and brine (1×). The diethyl ether layer was collected, dried over sodium sulfate, and concentrated to dryness by rotary evaporation. The crude material was eluted from a flash column with 20% ethyl acetate in hexanes, and the material was then dissolved in diethyl ether and rinsed with a 15% solution of sodium hydroxide in water

(5x). The diethyl ether layer was dried over magnesium sulfate and concentrated to dryness by rotary evaporation. Drying the material under high vacuum yields 742 mg (56%) of product as a white solid. ^{1}H NMR ($CDCl_3$ (w/TMS), ppm): δ 6.64 (s, 2H), 4.80 (br s, 1H), 3.97 (t, J = 6.0 Hz , 2H), 3.31 (q, J = 6.3 Hz, 2H), 2.38 (s, 6H), 1.96 (p, J = 6.3 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$ (w/TMS), ppm): δ 157.4, 156.2, 139.3, 118.5, 114.6, 79.4, 66.0, 38.1, 29.7, 28.6, 24.2. HRMS (FAB+): *m*/*z* calc for $C_{16}H_{24}NO_3Br$: 359.0919, found 359.0912.

***tert*-Butyl 3-(4-bromo-3,5-dimethylphenoxy)propylmethylcarbamate (20).** A flame-dried round-bottom flask, equipped with a stir bar and purged with argon, was charged with compound **19** (578 mg, 1.6 mmol), iodomethane (1 mL, 16 mmol, 10 equiv), and dry, degassed THF (8.1 mL) and cooled to 0 °C. Sodium hydride (60% in mineral oil, 202 mg, 5.0 mmol, 3.1 equiv) was added, and the reaction was allowed to continue at 0 °C for 40 minutes under a positive argon pressure. The flask was then equipped with a flame-dried condenser and refluxed (75 °C) 22 hours under a positive argon pressure. The reaction was then cooled to room temperature before quenching with excess water, transferred to a separatory funnel and extracted with dichloromethane (3×). The combined dichloromethane extracts were rinsed with brine (1×) and dried over sodium sulfate before removing the volatiles by rotary evaporation. Eluting the crude material from a flash column with 15% ethyl acetate in hexane yields 474 mg (79%) of pure product as a clear oil. ^{1}H NMR ($CDCl_3$, ppm): δ 6.63 (s, 2H), 3.92 (t, J = 6.0 Hz, 2H), 3.39 (t, J = 6.9 Hz, 2H), 2.87 (s, 3H), 2.37 (s, 6H), 2.04–1.92 (m, 2H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, ppm): δ 157.5, 156.0, 139.2, 118.3, 114.5, 79.5, 65.8 and 65.2 (Boc

rotamers), 46.0, 34.7, 28.6, 28.0 and 27.8 (Boc rotamers), 24.2. HRMS (FAB+): *m*/*z* calc for $C_{17}H_{27}NO_3Br$: 372.1174, found 372.1189.

***tert*-Butyl 3,3'-(4,4'-(ethane-1,2-diylbis(azanediyl))bis(3,5-dimethyl-4,1-phenylene))bis(oxy)bis(propane-3,1-diyl)bis(methylcarbamate) (21).** In a N_2-filled glove box, tris(dibenzylideneacetone)dipalladium(0) (14.1 mg, 0.015 mmol, 0.10 equiv), 2-(dicyclohexylphosphino)-2'-(*N*,*N*-dimethylamino)biphenyl (10.0 mg, 0.025 mmol, 0.17 equiv), and sodium *tert*-butoxide (42.0 mg, 0.44 mmol, 2.9 equiv) were weighed into a flame-dried Schlenk flask, which was equipped with a stir bar. The flask was sealed with a septum, removed from the box and brought under argon. Compound **20** (111 mg, 0.30 mmol, 2.0 equiv) was added as a solution in dry, degassed toluene (0.1 mL). To this mixture was added ethylene diamine (0.01 mL, 0.15 mmol) and dry, degassed toluene (0.5 mL). The septum was replaced by a ground glass stopper, and the flask was sealed and heated to 100 °C. The reaction was stirred at 100 °C for 24 hours. The dark green reaction mixture was cooled to room temperature, diluted with diethyl ether, and passed through a celite plug. Removal of the volatiles by rotary evaporation and purification by flash chromatography with 40% ethyl acetate in hexane yields 30.2 mg (31%) of product as an oil. ^{1}H NMR ($CDCl_3$ (w/TMS), ppm): δ 6.56 (s, 4H), 3.92 (t, J = 6.0 Hz, 4H), 3.39 (t, J = 6.9 Hz, 4H), 3.21–3.06 (br, 2H), 3.08 (s, 4H), 2.88 (s, 6H), 2.30 (s, 12H), 2.04–1.91 (m, 4H), 1.45 (s, 18H). ^{13}C NMR ($CDCl_3$ (w/TMS), ppm): δ 156.0, 154.2, 139.4, 132.0, 114.7, 79.5, 65.7 and 65.3 (Boc rotamers), 49.6, 46.1, 34.7, 28.6, 28.3 and 27.9 (Boc rotamers), 18.8. HRMS (FAB+): *m*/*z* calc for $C_{36}H_{58}N_4O_6$: 642.4356, found 642.4332.

1,3-Bis(4-(3-(*tert*-butoxycarbonyl(methyl)amino)propoxy)-2,6-dimethylphenyl)-4,5-dihydro-1*H*-imidazol-3-ium chloride (22). A flame-dried round-bottom flask, equipped with a stir bar and a condenser, was charged with compound **21** (1.23 g, 1.9 mmol), triethylorthoformate (4.8 mL, 29 mmol, 15 equiv), and ammonium chloride (109 mg, 2.0 mmol, 1.1 equiv). The reaction mixture was heated to 120 °C and allowed to continue at that temperature for 16 hours under a positive argon pressure. After cooling to room temperature, residual triethylorthoformate was removed *in vacuo*, and the crude material was purified by elution from a flash column with 11% methanol in dichloromethane to obtain 905 mg (68%) of product solid. ^{1}H NMR (DMSO-d_6, ppm): δ 9.00 (s, 1H), 6.83 (s, 4H), 4.41 (s, 4H), 3.96 (t, J = 6.0 Hz, 4H), 3.31 (t, J = 6.6 Hz, 4H), 2.78 (br s, 6H), 2.35 (s, 12H), 1.90 (p, J = 6.3 Hz, 4H), 1.36 (s, 18H). ^{13}C NMR (DMSO-d_6, ppm): δ 160.7, 159.0, 154.8, 137.2, 126.2, 114.4, 78.4, 65.5 and 65.2 (Boc rotamers), 51.0, 45.2, 34.1, 28.0, 27.2 and 27.0 (Boc rotamers), 17.5. HRMS (ESI+): m/z calc for $C_{37}H_{57}N_4O_6$: 653.4278, found 653.4281.

1,3-Bis(2,6-dimethyl-4-(3-(methylammonio)propoxy)phenyl)-4,5-dihydro-1*H*-imidazol-3-ium trichloride (23). A 1-dram vial, equipped with a stir bar, was charged with compound **22** (249 mg, 0.36 mmol) and a solution of concentrated hydrochloric acid in methanol (3 M HCl, 1.2 mL, 3.6 mmol, 10 equiv). The reaction was stirred at room temperature for 14 hours before removing the volatiles by rotary evaporation. Dissolving the crude material in minimal methanol and precipitation from acetone (~176 mL) yields an yellow-orange precipitate after incubation in the freezer (~14 hours). Isolation of the

precipitate yields 190 mg (94%) of a yellow-orange, solid product. ^{1}H NMR (DMSO-d_6, ppm): δ 9.46 (br s, 4H), 9.02 (s, 1H), 6.86 (s, 4H), 4.41 (s, 4H), 4.33 (br s, 4H), 4.11 (br s, 4H), 2.97 (br s, 6H), 2.35 (s, 12H), 2.10 (br s, 4H). ^{13}C NMR (DMSO-d_6, ppm): δ 160.7, 158.7, 137.3, 126.4, 114.5, 65.1, 51.0, 45.3, 32.3, 25.3, 17.6. HRMS (FAB+): *m*/*z* calc for $C_{27}H_{41}N_4O_2$: 453.3229, found 453.3241.

1,3-Bis(2,6-dimethyl-4-(3-(trimethylammonio)propoxy)phenyl)-4,5-dihydro-1*H*-imidazol-3-ium trichloride (10). A flame-dried round-bottom flask, equipped with a stir bar and a condenser and purged with argon, was charged with compound **23** (340 mg, 0.60 mmol), methanol (3 mL), iodomethane (0.38 mL, 6.0 mmol, 10 equiv), and potassium carbonate (337 mg, 2.44 mmol, 4.0 equiv). The reaction mixture was heated to 70 °C and stirred for 22 hours under an atmosphere of argon. Additional iodomethane (0.38 mL, 6.0 mmol, 10 equiv) and potassium carbonate (336 mg, 2.4 mmol, 4.0 equiv) were added, and the reaction was allowed to continue for an additional 10 hours at 70 °C under an atmosphere of argon. Upon cooling the reaction mixture to room temperature, the volatiles were removed by rotary evaporation. The product mixture was dissolved in methanol (46 mL) and cooled to 0 °C. Concentrated hydrochloric acid (15 mL) was added drop-wise, and the reaction was stirred at 0 °C for 10 minutes before heating to room temperature and stirring for an additional 3 hours. The product mixture was passed through a plug of celite, and the volatiles were removed by rotary evaporation. The material was dissolved in ethanol (15 mL) prior to the addition of acetone (~210 mL). The produced suspension was placed in the freezer for 1 hour before removing the precipitate by vacuum filtration through a fine frit. The filtrate was collected and

concentrated to dryness by rotary evaporation. Desalination was accomplished by loading the material onto a Waters' Sep-Pak Vac 35 cc (10g) C18 cartridge with methanol and repeatedly flushing the column with water (4×). Product was eluted with acetonitrile to obtain 255 mg (72%) of a yellow-orange solid. ^{1}H NMR (DMSO-d_6, ppm): δ 8.96 (s, 1H), 6.87 (s, 4H), 4.43 (s, 4H), 4.08 (t, J = 6.0 Hz, 4H), 3.53–3.44 (m, 4H), 3.12 (s, 18H), 2.36 (s, 12H), 2.24–2.12 (m, 4H). ^{13}C NMR (DMSO-d_6, ppm): δ 160.6, 158.6, 137.3, 126.5, 114.5, 65.1, 62.8, 52.3, 51.1, 22.5, 17.6.

5-(hydroxymethyl)-1,3-dimesityl-4,5-dihydro-1*H*-imidazol-3-ium chloride (24). Compound **24** was synthesized following a slight modification of literature procedures.[36] A flame-dried round-bottom flask, equipped with a stir bar and a condenser, was charged with 2,3-bis(mesitylamino)propan-1-ol (28.4 g, 71 mmol),[36] ammonium chloride (4.00 g, 75 mmol, 1.0 equiv) and triethylorthoformate (142 mL, 855 mmol, 12 equiv). The reaction was heated to 120 °C and allowed to continue for 10 hours at that temperature under a positive argon pressure. Upon cooling to room temperature, the precipitate was isolated by vacuum filtration and rinsed with excess hexanes and diethyl ether. The trimethylsilane-protected product was dissolved in methanol (~210 mL), and concentrated hydrochloric acid (18 mL, ~3 equiv) was added. The deprotection reaction was stirred for 30 minutes before removing the volatiles by rotary evaporation. The crude material was purified by flash chromatography with 10% methanol in dichloromethane to obtain 20.2 g (76%) of product as a white solid. ^{1}H NMR (DMSO-d_6, ppm): δ 9.14 (s, 1H), 7.07 (s, 4H), 6.16 (ψt, J = 5.1 Hz, 1H), 4.98–4.87 (m, 1H), 4.61–4.43 (m, 2H), 3.61–3.51 (m, 1H), 3.41–3.29 (m, 1H), 2.53–2.21 (m, 18H). ^{13}C NMR (DMSO-d_6, ppm): δ

160.1, 139.6, 139.2, 136.6, 135.8, 135.4, 135.3, 131.1, 129.7, 129.4, 129.3, 64.7, 58.0, 51.7, 20.6, 20.5, 17.9, 17.4, 17.2. HRMS (FAB+): *m*/*z* calc for $C_{22}H_{29}N_2O$: 337.2280, found 337.2270.

(1,3-dimesityl-4,5-dihydro-1*H*-imidazol-3-ium-5-yl)methyl sulfate (25).[37] A flame-dried round-bottom flask, equipped with a stir bar and purged with argon, was charged with compound **24** (3.00 g, 8.0 mmol), sulfur trioxide pyridine complex (6.41 g, 40 mmol, 5.0 equiv) and chloroform (161 mL). The reaction was allowed to continue for 6 hours at room temperature under a positive argon pressure. The volatiles were removed by rotary evaporation, and the material was dissolved in methanol (~161 mL) and stirred for ~14 hours at room temperature. Concentrating the mixture to dryness by rotary evaporation produces a yellow oil, which solidifies over time. The crude product was purified by flash chromatography with 4% methanol in dichloromethane to obtain 2.51 g (75%) of a white solid. ^{1}H NMR (DMF-d_7, 70 °C, referenced to DMF's aldehyde proton, ppm): δ 9.08 (s, 1H), 7.10 (s, 4H), 5.36–5.25 (m, 1H), 4.78 (ψt, J = 12 Hz, 1H), 4.70–4.61 (m, 1H), 4.11 (dd, J_{dd} = 12 Hz, J_d = 2.7 Hz, 1H), 3.83 (dd, J_{dd} = 12 Hz, J_d = 2.3 Hz, 1H), 2.60–2.25 (m, 18H). ^{13}C NMR (DMF-d_7, 70 °C, referenced to DMF's aldehyde carbon, ppm): δ 161.9, 141.2, 140.9, 138.2, 136.7, 132.4, 131.1, 131,0, 130.8, 130.6, 64.9, 63.9, 53.6, 21.3, 21.3, 18.6. HRMS (FAB+): *m*/*z* calc for $C_{22}H_{29}N_2O_4S$: 417.1848, found 417.1849.

Ruthenium complex 27. In a N_2-filled glove box, a 20 mL vial, equipped with a stir bar, was charged with compound **25** (140 mg, 0.34 mmol) and dry, degassed THF (9 mL).

Also in the glove box, ruthenium complex **1** (304 mg, 0.37 mmol, 1.1 equiv) was weighed into a flame-dried round-bottom flask equipped with a stir bar. The vial was sealed with a septa-cap and the flask with a septum, and both vessels were removed from the glove box. The seals of both vessels were reinforced with Teflon tape, and they were brought under a positive argon pressure. The *tert*-butyl lithium solution in *n*-pentane was prepared by passing 1.7 M *tert*-butyl lithium in *n*-pentane (2.5 mL) through an oven-dried micro-filter into a flame-dried 20 mL vial that was sealed with a septa-cap and purged with argon. The actual concentration of the *tert*-butyl lithium solution was determined by titrating the filtered solution against recrystalized 2,6-di-*tert*-butyl-4-methylphenol (BHT) (202 mg) in dry, degassed THF (2 mL) at –78 °C with fluorene as an indicator. (Note: *tert*-Butyl lithium in *n*-pentane is pyrophoric. Handle with care under inert conditions. Be careful to know how to quench any residual *tert*-butly lithium solution prior to running this reaction.) The filtered *tert*-butyl lithium solution (1.4 M, 0.25 mL, 0.35 mmol, 1.0 equiv) was added to the vial containing the solution of compound **25** in THF at –78°C. This mixture was stirred at –78 °C for 20 minutes under a positive argon pressure to form NHC ligand **26**. This solution was transferred to the flask containing complex **1,** precooled to 0 °C, using a cannula. The reaction mixture was stirred at 0 °C for 20 minutes before warming to room temperature. The reaction was allowed to continue at room temperature for 16 hours. Using standard Schlenk techniques, the crude material was passed through a flame-dried fine frit into a flame-dried round-bottom flask under a positive argon pressure. Dry, degassed THF rinses were used to ensure quantitative transfer, and the THF was removed *in vacuo*. Degassed *n*-pentane (270 mL), pre-cooled to 0 °C, was added to the product solid, and the suspension was stirred at 0 °C for 30

minutes. Isolating the precipitate by vacuum filtration and drying under high vacuum provides 225 mg (69%) of a maroon, solid product. As described above, NMR characterization of complex **27** is complicated by restricted rotation around the NHC carbon-ruthenium bond, which yields broad peaks. Therefore, only peak locations and multiplicities are provided. ^{1}H and $^{31}P\{^{1}H\}$ NMR spectra are provided in Appendix 1. ^{1}H NMR (CD_2Cl_2, ppm): δ 19.1 (s), 8.91 (s), 7.72–6.37 (m), 5.73 (s), 4.74–3.38 (m), 3.01–0.56 (m). $^{31}P\{^{1}H\}$ NMR (CD_2Cl_2, ppm): δ 29.6, 29.2.

Ruthenium complex 28. In an N_2-filled glove box, a 20 mL vial, equipped with a stir bar, was charged with compound **15** (693 mg, 1.45 mmol, 1.2 equiv), potassium *tert*-butoxide (95%, 172 mg, 1.46 mmol, 1.2 equiv), and dry, degassed THF (12 mL). The suspension was stirred for 10 minutes at room temperature over which time a yellow solution forms. This solution was transferred to a round-bottom flask and charged with ruthenium complex **1** (1.0g, 1.21 mmol). Additional THF (12 mL) was added to the reaction mixture; the flask was capped with a septum, and the reaction was stirred for 17 hours at room temperature. Upon reaction completion, the reaction flask was removed from the glove box, and the THF was removed *in vacuo*. The crude product was purified by anaerobic chromatography (as previously described in the General considerations section) on TSI silica gel-60 with 25% diethyl ether in *n*-pentane, though the product was loaded with degassed benzene. The product was lyophilized from degassed benzene and extensively dried under high vacuum (~24 hours) at 45 °C to obtain 721 mg (61%) of a fine, magenta powder. (Note: Product is air-sensitive in solution. Performing product collection and eluant removal under aerobic conditions yields product contaminated with

a small amount of tricyclohexylphosphine oxide.) As described above, NMR characterization of **28** is complicated by restricted rotation around the NHC carbon-ruthenium bond yielding broad peaks. Therefore, only peak locations and multiplicities are provided. ^{1}H and $^{31}P\{^{1}H\}$ NMR spectra are provided in Appendix 1. ^{1}H NMR (CD_2Cl_2, 40 °C, ppm): δ 19.23–19.11 (s with broad shoulder), 7.38 (ψt, J = 7.4 Hz), 7.11 (ψt, J = 7.6 Hz), 7.04 (s), 7.01 (s), 5.05–4.80 (br), 4.40–4.22 (br), 4.10 (ψt, J = 11 Hz), 3.97 (ψt, J = 11 Hz), 3.82–3.61 (m), 3.44–3.07 (m), 2.88–2.05 (m), 1.90 (s), 1.65–1.20 (m), 1.16–0.73 (m). $^{31}P\{^{1}H\}$ NMR (CD_2Cl_2, 40 °C, ppm): δ 29.4, 28.5. HRMS (FAB+) *m*/*z* calc for $C_{52}H_{76}N_3O_2Cl_2PRu$: 977.4096, found 977.4143.

General procedure for ring-closing metathesis reactions with catalyst 27. In a N_2-filled glove box, a 1-dram vial was charged with catalyst **27** (8.6 mg, 0.0086 mmol, 0.050 equiv) and deuterated solvent (0.5 mL). This vial and a screw-cap NMR tube were sealed with septa-caps and removed from the glove box. The seals of both the vial and the NMR tube were reinforced with Teflon tape, and both vessels were brought under a positive pressure of argon. DEDAM (42 μl, 0.17 mmol) was added to the vial containing **27**, and the reaction mixture was transferred to the screw-cap NMR tube by syringe. The reaction was allowed to continue for 12 hours at room temperature before determining its conversion by ^{1}H NMR spectroscopy. All reported conversions are the average of two trials.

Attempt to synthesize ruthenium complex 29. An oven-dried 20 mL vial, equipped with a stir bar and charged with ruthenium complex **27** (196 mg, 0.20 mmol), was

brought into an N_2-filled glove box. Dry, degassed dichloromethane (0.66 mL) and dry, degassed pyridine (0.66 mL, 8.2 mmol, 40 equiv) were added to the vial, and the reaction was stirred at ambient temperature for 15 minutes. The reaction mixture was transferred, drop-wise, to a flame-dried round-bottom flask, which contained ~50 mL of dry, degassed *n*-pentane and a stir bar. The flask was capped with a septum, removed from the glove box and brought under a positive argon pressure. The suspension of green, precipitated product in *n*-pentane was stirred at room temperature for 30 minutes prior to isolating the product by vacuum filtration. This material was dried under vacuum to obtain 166 mg of a green, solid product as a mixture of compounds. ^{1}H NMR (CD_2Cl_2, benzylidene proton resonances, ppm): δ 19.0 (s, relative integration: 2.5), 17.9 (s, relative integration: 1.0), 17.5 (s, relative integration 3.2). The ^{31}P NMR spectrum indicated the absence of any phosphorus-containing compound.

Attempt to synthesize ruthenium complex 30. In an N_2-filled glove box, a 1-dram vial, equipped with a stir bar, was charged with $Cl_2Ru(=CH\text{-}o\text{-}O\text{-}i\text{-}PrC_6H_4)PPh_3$[44] (19.2 mg, 0.033 mmol), complex **25** (21.0 mg, 0.050 mmol, 1.5 equiv), potassium hexamethyldisilazane (95%, 10.7 mg, 0.051 mmol, 1.5 equiv), and dry, degassed THF (1 mL). The reaction was allowed to continue at room temperature for 6 hours before. Upon reaction completion, the product mixture was passed through a fine frit and precipitated into diethyl ether to obtain a green solid, which was further purified by flash chromatography on TCI silica gel 60 with 10% methanol in dichloromethane. An impure, green solid product was obtained in low yield. ^{1}H NMR (CD_3OD, benzylidene proton

resonance, ppm): δ 16.6 (s). The ^{31}P NMR spectrum indicated the absence of any phosphorus-containing compound.

Attempt to synthesize ruthenium complex 31. In an N_2-filled glove box, a 1-dram vial was charged with ruthenium complex **27** (20.5 mg, 0.021 mmol), compound **32** (5.6 mg, 0.021 mmol, 0.98 equiv), and copper(I)chloride (2.3 mg, 0.023 mmo, 1.1 equiv) and equipped with a stir bar. The vial was sealed with a septa-cap and removed from the glove box. Dry, degassed dichloromethane (0.5 mL) was added to the vial, and its seal was reinforced with Teflon tape. The reaction mixture was heated to 40 °C, and the reaction was allowed to continue at that temperature for 1 hour. After cooling to room temperature, the product mixture was passed through a plug of celite, and the volatiles were removed by rotary evaporation. The crude material was purified chromatographically on neutral, Brockman grade III alumina with 20% methanol in dichloromethane to obtain a somewhat impure green solid product in low yield. ^{1}H NMR (CD_3OD, benzylidene proton resonance, ppm): δ 16.7 (s). The ^{31}P NMR spectrum indicated the absence of any phosphorus-containing compound.

Attempt to synthesize ruthenium complex 33. A flame-dried round-bottom flask, equipped with a stir bar, was charged with ruthenium complex **4** (51.4 mg, 0.071 mmol, 1.0 equiv), bis(*p*-sulfonatophenyl)phenylphosphine dihydrate dipotassium salt (31.5 mg, 0.069 mmol) and dry, degassed DMF (6.9 mL). The reaction was stirred at room temperature for 20 minutes under a positive argon pressure. The DMF was then removed *in vacuo* at an elevated temperature (40–60 °C). The product was then dissolved in

methanol and precipitated into diethyl ether. The precipitate was isolated by vacuum filtration and rinsed with diethyl ether (2×) to obtain 59.5 mg of a light-pink material. Both ^{1}H and ^{31}P NMR spectroscopy of this material in deuterated methanol reveal the presence of multiple complexes.

Attempt to synthesize ruthenium complex 34. A flame-dried, two-necked round-bottom flask, equipped with a stir bar, was charged with ruthenium complex **5** (17.0 mg, 0.023 mmol), sodium pyridine-3-sulfonate (**37**) (8.5 mg, 0.047 mmol, 2.0 equiv), dry, degassed methanol (0.6 mL), and dry, degassed toluene (1.7 mL). The reaction mixture was stirred for 30 minutes at room temperature and the volatiles were removed *in vacuo*. Additional dry, degassed methanol (0.6 mL) and dry, degassed toluene (1.7 mL) were added, and the reaction mixture was stirred for 15 minutes before removing the volatiles *in vacuo*. This process of methanol and toluene addition followed by stirring and volatile removal was repeated two more times. Drying under high vacuum for 4 hours yields a green solid product of questionable purity and identity. ^{1}H NMR (CD_3OD, benzylidene proton resonances, ppm): δ 18.4 (s, relative integral: 2.45), 17.5 (s, relative integral: 1.00).

References and Notes

Portions of this chapter have been published as: Jordan, J. P.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 5152–5155. and Jordan, J. P.; Kuo, L.; Hong, S. H.; Grubbs, R. H. to be published, 2007.

(1) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003.

(2) Connon, S. J.; Blechert, S. In *Ruthenium Catalysts and Fine Chemistry*; Bruneau, C., Dixneuf, P. H., Eds.; Topics in Organometallics Chemistry 11; Springer-Verlag: Berlin, 2004; pp 93–124.

(3) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140.

(4) Frenzel, U.; Nuyken, O. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 2895–2916.

(5) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerizations*; Academic Press: San Diego, 1997.

(6) Kilbinger, A. F. M.; Cantrill, S. J.; Waltman, A. W.; Day, M. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 3281–3285.

(7) Badjic, J. D.; Cantrill, S. J.; Grubbs, R. H. Guidry, E. N.; Orenes, R.; Stoddart, J. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 3273–3278.

(8) Guidry, E. N.; Cantrill, S. J.; Stoddart, J. F. *Org. Lett.* **2005**, *7*, 2129–2132.

(9) Mohr, B.; Lynn, D. M.; Grubbs, R. H. *Organometallics* **1996**, *15*, 4317–4325.

(10) Lynn, D. M.; Mohr, B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 1627–1628.

(11) Lynn, D. M.; Mohr, B.; Grubbs, R. H.; Henling, L. M.; Day, M. W. *J. Am. Chem. Soc.* **2000**, *122*, 6601–6609.

(12) Lynn, D. M. Ph.D. Thesis, California Institute Technology, 1999.

(13) Kirkland, T. A.; Lynn, D. M., Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904–9909.

(14) Gallivan, J. P.; Jordan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **2005**, *46*, 2577–2580.

(15) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415.

(16) Hong, S. H. Ph. D. Thesis, California Institute of Technology, 2007.

(17) Bielawski, C., W.; Grubbs, R. H. *Angew Chem. Int. Ed.* **2000**, *39*, 2903–2906.

(18) Trnka, T.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546–2558.

(19) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29.

(20) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.

(21) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *Organometallics* **2001**, *20*, 5314–5318.

(22) Garber, S. B.; Kingsburgy, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(23) Connon, S. J.; Blechert, S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1873–1876.

(24) Later results show that an NHC-containing olefin metathesis catalyst that only incorporates water-soluble groups onto a dissociating ligand competently mediates metathesis in water (Chapter 5).

(25) Krause, J. O.; Lubbard, S.; Nuyken, O.; Buchmeiser, M. R. *Adv. Synth. Catal.* **2003**, *345*, 996–1004.

(26) Krause, J. O.; Nuyken, O.; Wurst, K.; Buchmeiser, M. R. *Chem. Eur. J.* **2004**, *10*, 777–784.

(27) Halbach, T. S.; Mix, S.; Fischer, D.; Maechling, S.; Krause, J. O.; Sievers, C.; Blechert, S.; Nuyken, O.; Buchmeiser, M. R. *J. Org. Chem.* **2005**, *70*, 4687–4694.

(28) Huitric, A. C.; Gordon, W. P.; Nelson, S. D. *J. Chem. Eng. Data* **1982**, *27*, 474–475.

(29) Barrow, J. C.; Nantermet, P. G.; Selnick, H. G.; Glass, K. L.; Rittle, K. E.; Gilbert, K. F.; Steele, T. G.; Homnick, C. F.; Freidinger, R. M.; Ransom, R. W.; Kling, P.; Reiss, D.; Broten, T. P.; Schorn, T. W.; Chang, R. S. L.; O'Malley, S. S.; Olah, T. V.; Ellis, J. D.; Barrish, A.; Kassahun, K.; Leppert, P.; Nagarathnam, D.; Forray, C. *J. Med. Chem.* **2000**, *43*, 2703–2718.

(30) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575–5580.

(31) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35–37.

(32) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104.

(33) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723.

(34) Jordan, J. P.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 5152–5155.

(35) Jordan, J. P.; Kuo, L.; Hong, S. H.; Grubbs, R. H. to be published, 2007.

(36) Mayr, M.; Buchmeiser, M. R.; Wurst, K. *Adv. Synth. Catal.* **2002**, *344*, 712–719.

(37) Vidal, S.; Garcia, M.; Montero, J.-L.; Morere, A. *Biorg. Med. Chem.* **2002**, *10*, 4051– 4056.

(38) Sanford, M. S. Ph.D. Thesis, California Institute of Technology, 2001.

(39) In deuterated toluene the phosphorus and proton NMR resonances of complex **27** are very broad and not readily assigned. However, removing the toluene from this NMR sample and redissolving it in deuterated dichloromethane again provides the "normal" NMR spectra for complex **27**.

(40) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740–5745.

(41) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

(42) Grubbs, R. H. Transition Metal Catalyzed Reactions in Water: Olefin Metathesis and Isomerization. In *Aqueous Organometallic Chemistry and Catalysis*; Horváth, I. T., Joó, F, Eds.; Kluwar Academic Publishers: Netherlands, 1995; pp 15.

(43) Dinger, M. B.; Mol, J. C. *Eur. J. Inorg. Chem.* **2003**, 2827–2833.

(44) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J. Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.