Ruthenium-Based Olefin Metathesis Catalysts Coordinated with *N*-Heterocyclic Carbene Ligands: Synthesis and Applications

Thesis by

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To my family and my friends,

I'd never be here if you weren't there.

"No matter where you go, there you are."

— Buckaroo Banzai, as told to Earl Mac Rausch

[The *Hitchhiker's Guide to the Galaxy* is superior to this thesis in two respects.]

"First, it is slightly cheaper; and second, it has the words
DON'T PANIC
inscribed in large, friendly letters on its cover."

— Douglas Adams

Chapter 0: A Concise Synthesis of the Cocktail "Peter's Catalyst"

Experimental Section. **General.** All materials were used as obtained from the Athenaeum, Vons, or Ralph's. "Cranberry juice" may refer to any "cocktail" preparation. "Grapefruit juice" may also be a "cocktail" preparation, but not a "sour mix." Visual spectroscopy is used to estimate color of final preparation.

Synthesis of "Peter's Catalyst" (Compound 1). A clean, dry whisky glass is charged with ice (3-5 cubes), grapefruit juice (1 oz., 1 equiv.), cranberry juice (4 shots, approximately 2 equiv.), blue curacáo (0.5 shot, 0.25 equiv.), and vodka (1-2 shots, 0.5-1.0 eq. to taste). The reaction mixture is stirred briefly until the color is homogeneous (5 s). An additional aliquot of cranberry juice is added until the reaction mixture has achieved a dark purplish color. Quantitative yield.

Acknowledgements. The author thanks Professor Harry Gray for funding many nights at the bar during which this research was carried out. The author also thanks the taste-testers, Libby Mayo and Susan Schofer, for helpful discussions and encouragement.

Enjoy!

Acknowledgements

First of all I have to thank God for getting this far. It's been a wild ride through two labs, and on (and off) many, many projects: I'd be remiss if I didn't recognize the influence of divinity. Of course the next set of accolades goes to my advisor, Robert H. Grubbs, for innumerable reasons. I am fond of saying that "everything I tried that worked" is one of Bob's ideas, and I think I might be only stretching the truth "a little bit." The document you now hold in your hands owes much to Bob's guidance, and this thesis is only a small reflection of what I've gained, both personally and professionally, from being in Bob's lab. I am overly grateful to Bob for taking me in after the Myers' exodus; I immediately got the sense that Bob and the Grubbs group are a fantastic bunch of people to spend 4+ years with. Thanks, Bob. It's truly been a wonderful time.

My committee members, both past and present, get next billing. Professor Harry Gray, what can I say? You've been supportive in everything I've ever tried to do and you've always given me invaluable advice. Your care for students and generosity are second-to-none. Professor Brian Stoltz, you've been a wonderful sounding board for many of my ideas, both science-wise and career-wise. I believe your dedication to teaching and overall education is one of your strongest assets. Professor Doug Rees, I appreciate your insight and help over the years, from the early days of Bi/Chem 170 through the end. Your patience is greatly appreciated, especially in light of some of my more questionable proposal ideas(?)

Professor Barbara Imperiali is also gratefully acknowledged for serving as my early chairperson. Professor Andrew G. Myers was my first mentor in graduate school, and I believe I learned a great deal from him on how to approach problems in a

professional manner. Andy is also part of the reason that I now write these words, for his support during my transition to Bob's lab was indispensable. I thank Andy for taking me on and believing in my early abilities.

The base reality of Caltech is often under-appreciated: many staff members hold this place together at the seams, and for that they deserve more praise that I will give here. Dian Buchness has been a tremendous help in everything I've ever done that involves the Caltech "machine." She has saved me many times when I've turned in forms horribly late, and she's also helped me pay Caltech back when they inadvertently tried to double my salary (although I didn't have a problem with the latter). It goes without saying that she's a shining light that you can always depend on for advice or just a chat. Paul Carroad has also made it possible for all of us to get our work done, both in research and in teaching. Steve Gould in the purchasing office made my orders come in on time, and Joe Drew was quick with a smile and a package full of "wonderful chemicals." Chris Smith has always been a great person to chat with, and I admire her ability to live life to the fullest, on trips, at restaurants, or even at work. Caltech lost one of their best when they lost Fenton Harvey. He made Chemistry 5a (and the elemental facility) fun places to work. Fenton often took responsibility without having to be asked, which has been a fantastic help. Fenton had an easy camaraderie with students that I hope to successfully emulate someday.

Now I can move on to the students/postdocs who colored my day-to-day living at Caltech. There are five people without whom I could not have made it through graduate school. In no particular order they are Eric Connor, Pavel Strop, Andreas Kilbinger (and his wife, Sara), and Tina Trnka. Eric has been a great friend from day one in the Grubbs

lab. His enthusiasm is fantastic and his interest in science is far-reaching. If you couldn't find Eric or me in the lab, chances are we've gone to the Crary house for a tea and a chat about science, kayaking, or relationships. Eric's support throughout my career has been essential to my "staying afloat" in graduate school. After I moved into Crary, Pavel and I became good friends. He is truly one of the "lads" as Eric would say. Some of the best times I've had here involve talking about life, the universe, and everything with Pavel, usually over a marrionberry cake at 2 in the morning. Andreas and Sara became great friends later in my career, and I thank God (again) for Andreas' proximity to me in the laboratory, which allowed our friendship to grow. Andreas gave us "bar crawls" and the "Wednesday night drinking session," teaching us Americans the meaning of a good time. Sara has been a fantastic friend, giving me the much-needed "female friend perspective" on things when I really wanted it.

Tina has been a continuous support, both personally and professionally, thoughout our entire graduate careers. Her ideas about chemistry never cease to amaze me in their cleverness, and her ability to get science "done" is a constant inspiration. It is her presence that gives me much strength. I need to thank her, as a girlfriend and a colleague, for always being there when I needed her.

Drs. Tom Wilhelm, Sharad Hajela, Jennifer Love, and Melanie Sanford have been great coworkers. I have learned much in both science and ethics from them, throughout the ups and downs of our Caltech experience. I wish all of them good fortune, particularly Jen and Melanie as they begin their pursuit of academic careers. Along with them I need to thank all of my coworkers, past and present, for making graduate school an "interesting" place to work and play. I hate to mindlessly name lists, so I'll just say

"You know who you are." I will mention 214 Church, a bastion of good people: Eric Connor, Dan Sanders, Marcus Weck, Adam Matzger, Andreas Kilbinger, Thomas Braig, Jason Henderson, Jen Love, Diego Benitez, Brian Connell, Delwin Elder, and particularly, Mike Ulman. Mike's been a great friend as well. His easygoing nature and his ability to have fun with life make him one of the best people you'll ever get to know. Christie Morrill deserves special consideration – we often mucked through things early on, but I think we both got something out of it. I give her my best wishes in her future graduate career, and I hope I've been at least somewhat helpful in her early graduate years.

Just a few more, I promise. Dr. Andrew Morehead has been instrumental in my acclimation to the Grubbs group at a time when I needed support. I wish him good fortune and Godspeed in his future plans. Arnab Chatterjee has been a good friend and our friendship has led us into some remarkable adventures in Vegas and Beyond. Bill Ward and Andrew Waltman also deserve mention for introducing us to the "Big Rock Candy Mountain" and how graduate school is like hobo life. Mike Echevarria from the Rathskeller has been a good friend to chat with about life and bartending, and he has made many a Friday evening more enjoyable.

Daniel "Hern" Paik has been a great friend from day one of Haverford College, and he deserves special credit: without his help and support I wouldn't have made it this far in chemistry. Speaking of Haverford, Claude Wintner has been a tremendous inspiration to me in both teaching and mentoring. Seeing Claude give a lecture on organic chemistry reminds us that there really is "art" in chemistry after all. Fran Blase has been extremely supportive and helpful throughout my career, and I appreciate her

influence: she's the one who (personally) taught me just about everything I know about how to "do" organic chemistry in the laboratory. Haverford College owes much to her continuing influence.

I've been helped by many a group at Caltech, including the Stoltz, Myers, MacMillan, Dougherty, Dervan, and Imperiali groups, and I like to thank them as well. I thank all of the Chemistry 5a teaching assistants that I've worked with over the years; if it wasn't for your help we'd be in dire straits now. Late night work would not be the same if it weren't for my heroes Adam Carolla and Dr. Drew Pinsky. These two have certainly kept me entertained when the chemistry was in the toilet.

For financial support I thank Caltech, Hitachi, the National Institutes of Health, and the National Science Foundation. This thesis is also dedicated to those men and women who were so cruelly robbed of their lives a year and a day prior to its submission; you all remain in our hearts and in our minds.

Finally, I'd like to thank my family and close (non-Caltech) friends. Their love and support has never wavered, and I could not ask for better parents and grandparents than my own. I hope that in some small way, these 15,000 hours were well spent. I think they were.

Abstract

The improved synthesis and olefin metathesis activity of *N*-heterocyclic carbene (NHC)-coordinated ruthenium alkylidenes of the form $(NHC)(L)_x(Cl)_2Ru{=}CHR$ (x = 1 or 2) are reported. In order to circumvent the handling of highly sensitive free carbenes, *N*-heterocyclic carbene "adducts" were prepared in high yields by the reaction of nucleophilic bases with *N,N'*-diarylimidazolium salts. Most notably, the addition of trichloromethyl anion to *N,N'*-dimesityl-4,5-dihydroimidazolium chloride produced an air-, moisture-, and temperature-stable crystalline adduct, 2-trichloromethyl-4,5-dihydro-imidazolidine. When this species is heated above the critical temperature of 55°C in the presence of $(PCy_3)_2(Cl)_2Ru{=}CHPh$, a single, clean phosphine substitution reaction occurs to form the NHC-coordinated benzylidene $(NHC)(PCy)_3(Cl)_2Ru{=}CHPh$ in 84% isolated yield. This procedure has been successfully scaled up to industrial production and remains the most effective catalyst synthesis to date.

The NHC-coordinated catalysts show dramatically expanded activity relative to their *bis*-phosphine counterparts. The high yielding, *trans*-stereoselective cross metathesis of various acroyl substrates is the first example of the ruthenium-catalyzed metathesis of olefins directly substituted with electron-withdrawing functionality. Ring-opening cross metathesis of acroyl species with relatively high ring strain cyclooctadiene and norbornene monomers has also been achieved in good yields and perfect regioselectivity when the norbornene is asymmetrically substituted with a bridgehead methyl group.

Further expansion of the substrate scope was achieved when the catalyst's phosphine ligand was replaced with more weakly bound 3-bromopyridine (3-Br-pyr)

ligands. The resulting catalyst (NHC)(3-Br-pyr)$_2$(Cl)$_2$Ru=CHPh produced synthetically useful yields (≥ 67%) in the cross metathesis of acrylonitrile and terminal olefins (as opposed to less than 30% yield with the phosphine-coordinated catalyst). NHC-coordinated catalysts therefore allow *both* electron-rich and electron-poor olefins to undergo metathesis in the same pot, potentially leading to synthetically valuable products containing electronically differentiated olefins.

The lower activity of phosphine-coordinated catalysts relative to those coordinated with 3-bromopyridine can be addressed by the addition of "phosphine scavengers" to the former. Higher pK_a carboxylic acids (such as acetic and benzoic acids) are capable of accelerating catalysis as effectively as the much stronger hydrochloric acid, without concomitant catalyst decomposition. These properties make carboxylic acids the optimal choice for use with sensitive organic substrates.

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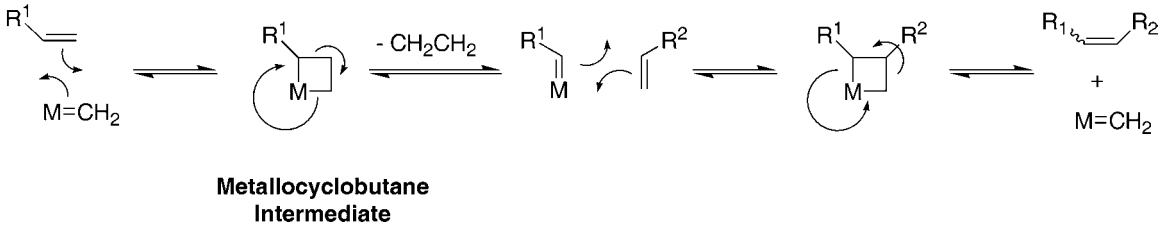
Chapter 1. Introduction to Olefin Metathesis and Background on Catalyst Design

The field of olefin metathesis has grown from its humble roots as a chemical curiosity to an extremely powerful method for the construction of diverse small molecules and polymers.[1] The term "olefin metathesis," first used by Calderon, refers to the exchange of olefinic carbons between substrates, a process that is synthetically valuable as a carbon-carbon bond-forming process (Scheme 1).[2] The basic reaction mechanism has been detailed by Hérrison and Chauvin in the early 1970's, and was postulated to involve discrete metal carbene $M{=}CR_2$ (alkylidene) species.[3] The reaction of these carbenes with olefins was believed to occur through a [2+2] addition-cycloreversion mechanism, with a metallocyclobutane as intermediate. To this day, this mechanism remains the generally accepted mode of catalysis by discrete, single-component metal alkylidenes.

Scheme 1. The general reaction pathway for olefin metathesis: The "Chauvin Mechanism."

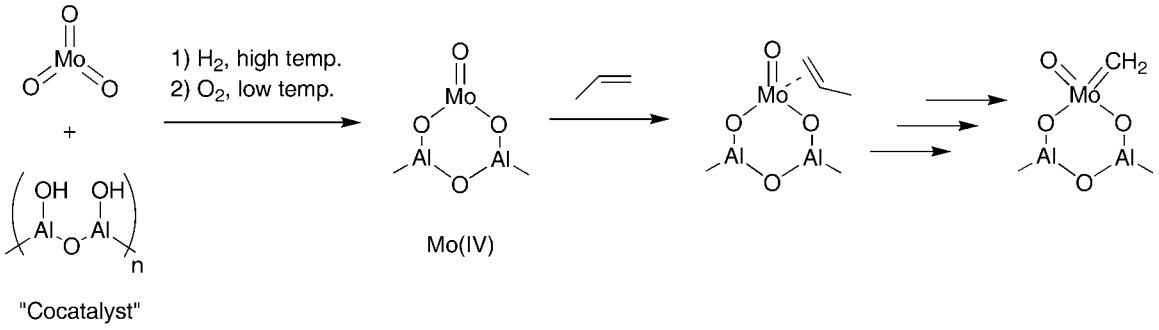


Overall:

From the late 1960's through the early 1980's, the majority of olefin metathesis reactions were carried out with ill-defined multicomponent systems containing an early transition metal oxide and a main group metal or metalloid "cocatalyst."[1(a)] These catalyst preparations were believed to be high-valent species that formed alkylidenes

upon insertion into the substrate olefin (Scheme 2). Although these systems were highly active for the metathesis of unfunctionalized terminal olefins, they were readily deactivated in the presence of air, water, or polar functional groups. The olefin metathesis reaction was therefore limited to hydrocarbon/fuel chemistry, for the formation of higher olefins from cheaper feedstocks.

Scheme 2. Early transition metal multicomponent olefin metathesis catalysts (e.g., molybdenum trioxide-alumina).

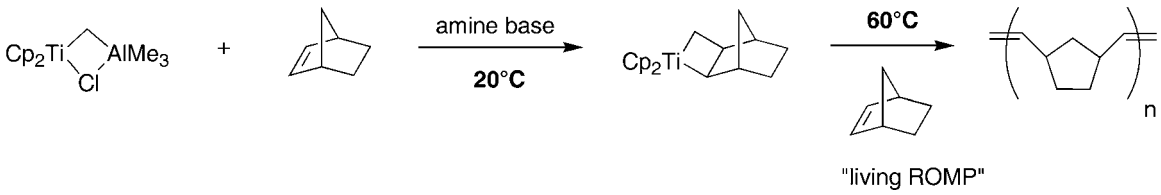


In the early 1980's, Tebbe and Grubbs extended the classic "Tebbe reagent" ($Cp_2TiCH_2(AlClMe_3)$) to olefin metathesis applications.[4] Although not a discrete metal carbene, this species presumably forms $Cp_2Ti{=}CH_2$ *in situ*. In the presence of coordinating amine base, the Tebbe reagent was found to react with norbornene, at room temperature, to form a metallocyclobutane that could then independently initiate the living ROMP of norbornene (Scheme 3).[5] These initial results with single component, well-defined titanium catalysts, foreshadowed the development of discrete metal alkylidenes in the early 1990's. Tsuji et al. encompassed the challenge facing olefin metathesis in the following statement:

"In order to exploit the metathesis reaction as a truly useful synthetic methodology, it is essential to discover a new catalyst system which can tolerate the presence of functional groups in olefin molecules."[6]

These researchers thus delineated the next major goal of olefin metathesis chemistry: generality.

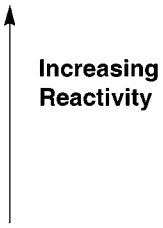
Scheme 3. Reaction of the "Tebbe Reagent" with norbonene at room temperature yields a metathesis-active titanocyclobutane.



Unfortunately, functional group tolerance and activity were found to be opposing periodic trends as the catalyst systems were varied from early to late transition metals (Table 1).[7] Although the early transition metals showed high activity, they react readily with polar functional groups such as carbonyls.[8] Conversely, the late transition metals showed higher reactivity toward olefins, but the overall catalyst reactivity was severely depressed relative to the titanium and molybdenum systems. Nevertheless, Novak and Grubbs noted that ruthenium salts were active for the ROMP (ring-opening metathesis polymerization) of strained cycloolefins (such as norbornene) in organic solvents.[9] This promising reactivity suggested that ruthenium may be the metal of choice for a potential well-defined late transition metal olefin metathesis catalyst.

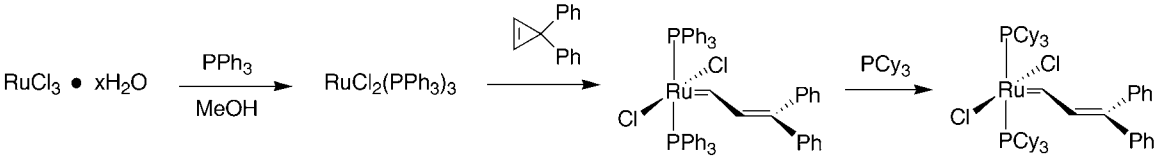
Table 1. Functional group tolerance of early and late transition metal catalysts.

Titanium	Tungsten	Molybdenum	Ruthenium
Acids	Acids	Acids	**Olefins**
Alcohols, Water	Alcohols, Water	Alcohols, Water	Acids
Aldehydes	Aldehydes	Aldehydes	Alcohols, Water
Ketones	Ketones	**Olefins**	Aldehydes
Esters, Amides	**Olefins**	Ketones	Ketones
Olefins	Esters, Amides	Esters, Amides	Esters, Amides



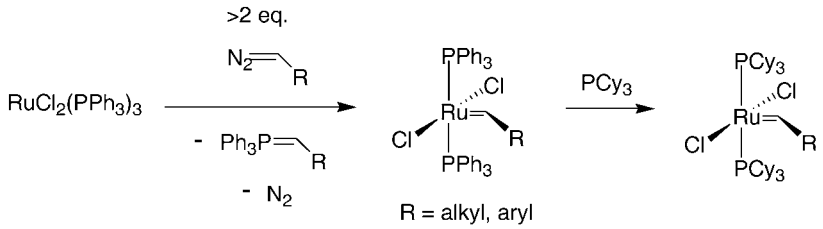
Nguyen and Grubbs expanded on this lead by performing a ring-opening reaction of 3,3-disubstituted cyclopropenes with ruthenium systems.[10] Upon combining *tris*-triphenylphosphine-ruthenium(II) chloride with 3,3-diphenylcyclopropene, the first well-defined ruthenium alkylidene was formed (Scheme 4). This catalyst was active for the ROMP of highly strained cycloolefins, but was inactive for the metathesis of acyclic olefins. A critical advance was then implemented by replacing the triphenylphosphine ligands with sterically larger and more electron-donating tricyclohexylphosphines. A systematic study of the properties of these "L-type" ligands found that larger phosphines which are more electron-rich produced the most active catalysts.[11] The new PCy_3-coordinated catalyst was active for the ROMP of high and low strain cycloolefins as well as for the aforementioned acyclic cases.

Scheme 4. Development of the first discrete metathesis-active ruthenium alkylidene.



Although this catalyst showed the highest activity of any ruthenium system known at the time, its synthesis remained difficult and impractical for large-scale preparations. In particular, the cyclopropene is relatively unstable to storage, requiring that the entire synthesis be peformed in one continuous process. An alternative route was developed by France, Schwab, and Grubbs, in which ruthenium(II) species were found to insert into α-diazoalkanes.[12] The reaction of *tris*-triphenylphosphineruthenium(II) chloride with phenyldiazomethane and tricyclohexylphosphine was found to produce a ruthenium(II) benzylidene of wide academic and commercial utility (Scheme 5). This new catalyst preparation has been the backbone of ruthenium alkylidene synthesis for the past six years, and the benzylidene (R = Ph) is now the most widely used olefin metathesis catalyst.

Scheme 5. Synthesis of ruthenium alkylidenes by insertion into α-diazoalkanes.



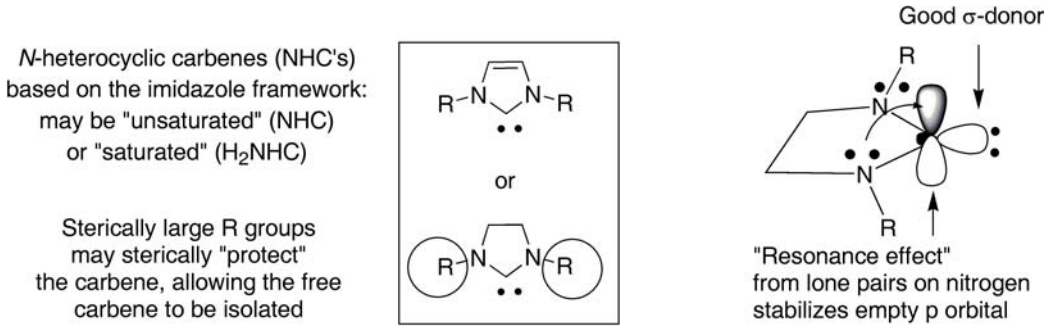
Due to the commercial availability of this ruthenium(II) benzylidene, olefin metathesis has been widely applied to the synthesis of fine chemicals, from

pharmaceuticals to polymers. The interested reader is directed to many reviews and monographs on the subject; a full discussion of the applications is beyond the scope of this text.[1,13] Although metathesis could now be applied successfully in the presence of functional groups, the reacting olefins needed to be relatively isolated and electronically insulated from functionality. Poor yields were obtained for metathesis reactions of directly (α)-functionalized olefins, including both electron-rich (enol ethers) and electron-poor (α,β-unsaturated carbonyl) functionality. Sterically, the catalyst was also quite sensitive to bulk on the olefin substrates. In particular, tri- and tetra-substituted olefins were not readily formed by this current generation of ruthenium alkylidenes. In spite of these limitations, the overall victory has been achieved: widespread application of olefin metathesis has been realized.

In order to successfully address the above problems facing the current generation of catalysts, ligand variation of the basic (L)(L')X_2Ru=CHR catalyst structure was extensively studied. For synthetic ease most effort was focused on the semi-systematic alteration of the alkylidene and L-type ligands. Two directions were investigated: L-type ligands of both increased and decreased donor strength were examined. These strategies were based on early mechanistic work suggesting that the active metathesis species was the 14-electron complex coordinated with only *one* L-type ligand (LX_2Ru=CHR).[14] Therefore one L-type ligand had to remain coordinated (the "strong" donor ligand) and the other had to be labile (the "weak" donor ligand). Catalyst activity could presumably be increased by increasing the donor strength of one ligand at the expense of the other. A combination of strong and weak donor ligands should produce the most active catalysts, but until recently L-type ligands other than phosphines had not been extensively examined in ruthenium metathesis chemistry.

Within the last five years, *N*-heterocyclic carbene (NHC) ligands have filled this gap in viable, two-electron donor L-type ligands (Figure 1).[13,15] The strong donor character of NHC's coupled with the weaker donor phosphines results in the most active catalysts known to date. The development and study of NHC-coordinated ruthenium alkylidenes are a particular focus of this thesis. A continued description of the NHC's contribution to the history of olefin metathesis can be found in the introductory remarks of Chapter 2.

Figure 1. Pertinent information about *N*-heterocyclic carbenes.

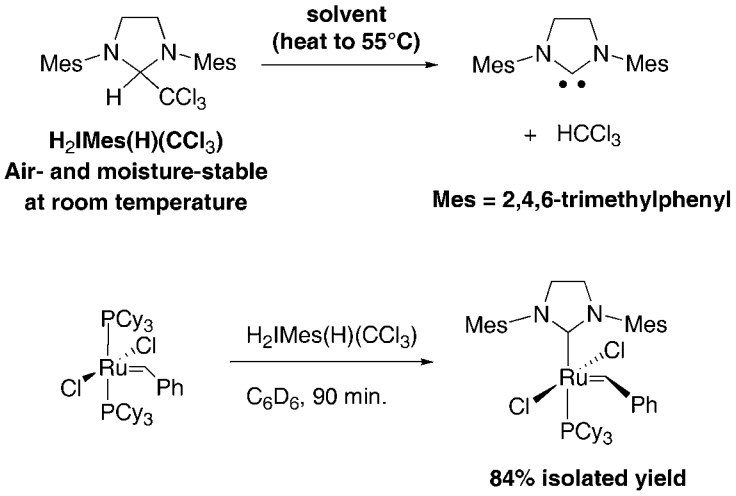


Thesis Research

The initial problem facing the development of NHC-coordinated catalysts is the known air and water-sensitivity of free NHC's.[16] These ligands are true singlet carbenes that are also relatively strong non-ionic organic bases (pK_a of the imidazolium salt is approximately 24 in DMSO).[17] In Chapter 2, a viable solution to this sensitivity issue is reported: small-molecule "adducts" of the free NHC's can be synthesized without requiring the prior isolation of the sensitive free carbene. At elevated temperatures (55-80°C) these adducts can form the free carbenes by extrusion of the protonated small molecule (Scheme 6). When combined with a ruthenium precursor of the form

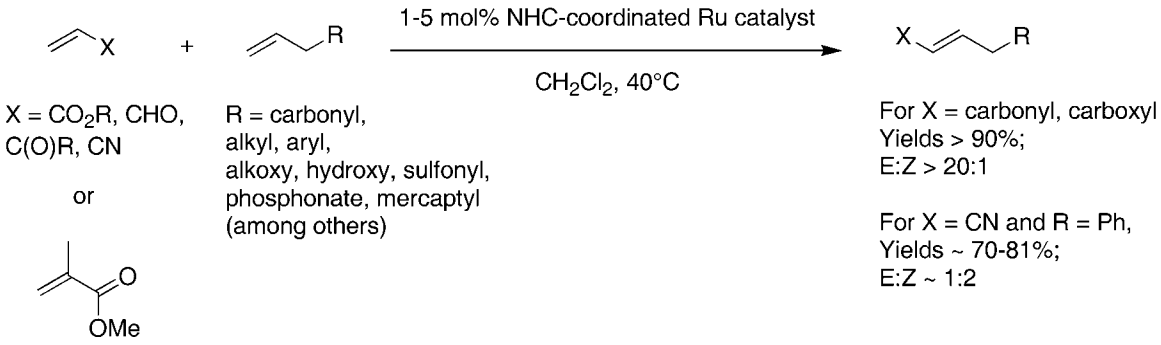
$(PR_3)_2(X)_2Ru=CHR'$, these adducts can cleanly form the NHC-coordinated catalyst $(NHC)(PR_3)_2(X)_2Ru=CHR'$, circumventing the need to manipulate free NHC's. This method represents the highest yielding synthesis of NHC-coordinated ruthenium alkylidenes known to date.

Scheme 6. "Chloroform adduct" reactivity and application to catalyst synthesis.



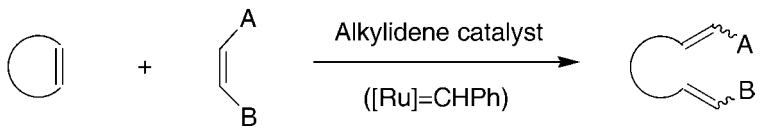
Once NHC-coordinated catalysts were in hand, their application to the metathesis of directly functionalized olefins could be examined (reported in Chapters 3 and 4). In particular, the NHC-coordinated catalysts were the first ruthenium alkylidenes that could successfully catalyze the cross metathesis of electron-poor α-functionalized olefins, including α,β-unsaturated carbonyl species and acrylonitrile (Scheme 7). These results allow the cross metathesis reaction to be directly applied to a wide range of syntheses that previously required extensive protection and deprotection strategies to electronically "mask" the α-functionality.

Scheme 7. General cross metathesis reaction of a terminal olefin with a cross partner that is directly substituted with electron-withdrawing functionality.

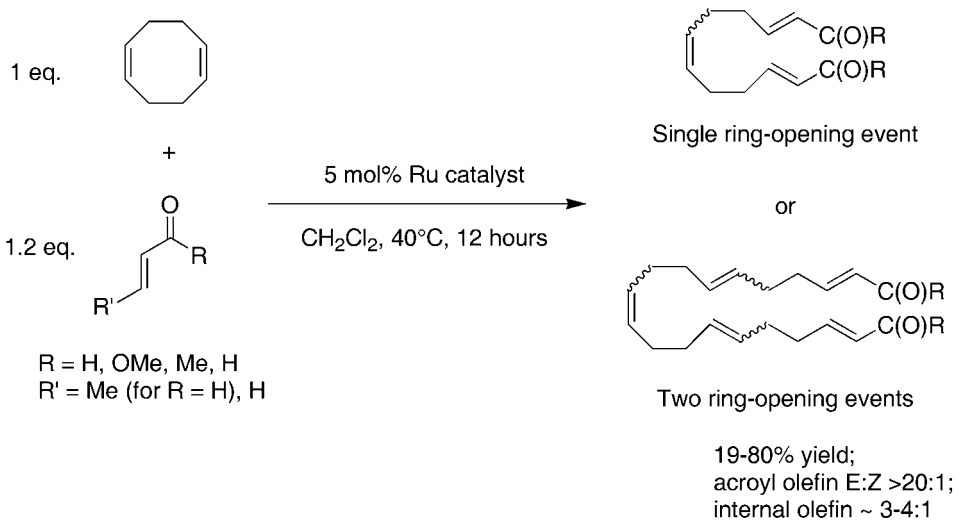


Another area that is widely applicable to small molecule synthesis is ring-opening cross metathesis (Scheme 8). "First generation" bisphosphine ruthenium alkylidenes could not electronically differentiate olefins by ROCM because these catalysts did not react well with electron-poor olefins. The above cross metathesis results indicated that ROCM may now become a powerful method to generate densely functionalized small molecule scaffolds in which the two olefin termini are differentially substituted. This strategy is discussed in the context of the ring-opening of COD to form acrylate-capped oligomers that contain electron-rich internal olefins and electron-poor acrylates (Scheme 9). The internal olefins can then be split with another olefin metathesis reaction to yield end-differentiated products.

Scheme 8. General ring-opening cross metathesis (ROCM) reaction.

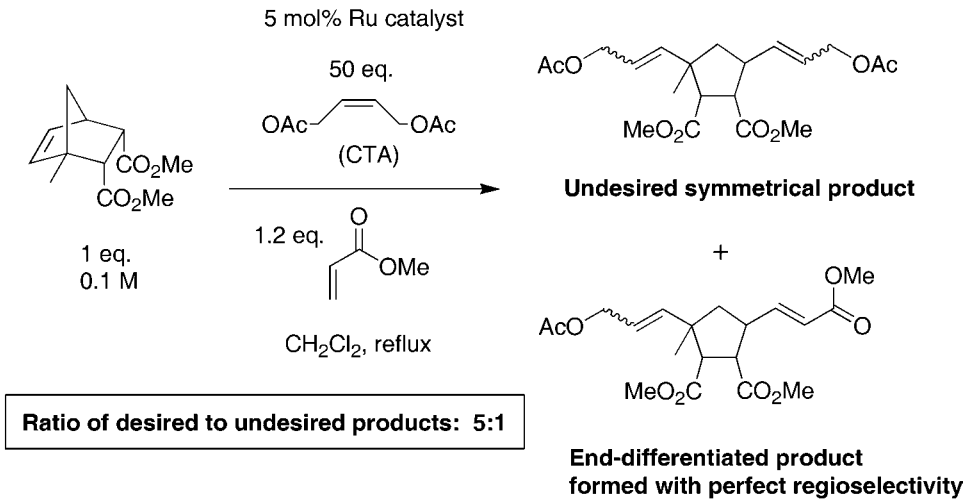


Scheme 9. Controlled ring-opening cross metathesis of a relatively high strain monomer (COD) with acroyl species yields products containing electronically differentiated olefins.



In the event that the cycloolefin is differentially substituted (i.e., asymmetric), regioselective functionalization by ROCM can be achieved, placing the electron-poor function (an acrylate) on the less "crowded" olefin terminus (Scheme 10). This method is applied to the ring-opening of substituted norbornenes to form cyclopentane dienes that are sterically and electronically differentiated in a predictable way. Overall the simply prepared bridged bicyclic olefin is converted *in a single, convergent, highly controlled step* to a densely functionalized carbocyclic product.

Scheme 10. Three-component ROCM reactions.



Although the NHC-coordinated catalysts are generally found to be highly active, the methylidene species $(NHC)(PR_3)(X)_2Ru{=}CH_2$ was found to be dramatically less active than its alkylidene (Ru=CHR) counterparts.[18] In order to increase the reactivity of the methylidene, phosphine scavengers were utilized to labilize the "weak" donor phosphine ligand (Scheme). As Grubbs et al. have shown, the removal of a phosphine ligand will promote the reaction by forming the active 14-electron species $(NHC)(X)_2Ru{=}CH_2$.[14,19] Common phosphine scavengers (such as the mineral acids or CuCl) are Brønsted or Lewis acids that can rapidly decompose the ruthenium catalysts.[14] Carboxylic acids are appropriate alternatives due to their higher pK_a (0-5 in H_2O); they are among the weakest organic acids.[20] In particular, commercially available benzoic and acetic acids were found to be the most effective phosphine scavengers: they accelerate methylidene turnover by a factor of 4-5 without significantly increasing the catalyst decomposition rate. These carboxylic acid scavengers are also the most amenable to the presence of delicate organics that would be deprotected or destroyed by stronger mineral or Lewis acids.

The following work is designed to demonstrate a progression from catalyst development to novel catalytic applications. The desire to accomplish the latter has motivated the former, resulting in the production of highly active ruthenium alkylidenes. It is the interplay between these two "halves" of catalysis that is the main theme of this thesis. Lessons learned in organic applications have been applied to the activation and manipulation of the catalyst species. Consequently advances in the scope, width, and breadth of metathesis continue to depend on this critical "cooperation."

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Chapter 2. Development of *N*-Heterocyclic Carbene-Coordinated Ruthenium Olefin Metathesis Catalysts: Synthesis and Reactivity[1]

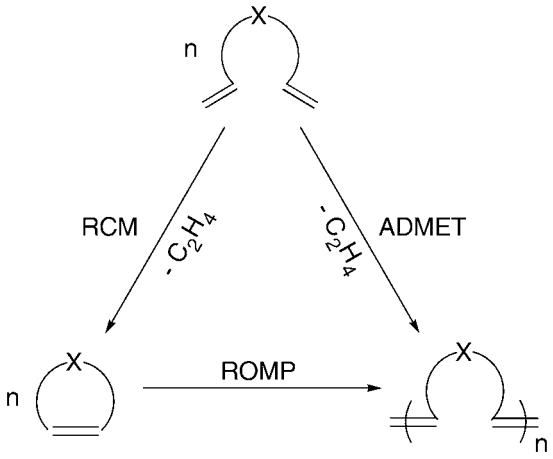
Part I. Introduction and Background for the Synthesis of "Next Generation" Olefin Metathesis Catalysts

Ruthenium-based olefin metathesis catalysts have revolutionized the field of synthetic chemistry by rendering this reaction amenable to a variety of small molecule and polymer applications.[2] These catalysts demonstrate many desirable characteristics, including high activity, stability to air and moisture, and straightforward preparation. The first generation catalysts of the type $L_2X_2Ru{=}CHR$ (L = trialkylphosphine, X = chloride, R = phenyl, Compound **1**)[3] were found to be especially robust organometallics that can effect each transformation shown in Figure 1. Ring-opening metathesis polymerization (ROMP) could be performed on cyclic molecules of high and low ring strain to yield polymers of controllable molecular weight. With regard to small molecules, α,ω-dienes could be readily ring-closed to form cyclic products by extrusion of ethylene in a process called RCM (ring-closing metathesis). The intermolecular variant of RCM, cross-metathesis (CM), could be used to join two terminal olefin partners into a difunctionalized internal olefin. Alternatively an α,ω-diene could be polymerized by successive CM reactions that are collectively termed ADMET, acyclic diene metathesis polymerization. The ability to carry out these transformations in a controlled, predictable manner using easily handled catalysts has become a valuable asset to the synthetic chemist.

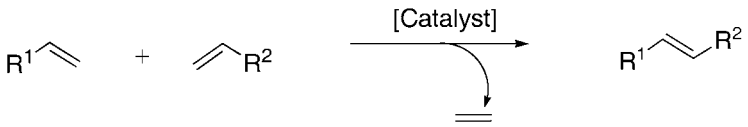
Although **1** was sufficiently active for many olefins of interest, the substrate scope of these transformations remained partially limited, requiring that the metathesis-active olefins remain electronically isolated from functional groups.[4] Any function at the vinylic position was not tolerated by these first-generation $(PCy_3)_2Cl_2Ru{=}CHR$ catalysts,

including carbonyl groups, phosphonates, nitriles, halides, and alkoxy or amine groups. Metathesis was therefore limited to an intermediate step in a synthesis; α-functionalization of the olefin had to be carried out after the metathesis reaction. This limitation also prevented the olefin metathesis reaction from becoming as prevalent as the venerable aldol or Wittig-type reactions, which had traditionally been used to generate α,β-unsaturated carbonyl and phosphinyl functionality in a predictable way.[5]

Figure 1. Metathesis as a general route to functionalized olefins.



Cross Metathesis (CM, or XMET) is similar to ADMET:



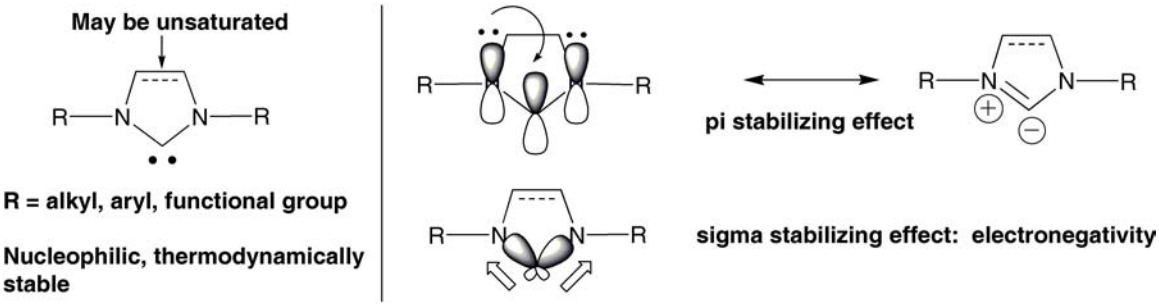
Highly functionalized molecules can be synthesized with a catalyst tolerant of coordinating heteroatoms in R^1 and R^2

In an effort to overcome these limitations of the first-generation catalysts, the identity and properties of the L- and X-type ligands have been widely studied and distinct trends have emerged. In the case of the X-type ligands, the halogens produce the most active metathesis catalysts, and among these chloride appears to provide the most active

and stable catalysts. Other X-type ligands, such as alkoxides and amides, are generally less desirable because ruthenium catalysts coordinated with these ligands tend to decompose rapidly or are difficult to isolate.[6] In contrast, ruthenium olefin metathesis catalysts are tolerant of a wide electronic and structural variety of L-type ligands. The experiments detailed in this chapter will focus entirely on the manipulation of these L-type ligands to create new mixed ligand catalysts of the form $L^1L^2X_2Ru{=}CHR$ that are significantly more active than **1**.

During the past ten years, an alternate L-type ligand, the *N*-heterocyclic carbene (NHC, Figure 2), has gained prominence over its phosphine counterparts.[7] The nature of an *N*-heterocyclic carbene species has been a matter of speculation and investigation for over forty years, and recently NHC's have been used successfully in both organic and organometallic applications. First postulated in the 1960's by H.-W. Wanzlick, these NHC's were predicted to be stabilized by both pi and sigma effects.[8] A true singlet carbene would have a lone pair in an sp^2 orbital and an empty p-orbital normal to the plane of the sp^2 orbitals.[9] In order to stabilize this configuration, the lone pairs on nitrogen are predicted to donate electron density into the empty p orbital (π-effect). Additionally the electronegativity of nitrogen is predicted to stabilize the carbene itself by removing electron density through an inductive effect (σ-effect). Although Wanzlick and his contemporaries suggested that free (uncomplexed) NHC's could potentially be isolated due to these stabilizing effects, it was thirty years later when the early researchers were vindicated by the isolation of *N,N'*-bis-adamantyl-imidazol-2-ylidene by Arduengo et al.[10] This isolation opened up myriad new possibilities for using NHC's as ligands in metal-catalyzed reactions.

Figure 2. An *N*-heterocyclic carbene: the stabilizing influence of nitrogen lone-pairs.

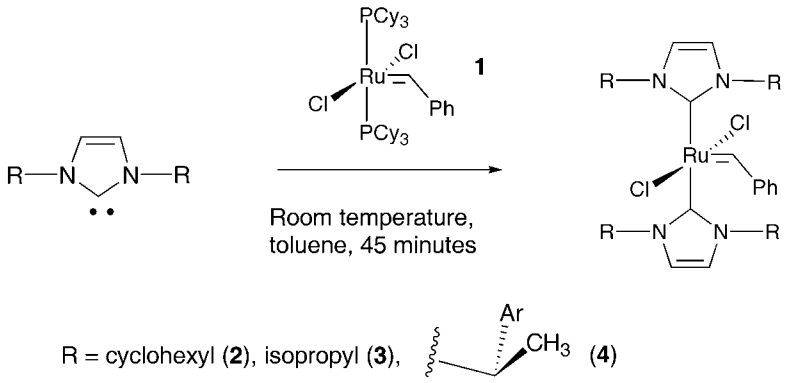


Recently a variety of NHC ligands have been coordinated to both main group and transition metals, and the reader is directed to many reviews that have been written on this topic.[7] NHC ligands can now be successfully applied to late transition metal catalysis, including Heck/Suzuki/Stille coupling, aryl amination, hydrogenation, and hydroformylation.[11] In each case the NHC ligands often show dramatic improvements over their phosphine counterparts, providing higher yields and/or shorter reaction times (i.e., translating into higher catalyst turnover numbers). It is the opinion of many investigators in the field that the NHC ligands are stronger σ-donors than are phosphines. This property allows them to remain coordinated to a putative metal center for a longer period of time before decomposition ensues, resulting in higher turnover and more effective catalysis.

Having investigated these general properties of NHC's as ligands for transition metals, Herrmann et al. extended their study to ruthenium-based olefin metathesis catalysts in 1997.[12] They successfully substituted both phosphines in **1** for alkyl-substituted NHC's (Scheme 1). As predicted, the stonger σ-donor character of NHC's relative to phosphines made the resulting catalysts **2**-**4** *less* active for the ROMP of cyclooctene, according to the generally accepted metathesis mechanism developed by

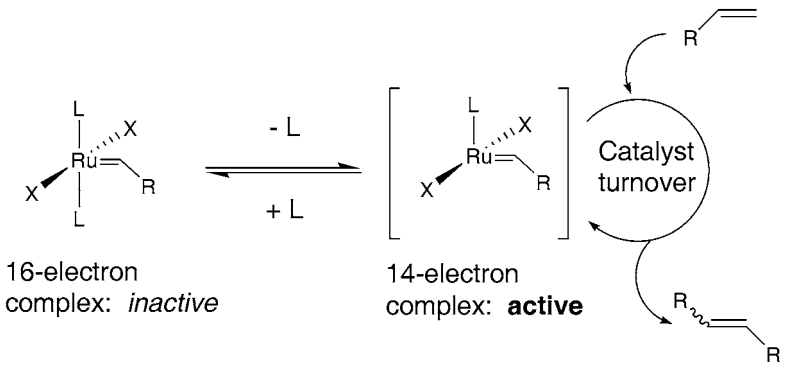
Grubbs et al. (Scheme 2).[13] In this mechanism, the active metathesis species is predicted to be the phosphine-dissociated 14-electron complex, as opposed to the 16-electron precatalyst **1**. Substitution of *both* phosphines for ligands of increased donor character therefore produced catalysts of lower activity.

Scheme 1. *bis*-NHC catalysts described in Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2490-2493.



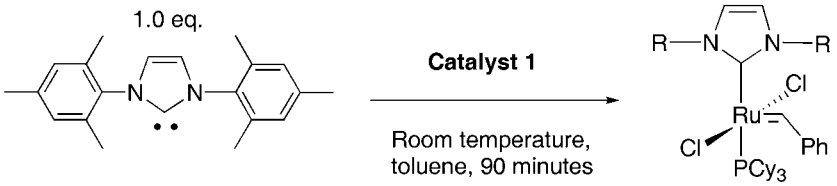
A more attractive alternative would be the combination of the strongly donating NHC with a more labile ligand that could readily dissociate to form the active 14-electron complex. The NHC would then remain coordinated to the metal center, stabilizing the highly unsaturated ruthenium(II) center as it does for the palladium-mediated Suzuki/Heck type couplings detailed above.[14] This "synergy" of strong and weak donors was engineered by both the Grubbs and Nolan groups in their independent production of catalyst **5** (Scheme 3).[15]

Scheme 2. Simplified mechanism of olefin metathesis catalyzed by $L_2X_2Ru=CHPh$ complexes.



Use of a *diaryl*-substituted NHC was necessary to generate the mixed NHC-phosphine catalyst. Regardless of ligand stoichiometry, the isolated free carbene IMes (*N*,*N'*-dimesityl-imidazol-2-ylidene) was only observed to cleanly substitute one of the two phosphines on the metal. At the time this behavior was explained by the sterically large size of the IMes NHC: the mesityl groups were believed to be sufficiently large to prevent two IMes ligands from coordinating to the ruthenium center. This hypothesis was later proven incorrect by the successful isolation and characterization of the *bis*-NHC complex $(IMes)_2(Cl)_2Ru=CHPh$.[1(c)] Additional mechanistic work demonstrated that the phosphine dissociation rate in **1** was significantly faster than in **5**, suggesting that the dissociative substitution of one phosphine is much more facile than the substitution of both.[13(c)]

Scheme 3. Original preparation of a mixed NHC-phosphine catalyst containing the *N,N'*-dimesityl-imidazol-2-ylidene ligand.



5, 85% yield

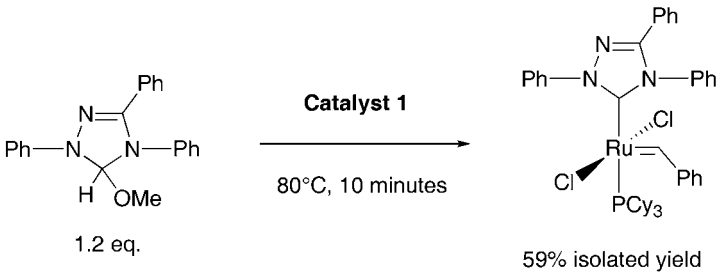
Catalyst **5** was found to be superior to catalyst **1** in many ways, most notably reaction time in RCM reactions (often reducing reaction times by a factor of five or more). Additionally, considerably smaller catalyst loadings could be used in polymerization (from 500:1 monomer:catalyst ratio to 10,000:1).[16] This behavior suggested that the IMes systems represented the "next generation" olefin metathesis catalysts.

Although catalyst **5** was the first to be synthesized in this catalytic series, no evidence suggested that it was necessarily the most active member of the family. In order to explore the stereoelectronic effect of different NHC ligands on olefin metathesis activity, a diverse pool of catalysts of the form $(NHC)(PR_3)(Cl)_2Ru{=}CHR$ needed to be prepared, isolated, characterized, and subjected to rigorous activity tests. Unfortunately, the established preparation of catalyst **5** was not suitable for generalization. Most significantly, the reaction required manipulation of free IMes carbene, an air- and moisture-sensitive compound that had to be prepared in and isolated from liquid ammonia.[17] The catalyst synthesis could then only be readily accomplished in a drybox environment or with careful Schlenk technique. Although such delicate handling is possible in an organometallic laboratory, the speed of catalyst screening would be

dramatically lengthened. In order to alleviate this problem, air- and moisture-stable routes to NHC-coordinated catalysts needed to be developed.

Along these lines Trnka and Grubbs discovered that an alkoxide adduct of a free triazolium carbene could behave as a "protected" carbene source (Scheme 4).[1(c)] When the methoxide adduct was heated with **1**, one of the phosphines was substituted with the triazolium NHC. Enders et al. had previously synthesized this adduct and shown that it can extrude methanol at 80ºC under high vacuum (less than 100 mtorr) to generate the free NHC.[18] Currently the methoxide adduct is believed to follow this same pathway at elevated temperatures in solution to generate a free NHC *in situ*. This NHC is then clearly capable of behaving similarly to the free IMes carbene; that is, the triazolium NHC can readily substitute a phosphine in **1**. This methoxide adduct chemistry presented us with a significant synthetic advantage, allowing the straightforward production of mixed NHC-phosphine catalysts.

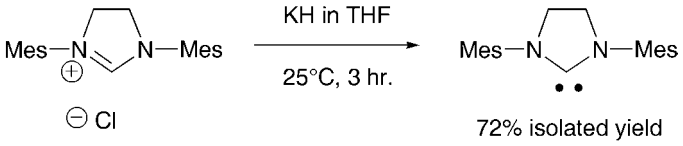
Scheme 4. Original preparation of a triazolylidene-coordinated ruthenium alkylidene. Trnka, T. M.; Grubbs, R. H. Unpublished results.



The NHC's studied to this point (including IMes and the triazolium systems) were stabilized not only by σ- and π-effects but also by resonance. Early studies suggested that the remarkable thermal stability of IMes and related systems resulted from this

ligand's 5-center-6-electron configuration (an aromatic configuration according to Hückel's rules).[19] Arduengo and coworkers succeeded in demonstrating that this delocalization was not absolutely necessary for the isolation of free NHC's.[20] This group isolated *N,N'*-dimesityl-4,5-dihydro-imidazolinylidene, a mesityl-substituted NHC with a *saturated* backbone (Scheme 5, hereafter referred to as $IMesH_2$ or H_2IMes). This species was predicted to be an even stronger σ-donor than IMes due to its lack of resonance stabilization/delocalization. Additionally Arduengo et al. remarked that the only base capable of generating free H_2IMes carbene was potassium hydride, a much stronger base than potassium *tert*-butoxide used in the IMes cases.[21] Overall these observations suggest that H_2IMes is both a stronger base and a better σ-donor than IMes.[22]

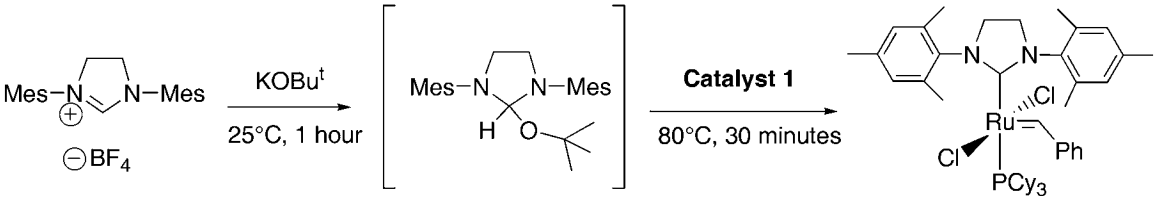
Scheme 5. Direct deprotonation of the salt *N,N'*-dimesityl-4,5-dihydro-imidazolin-2-ylidene, (H_2IMes) containing a saturated "backbone." Reported in Arduengo, A. J. III; Goerlich, J. R.; Marshall, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11027-11028.



For these reasons, H_2IMes was postulated to be a better ligand than IMes for ruthenium-based olefin metathesis catalysts. This belief was based on the established trend that the strong σ-donor NHC's were more effective ligands than the strongest σ-donor trialkylphosphines. H_2IMes should therefore lay among the strongest non-ionic σ-donors discovered to date. The adduct chemistry detailed by Trnka and Grubbs was subsequently extended to the H_2IMes systems in order to validate this assertion (Scheme 6).[23] In spite of the claims of Arduengo et al., potassium *tert*-butoxide was found to be a

competent base, but not for direct deprotonation. Instead *tert*-butoxide acts as a nucleophile, attacking the imidazolium salt to form a butoxide adduct **6** *in situ*. Catalyst **1** was then directly added to the reaction mixture and heat was applied (80°C for 30 minutes). The resulting catalyst, **7**, although structurally similar to **5**, was found to be the most active mixed NHC-phosphine catalyst that had been developed, particularly in the polymerization of high strain olefins such as DCPD (monomer:catalyst ratios of 50K:1 to 100K:1 yielded high molecular weight polymer).[24] Never before had late transition metal olefin metathesis catalysts achieved such a high level of reactivity, surpassing even the well-established Schrock molybdenum catalysts.

Scheme 6. Generation of H_2IMes-coordinated catalyst **7** via the *in situ* alkoxide adduct route. Reported in Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.



6, generated *in situ* **7**, 45% isolated yield

Although these landmarks in catalyst design and synthesis paved the way for future catalyst development, the alkoxide adduct syntheses remained inoptimal. In particular, the *tert*-butoxide adduct **6** is thermally unstable at room temperature. It can be isolated as a sticky semisolid that apparently decomposes upon standing in C_6D_6 solution over 2–3 hours at 25°C (see the Experimental Section for partial characterization of this adduct). This instability renders this large-scale production of **7** impractical due to variable yields and the inability to measure accurate weights/stoichiometries of **6**. A

preferable solution to this problem would be the development of an isolable, air- and moisture-stable adduct that can be easily handled on the benchtop. This problem (and progress toward its solution) is addressed in Part II of this chapter.

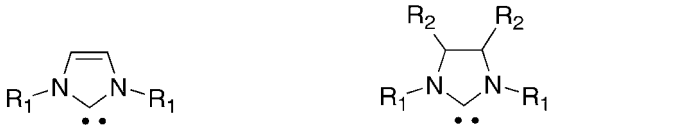
The alkoxide adduct technology developed in the course of our studies is of little practical value if it cannot be extended to other members of the NHC family. Part III of this chapter details the successful application of the *tert*-butoxide methodology to an NHC that is sterically larger than either the IMes or H_2IMes carbenes. A metathesis catalyst that is coordinated with this sterically large NHC demonstrates unique reactivity trends: it is sensitive to steric bulk in the metathesis substrates. This observation was the first example of an alteration in metathesis activity based on the steric disposition of the coordinated NHC ligand. This link between the NHC's structure and metathesis activity indicated that NHC ligands could be used to rationally influence the (stereo)selectivity of the metathesis process. General remarks on the outlook of catalyst synthesis conclude Part III.

Part II. Imidazolidines as N-Heterocyclic Carbene Synthons: Convenient Preparation and Ligand Substitution Reaction of 2-trichloromethyl-4,5-dihydroimidazolidine

Recently significant interest has centered on the use of *N*-heterocyclic carbene ligands as superior alternatives to phosphines.[7(a),2(a),25] The former offers many notable advantages, including readily tunable steric bulk, vastly increased electron donor character, and compatibility with a variety of metal species (Figure 3). The vast majority of research on these carbene ligands has focused on their generation and isolation, a feat finally accomplished by Arduengo and coworkers within the last ten years.[10,19,20] The

isolated carbenes are highly air- and water-sensitive, requiring that their manipulation be carried out under a dry, inert atmosphere. This sensitivity remains the primary obstacle to the widespread utilization of these ligands in organometallic catalysis.

Figure 3. Representative *N*-heterocyclic carbenes.



8: R_1 = aryl (i.e., mesityl, tolyl, 4-chlorophenyl); alkyl (i.e., isopropyl, cyclohexyl, n-alkyl)

9: R_1 = mesityl, substituted phenyl; R_2 = H, Ph, $-(CH_2)_4-$

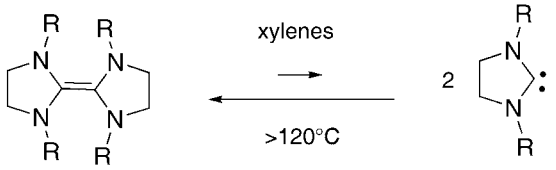
Early efforts sought to generate free *N*-heterocyclic carbenes from electron-rich olefins known as enetetraamines (Scheme 7, reaction (a)).[8,26] Unfortunately, these olefins are typically only slightly more air-stable than their constituent carbenes; they often undergo rapid oxidation in solution.[27] Even when these olefins are oxidatively stable, their productive thermal cleavage to free *N*-heterocyclic carbenes remains debatable, thereby preventing these olefins from serving as "protected" carbene sources.[28] As an additional drawback, these olefins cleave only at extremely high temperatures that are often incompatible with sensitive metal species.

The electron-rich nature of enetetramines has also led to the investigation of their cleavage by reaction with electrophiles (Scheme 7(b)). Regitz,[29] Hocker,[30] and coworkers suggest that a suitably chosen electrophile will react with the tetraamine to yield one equivalent of the carbene along with a carbene-electrophile adduct. Unfortunately, these reactions are generally unsuitable for use in organometallic

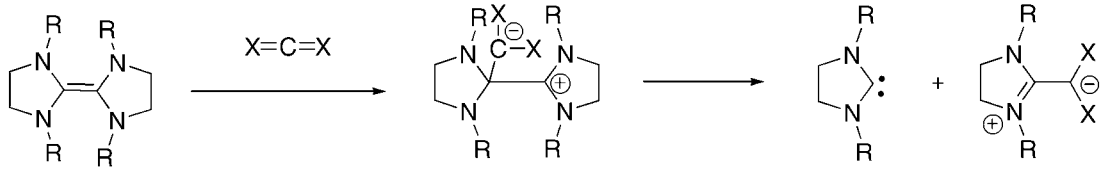
synthesis, given the possibility of diverse problems. For example, many nucleophilic metal species will not tolerate strong electrophiles (such as CO_2 and SO_2) that are required in the cleavage reactions. More importantly, the mechanisms of these electrophilic reactions remain poorly understood; the choice of optimal electrophile remains unclear. With these drawbacks, the "electrophilic" route appears ill suited for a general synthesis of *N*-heterocyclic carbene-coordinated metal species.

Scheme 7. Common base-free synthetic routes to form *N*-heterocyclic carbenes.

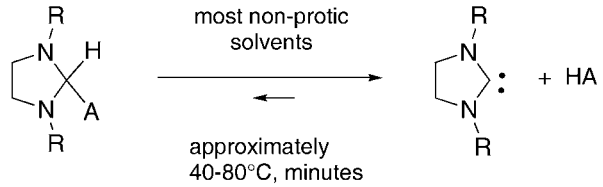
(a) Thermal cleavage of tetraaminoethylenes (enetetraamines)



(b) Cleavage of tetraaminoethylenes with electrophiles



(c) Thermal cleavage of imidazolidines (NHC adducts)



A more attractive possibility is the use of carbene "adducts" called imidazolidines (Scheme 7, reaction (c)).[8,31] In these species, a more labile "leaving group" could be thermally ejected, directly forming a free (uncomplexed) carbene. The combination of the imidazolidine and an appropriately chosen metallic precursor allows the direct, clean synthesis of *N*-heterocyclic carbene coordinated metal species at moderate temperatures. This method has been successfully utilized in the synthesis of ruthenium metathesis catalysts as well as a variety of platinum and palladium (II) dichlorophosphine species.[23,32]

Of relevance to organometallic synthesis are the "chloroform adducts," or trichloromethylimidazolidines (A = CCl_3 in Scheme 7(c)). Unlike other adducts that contain oxygen or nitrogen heteroatoms, the H_2IMes chloroform adduct (H_2IMes(H)(CCl_3), R = mesityl, A = CCl_3 in Scheme 7(c)) is a crystalline solid that is conveniently stored and weighed. This compound also exhibits excellent thermal, air, and water stability, particularly in the solid state. Its pronounced stability does not negate the imidazolidine's masked carbene character, however. In the presence of an appropriate metal species, these imidazolidines can be converted to free carbenes at low temperatures (lower than 80°C). In contrast, liberation of the free carbene from the imidazolidine typically does not occur at temperatures lower than 120°C in the absence of a metal "trap."

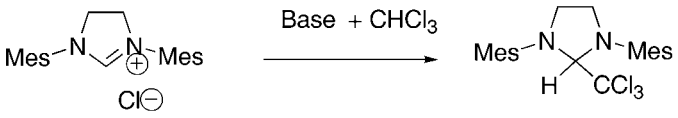
Syntheses of these species were originally accomplished by the direct condensation of *N,N'*-diaryl-1,2-diamines with chloral (trichloroacetaldehyde).[8] This route is no longer possible (or practical), for chloral is currently subject to distribution regulations, preventing its widespread availability. The reverse reaction of H_2IMes free carbene with chloroform has also been reported, although the reaction is very slow

(requiring 3 days at room temperature).[33] This observation confirms two important points. First, the synthesis of $H_2IMes(H)(CCl_3)$ (and other carbene adducts) is not efficiently accomplished from the free carbenes. Secondly, the high yields in the reaction strongly suggest that the trichloromethyl anion is not decomposing to dichlorocarbene over the course of the reaction. This latter observation suggests that the chloroform anion itself could be utilized as a nucleophile in a direct attack on an imidazolium salt ($[H_2IMes(H)][X]$, the precursor to the free carbene).

In order to test this hypothesis, chloroform was deprotonated with different *non-nucleophilic* bases (including alkali metal hydroxides) and the resulting solution was added to the chloride 4,5-dihydroimidazolium salt under varying temperature and solvent conditions (Table 1). After purification by recrystallization or column chromatography, the $H_2IMes(H)(CCl_3)$ adduct could be isolated on the gram scale in 83–90% yields as pure crystalline material. This high-yielding adduct synthesis, using the easily handled base potassium hydroxide, represents the simplest procedure developed to date for the production of $H_2IMes(H)(CCl_3)$. The synthesis can be readily carried out on the benchtop with non-dry, non-degassed solvents, and the use of potassium hydroxide prevents any large-scale flammability or reactivity problems. Exposure to potentially toxic chlorinated solvents (i.e., chloroform) in this procedure is also kept to a minimum.

It is also possible to deprotonate chloroform with even stronger non-nucleophilic bases such as florene and alkyllithiums (*tert*-butyllithium). These examples are noteworthy for their solubility in other non-polar solvents (such as hexanes or diethyl ether) which may be used. In a variety of cases these non-polar solvents should be ideal to limit the solubility of the imidazolium salt, thereby minimizing the side reactions from any amount of dichlorocarbene formed in the reaction.

Table 1. Variation of reaction parameters for the nucleophilic addition of trichloromethyl anion to 4,5-dihydroimidazolium salts.[a]



Number of equiv. $CHCl_3$	Solvent	Base	Temperature	Reaction Time	Yield[b]
As solvent	$CHCl_3$	NaOH	25°C	2 hr.	54%
3.0	THF	NaOH	reflux	2 hr.	59%
3.0	C_6H_6	NaOH	25°C	1.5 hr.	67%
3.0	toluene	KOH	25°C	2 hr.	**83%**
As solvent	$CHCl_3$	NaH	25°C	15 hr.	**90%**

[a]Refer to the Experimental Section for full experimental details. [b]Isolated yields.

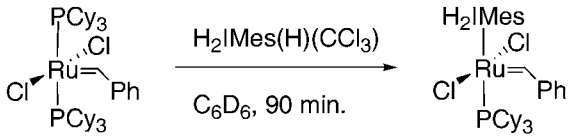
The KOH adduct synthesis is also tolerant of a variety of substitution patterns on the 4,5-dihydro-imidzolium salt, including R_1 = substituted aryl and R_2 = aryl or alkyl (in Figure 3). It is relevant to note that only 4,5-dihydroimidazolium salts (precursors to **9**) form base adducts—the aromatic imidazolium salts (precursors to **8**) are never observed to form these adducts under any conditions. Instead the latter species undergo immediate deprotonation to directly form the free carbene.

An alternate way of obtaining the compound $H_2IMes(H)(CCl_3)$ is by the reaction of an equimolar amount of a strong base (NaH) with chloroform in the presence of the imidazolium salt. By this route, higher yield and purity of the obtained product is achievable, eliminating any further purification. This reaction is relatively fast and takes place at room temperature. The trichloromethyl anion is formed in low concentration

from the reaction of the strong base sodium hydride with chloroform solvent. This basic solution can be pre-formed, standardized and stored for a short period at low temperature to prevent the formation of dichlorocarbene. Chloroform is also conveniently used because [H_2IMes(H)][Cl] is completely soluble in the reaction medium, accelerating the overall reaction. If equimolar amounts of base and imidazolium salt are dissolved in chloroform, the trichloromethyl anion is rapidly formed and readily reacts with the imidazolium salt. In minutes, the base is depleted and the resulting product remains in solution while sodium chloride (the only solid byproduct) precipitates. Using this method, reaction byproducts are minimized, thereby maximizing the yield and avoiding further purification.

Once the adduct is obtained in large quantity by the described method, it may be directly employed in a variety of ligand substitution reactions. Of particular note is the substitution of electron-rich phosphines in ruthenium(II)-based metathesis catalysts. As demonstrated in Table 2, the rate of this substitution reaction is strongly temperature-dependent. The reaction does not proceed at any appreciable rate below 55°C. At 80°C, the substitution rate remains much slower than the rate of phosphine dissociation ($9.6 \pm 0.2\ s^{-1}$), suggesting that the rate-limiting step in these reactions is the decomposition of H_2IMes(H)(CCl_3) to the free carbene. Even at these high temperatures the ruthenium species appear to remain intact throughout the reaction, without the formation of hydrides or other byproducts.

Table 2. Phosphine ligand substitution reaction on ruthenium(II) olefin metathesis catalyst **1**.[a]



1 **7**

Number of equiv. $H_2IMes(H)(CCl_3)$	Concentration of $H_2IMes(H)(CCl_3)$	Temperature	Reaction rate (k_{obs} X 10^4, s^{-1})[b]
1.0	0.04 M	40°C	NA
1.0	0.04 M	60°C	8.53 ± 0.33
2.0	0.08 M	60°C	7.23 ± 0.12
5.0	0.20 M	60°C	28.8 ± 2.6
5.0	0.20 M	80°C	326 ± 14

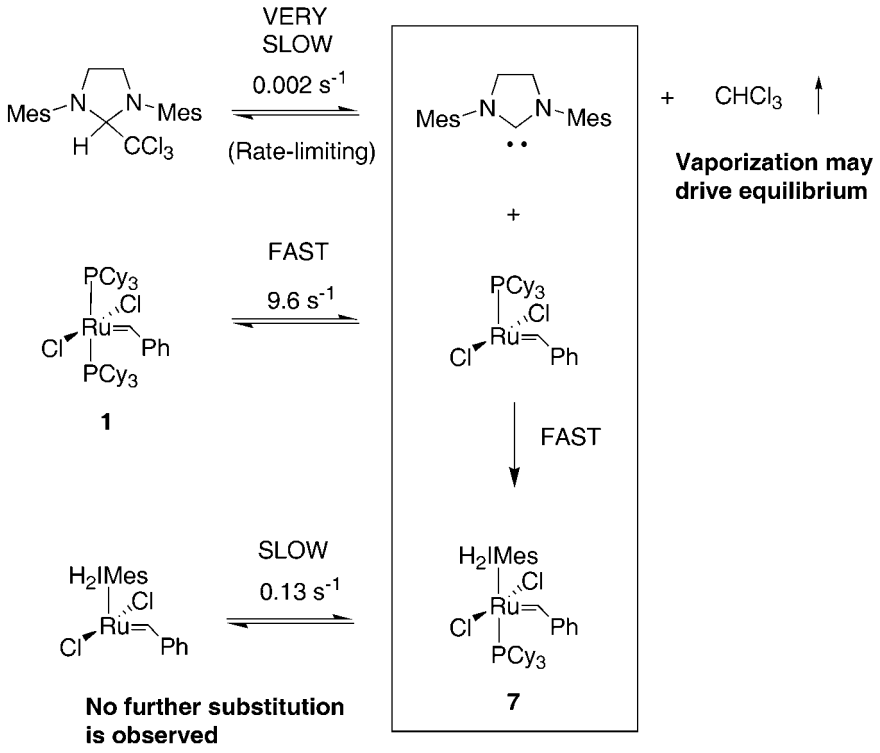
[a]Refer to the Experimental Section for full experimental details. [b]Determined by ^1H NMR spectroscopy on a 300 MHz Oxford Instruments NMR spectrometer. Kinetic data were fit to a first order exponential and half-lives were determined with the VNMR software package, Varian Associates, Inc.

The steady increase in reaction rate with increasing adduct concentration indicates that the reaction is not at saturation even with 0.20 M adduct at the lowest productive temperature (60°C). The saturation point was not extensively probed for practical reasons: a typical catalyst synthesis reaction would not be performed at higher temperatures or stoichiometries than absolutely necessary. At 60°C, the reaction with 0.08 M adduct (2 eq.) is complete in 90 minutes (100% conversion to catalyst **7**). This reaction time is practical on the large scale, circumventing the need to optimize the reaction under more extreme (i.e., rate-limiting) conditions. Two equivalents of adduct at

0.08 M concentration and 0.05 M ruthenium catalyst appears to be the optimal tradeoff between desirable reaction times and waste of the synthetically valuable $H_2IMes(H)(CCl_3)$. A similar protocol is now being investigated by industrial sources as a potential large-scale synthesis of catalyst **7**.

Further solvent and temperature optimization data is presented in Table 3. Careful temperature monitoring in benzene confirms that 55°C is the actual cutoff temperature below which no substitution occurs. This temperature is sufficiently close to the boiling point of chloroform (61°C) to suggest a reasonable mechanistic pathway for the ligand substitution reaction. As mentioned above, the reaction appears to be rate limited by the formation of the carbene from the adduct, and the reverse reaction (addition of chloroform to the free carbene) is possible, as demonstrated by Arduengo et al. These results suggest that a pre-equilibrium between the chloroform adduct and the free carbene is established prior to the actual ligand substitution (Scheme 8). Near its boiling point, the liberated chloroform may be readily vaporized to fill the headspace above the reaction. This vaporization may serve to drive the carbene formation equilibrium, raising the concentration of free carbene in solution. The free carbene can then readily substitute a phosphine ligand on the ruthenium catalyst.

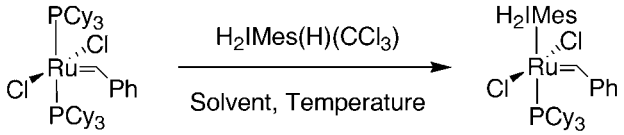
Scheme 8. A potential mechanistic pathway for the ligand substitution reaction. Rates are measured at 80°C. Rate for free carbene formation is not measured at saturation and therefore represents an approximation of the lower limit of the first order rate constant. Phosphine dissociation rates are reproduced from Sanford, M. S. Dissertation, California Institute of Technology, 2001.



Interestingly, the ligand substitution reaction is faster in more polar solvents, as demonstrated in Table 3. As the reaction medium is shifted from benzene/toluene to THF to dichlorobenzene, the overall rate increases by an order of magnitude. In particular, the shift from toluene to THF allows a twenty-degree decrease in temperature without compromising the reaction rate. This trend is consistent with a similar one observed by Sanford et al. for the phosphine dissociation rate of catalyst **1**.[34] This observation suggests that the overall substitution rate is accelerated by an increase in the rate of phosphine dissociation, providing more mono-phosphine 14-electron species to

react with the free NHC. This model suggests that both the carbene formation and the phosphine dissociation reactions are partially rate-limiting. However the large difference in rates between these reactions (four orders of magnitude) decreases the likelihood of this explanation.

Table 3. Solvent and temperature parameters for the ligand substitution reaction.[a]



1 **7**

Number of equivalents $H_2IMes(H)(CCl_3)$	Temperature	Solvent	Dielectric Constant	k_{obs} (s^{-1})[b]
1.2	50°C	Benzene	2.28	---
1.2	55°C	Benzene	2.28	$(4.4 \pm 0.6) \times 10^{-4}$
1.1	60°C	Benzene	2.28	$(8.5 \pm 0.1) \times 10^{-4}$
1.2	80°C	Toluene	2.38	$(1.9 \pm 0.1) \times 10^{-3}$
1.2	60°C	THF	7.52	$(1.9 \pm 0.01) \times 10^{-3}$
1.2	60°C	Dichlorobenzene	10.12	Greater than 2.1×10^{-3}

[a]Refer to the Experimental Section for full experimental details. [b]Determined by ^{1}H NMR spectroscopy on a 300 MHz Oxford Instruments NMR spectrometer. Kinetic data were fit to a first-order exponential and half-lives were determined with the VNMR software package, Varian Associates, Inc.

An alternative explanation can also be presented, based on the polarity of the free carbene. The free NHC is more polar than the chloroform adduct due to the former's juxtaposition of its partial positive empty p orbital and partial negative filled sp^2 orbital.

The more polar NHC will then be favored at equilibrium in more polar solvents, thereby shifting the carbene formation equilibrium. Currently no evidence can be presented in support of this explanation because the carbene formation reaction cannot be spectroscopically monitored under ligand substitution conditions.[35]

The manipulation of imidazolidine adducts offers a much more practical alternative to the synthesis and handling of free *N*-heterocyclic carbenes. The chloroform byproduct is generally innocuous toward various organometallic species, and ligand substitution with these adducts is facile at fairly low temperatures. The straightforward synthesis of chloroform adducts by nucleophilic addition to imidazolium salts allows these protected carbenes to be realized on the large scale. An ongoing study to expand the realm of nucleophiles amenable to this synthesis is currently underway.

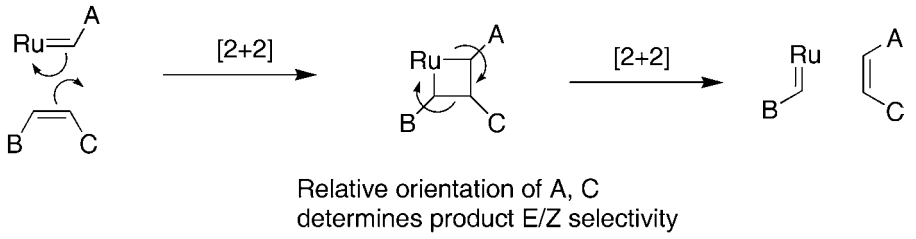
Part III. Extension of the NHC Adduct Methodology to NHC's other than H_2IMes: Synthesis of a Novel Alkoxide Adduct and Its Use in Catalyst Synthesis

The success of *N*-heterocyclic carbene-coordinated olefin metathesis catalysts was believed to be based largely on the electronic properties of the NHC ligands. Stronger σ-donor NHC's are presumably capable of stabilizing the active 14-electron complex (Part I of this chapter). Alternatively, the sterically large mesityl groups on the NHC nitrogens were believed to play a rather different role. Arduengo et al. suggested that large *N*-substituents were necessary to prevent dimerization of the free NHC's to enetetraamines (Part II of this chapter). The implication of this statement was the idea that large *N*-substituents sterically "blocked" the *ipso* carbons of two carbenes from coming within reactive proximity. If this statement is true, then the *N*-substituents on an

NHC coordinated to a metal may sterically influence the geometry of other ligands on the metal center. The overall result may be a change in the stereoselectivity of a metal catalyzed reaction.

For metathesis catalysts in particular, a relevant stereochemical question is that of E/Z stereoselectivity of the olefin products. The prototypical metathesis reaction that joins two terminal olefins to form an internal olefin may result in either a cis or trans disposition of the substituents on the product olefin. This stereochemical outcome is determined by the 2+2 mechanism of olefin metathesis originally detailed by Chauvin (Scheme 9).[36] In this mechanism a metallocyclobutane is formed by a 2+2 reaction and the product is generated by a subsequent cycloreversion. It is clear that the arrangement of substituents in the metallocyclobutane will determine the cis or trans disposition of substituents in the metathesis products. Influencing metallocyclobutane stereochemistry is therefore key to the question of metathesis stereoselectivity.

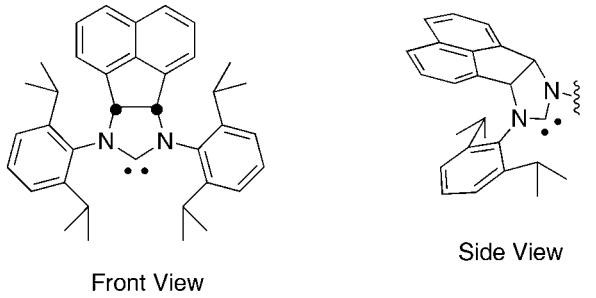
Scheme 9. Chauvin's metallocyclobutane mechanism for olefin metathesis.



Clearly, sterically larger ligands should have more influence than smaller ones on the formation of a putative metallocyclobutane, ignoring electronic effects. This hypothesis led us to design an NHC of considerably larger steric size than either IMes or H_2IMes (Figure 4). The ligand was based on acenaphthalenequinone and 2,6-

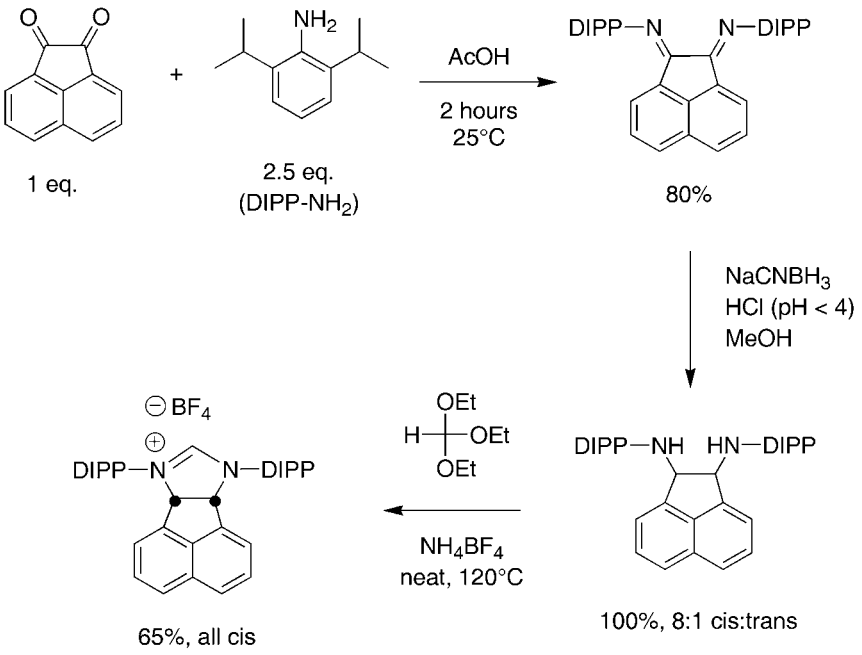
diisopropylaniline as commercially available starting materials. The ligand itself thus incorporated both large *N*-substituents and a large "backbone," both of which were deemed critical to maximize steric pressure on a potential metal center. In the absence of a large backbone, the *N*-substituents may be displaced away from the metal center by the other sterically large ligands that comprise the coordination sphere. The naphthalene backbone therefore serves to "compress" the *N*-substituents toward the ruthenium metal center.

Figure 4. "BIAN" *N*-heterocyclic carbene and its cisoid configuration.



The relatively straightforward ligand synthesis is detailed in Scheme 10. Elsevier et al. describe the formation of the bis-imine, and as expected it is in an E,E-configuration.[37] Reductive amination is then relatively straightforward, yielding an 8:1 mixture of cis and trans isomers, respectively. As expected, the cis compound dominates due to the fact that the molecule becomes convex upon the first imine reduction. The second imine reduction is therefore more favorably accomplished from the same face (in this case the "convex" or β face). The final generation of the imidazolium salt by the procedure of Saba et al. was successful, producing the desired tetrafluoroborate salt in 65% yield.[38]

Scheme 10. Synthesis of BIAN imidazolium salt from commercially available starting materials.



Although both cis and trans diamine products were present in the salt formation reaction, only the cis diamine cyclized under these conditions. This result was confirmed by obtaining a crystal structure of the salt, which clearly showed the cis linkage.[39]

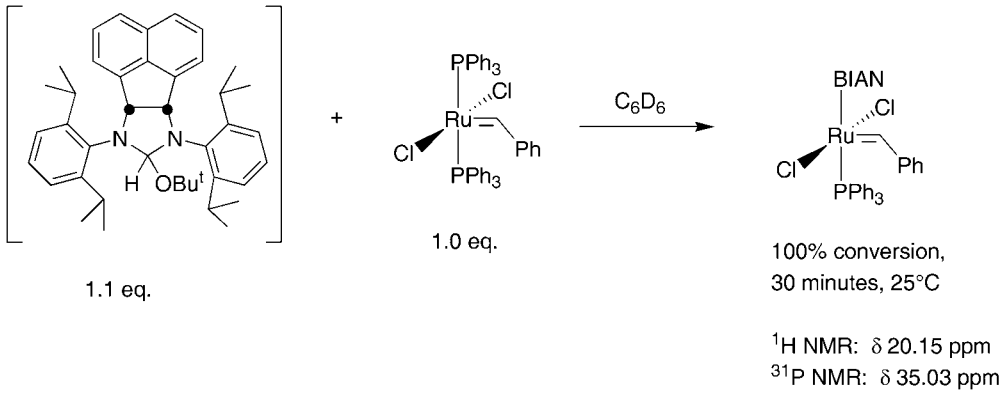
Subjecting the salt to a variety of *in situ* deprotonation conditions ($KOBu^t$, NaH/DMSO, BuLi, NaOMe) failed to generate any free NHC, and addition of **1** to the mixture was unproductive (no new alkylidenes were observed). In order to probe the fate of the salt, deprotonations with NaH and $KOBu^t$ in the *absence of **1*** were attempted. In the first case no free NHC was formed and only imidazolium salt starting material was obtained at the conclusion of the reaction. In the latter case a yellowish orange solid remained after the solvent was removed *in vacuo*.

This solid was handled carefully under air- and moisture-free conditions, but it eluded full characterization. Its solubility was extremely high in both polar and non-

polar organics (including hexanes and methanol), preventing crystal structure determination. GC-MS and high resolution MS were inconclusive (both only showed mass peaks corresponding to the cation of [BIAN(H)][BF_4]). Only NMR presented leading evidence for the structure of this unknown compound: a new peak in the ^1H NMR was present at δ 5.612 ppm in C_6D_6, and no evidence of the salt proton at 9–10 ppm was visible. *tert*-Butyl peaks were observed at δ 1.25 ppm, suggesting that a *tert*-butyl moiety was in fact incorporated into the product. There was also no carbene carbon in ^{13}C NMR at approximately δ 250 ppm, demonstrating that the unknown was *not* a free NHC. In total, the spectroscopic evidence suggested that the salt had been transformed into a *tert*-butoxide adduct.

This result was confirmed when the proposed adduct was mixed with $(PPh_3)_2(Cl)_2Ru{=}CHPh$ at room temperature (Scheme 11).[40] One of the triphenylphosphine ligands was cleanly replaced with the novel NHC ligand (hereafter referred to as BIAN, *B*is-di*I*sopropyl*A*ce*N*aphthalene carbene). Unfortunately the new mixed NHC-PPh_3 catalyst decomposed readily upon attempted isolation and could not be completely characterized. However this experiment did empirically demonstrate that the isolated yellow compound was in fact a *tert*-butoxide adduct (hereafter referred to as BIAN(H)(OBu^t) that could readily form the free NHC BIAN even at low temperatures (25°C).

Scheme 11. Reaction of BIAN(H)(OBu^t) with $(PPh_3)_2(Cl)_2Ru{=}CHPh$.

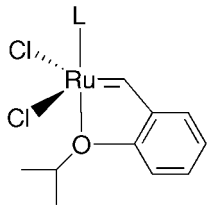


Interestingly, the BIAN(H)(OBu^t) adduct did not react with **1** at temperatures up to 80°C, in contrast to the chloroform adducts described in Part II, which react readily at temperatures above 55°C. Phosphine dissociation rate constants are consistent with this behavior, however. In particular, the rate of dissociation of PPh_3 in $(PPh_3)_2(Cl)_2Ru{=}CHPh$ is significantly faster than the rate of dissociation of PCy_3 in **1**.[41] This difference in behavior between the H_2IMes chloroform adduct and BIAN(H)(OBu^t) suggests that the BIAN and H_2IMes free carbenes differ in coordination ability, basicity, nucleophilicity, or all of the above. Their similar structures suggest that any differences in coordination ability between BIAN and H_2IMes must arise from the increased steric bulk in the former. If this supposition were true, BIAN may accomplish the stated goal of influencing metathesis stereoselectivity through steric congestion.

In order to investigate this possibility, a stable BIAN-coordinated catalyst needed to be synthesized. To accomplish this goal, more straightforward means of purification and workup of new catalysts were necessary. At approximately the same time that the BIAN(H)(OBu^t) adduct was synthesized, Hoveyda and coworkers addressed this problem by reporting their development of a ruthenium olefin metathesis catalyst that could be

purified effectively by column chromatography (Figure 5).[42] This catalyst was chelated with an isopropoxy function in the place of the phosphine ligand, resulting in increased thermodynamic stability. This ability to use chromatography to purify catalysts had remained largely unexplored, although catalyst **5** was originally purified (in low yields) by preparative TLC.[43] If the PCy_3 ligand in these isopropoxychelate catalysts could be replaced with a BIAN NHC, the resulting complex should also be stable to column chromatography. The stronger σ-donor character of the NHC's relative to phosphines suggests that the NHC-coordinated isopropoxychelate catalysts should be even more stable to chromatography than their phosphine counterparts.

Figure 5. Isopropoxychelate catalysts. Originally reported in Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791-799.

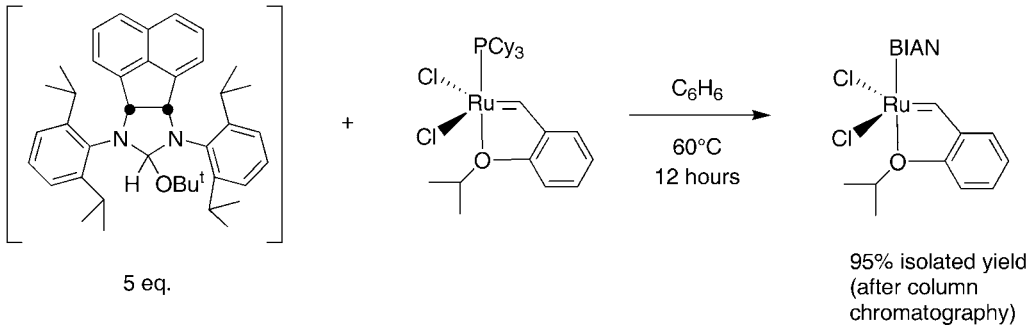


L = phosphine, *N*-heterocyclic carbene

Upon treatment of the PCy_3-coordinated catalyst ($(PCy_3)(Cl)_2Ru$=CH-*o*-$OPr^iC_6H_4$) with excess BIAN(H)(OBu^t) for 12 hours at elevated temperatures, the desired BIAN-coordinated catalyst was produced (Scheme 12). Although no intermediate species were observed, this substitution reaction was significantly slower than those performed with $(PPh_3)_2(Cl)_2Ru$=CHPh. In order to investigate the pathway of ligand substitution in these isopropoxychelate complexes, a set of NMR tube reactions was performed with the free IMes carbene. Combination of 1.5 equivalents of IMes with

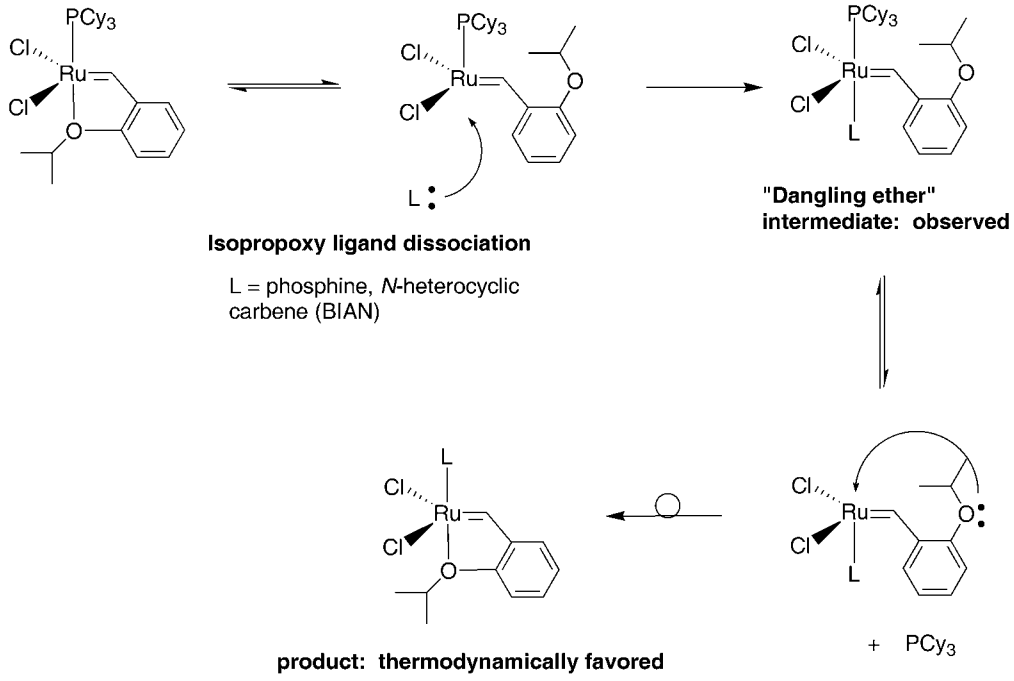
$(PCy_3)(Cl)_2Ru$=CH-*o*-$OPr^iC_6H_4$ at room temperature produced the desired product ($(IMes)(Cl)_2Ru$=CH-*o*-$OPr^iC_6H_4$) after 1 hour. An intermediate product was observed to grow in and subsequently be consumed over the course of this first hour. The NMR data for this intermediate were more similar to **5** and **6** than to a isopropoxychelate catalyst. In particular, the ^{1}H NMR data for the alkylidene proton is diagnostic: the benzylidene in a oxygen-ruthenium chelate is present at approximately δ 16–17 ppm in C_6D_6. The intermediate product benzylidene resonance is present at δ 20.6 ppm, a region much more typical of a catalyst coordinated with phosphines and/or NHC ligands. Additionally the intermediate has a ^{31}P resonance at δ 34.05 ppm, demonstrating that at least one phosphine remained bound to the ruthenium center. On the basis of this evidence, two structures can be proposed for this intermediate. The more probable case is the *bis*-phosphine system similar to **1** (that is, $(PCy_3)_2(Cl)_2Ru$=CH-*o*-$OPr^iC_6H_4$). The precise similarity of ^{1}H NMR resonances between **1** and this proposed intermediate is not surprising: both species have nearly identical environments around the metal center (two PCy_3 ligands, two chlorides, and a benzylidene). Although this possibility is attractive, the alternative intermediate coordinated by IMes and PCy_3 ligands cannot be ruled out without isolation and full characterization data.

Scheme 12. Reaction of BIAN(H)(OBu^t) with an isopropoxychelate catalyst.



In either event, an intermediate containing a "dangling" ether moiety is proposed (Scheme 13). This ether function then substitutes the more labile L-type ligand, which in either case is a PCy_3 ligand (due once again to its reduced σ-donor character relative to NHC). Overall, as expected, the catalyst synthesis is driven by the thermodynamic stability of the product relative to the starting material. Both $(IMes)(Cl)_2Ru{=}CH\text{-}o\text{-}OPr^iC_6H_4$ and its BIAN derivative are stable to column chromatography and can be isolated in 95% yield as yellowish orange air- and moisure-stable solids.[44]

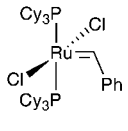
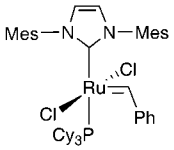
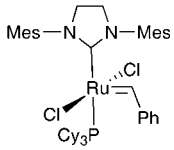
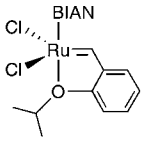
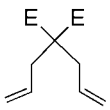
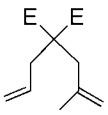
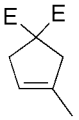
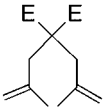
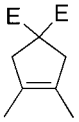
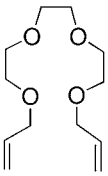
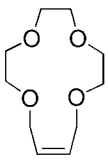
Scheme 13. Reaction pathway of an L-type ligand with an isopropoxychelate catalyst.



Now that synthetically useful quantities of a BIAN-coordinated catalyst could be readily prepared, its relative activity to **1**, **5**, and **6** could be ascertained. To this end, sample ring closing reactions are detailed in Table 4. These results make it clear that **6** can perform RCM to di- and tri-substituted olefin products significantly faster than **1** or even **5**.[23] An unexpected result comes from the (BIAN)$(Cl)_2$Ru=CH-*o*-$OPr^iC_6H_4$ catalyst: it is apparently sensitive to steric bulk in the substrates. For unhindered substrates such as diethyldiallylmalonate, the reaction was finished within 2 minutes (before the first NMR spectrum could be recorded). This result represents the fastest known ring closure rate for the reaction of this malonate substrate. The ring closures to form tri- and tetra-substituted olefins (entries 2 and 3) are significantly slower for the BIAN catalyst than for either **5** or **6**, suggesting that these more sterically hindered olefins are more difficult to form with sterically large catalysts. Clearly the

metallocyclobutane intermediate formed during the ring closure to tri- and tetra-substituted olefins is sterically "crowded," requiring a less bulky catalyst to successfully close. Because the (BIAN)$(Cl)_2$Ru=CH-*o*-OPr^iC_6H_4 catalyst and **6** are electronically similar, the differences in reaction rate must stem from steric influences.

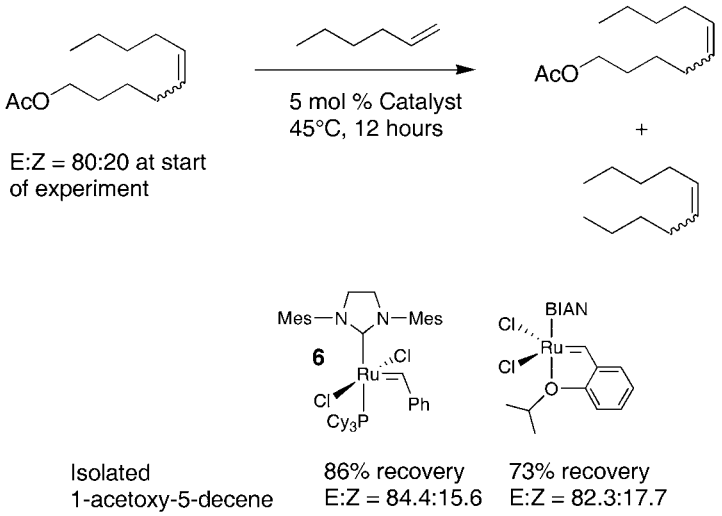
Table 4. Relative measurements of catalyst activity as expressed by ring-closing metathesis experiments.[a]

		Yield, E:Z w/ catalyst			
		1	**5**	**6**[b]	
E = CO_2Et					
Substrate	**Product**				
		30 minutes, 100%	30 minutes, 100%	10 minutes, 100%	5 minutes, 100%
		30 minutes, 82%	30 minutes, 100%	10 minutes, 100%	35 minutes, 100%
		N. R.	1.5 hrs., 40%	2 hrs., 31%	18 hrs. 10%
		1 hr., 39%, E:Z = 1.6:1	1 hr., 55%, E:Z = 2:1	1 hr., 35%, E:Z = 2:1	1 hr. 39%, E:Z = 2.2:1

[a]For details, see the Experimental Section. N. R. = No reaction. Yields are determined by ^{1}H NMR (CD_2Cl_2, 300 MHz), except for the ether crown substrate, in which case each isomer was isolated separately and compared to data in Maynard, H. D. Dissertation, California Institute of Technology, 1999. [b]Values originally reported in Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.

This realization led to a wide-ranging hypothesis: NHC ligands can be successfully engineered to sterically influence the outcome of metathesis reactions. The BIAN ligand was not an ideal test of this hypothesis, however, as evidenced by the relative cis/trans stereoselectivities in test reactions. The ring closure of an oligoether substrate described by Marsella et al. was found to exhibit similar E:Z stereoselectivity using either the BIAN catalyst or **6** (Table 4, entry 4).[45] Similar results were obtained in simple cross metathesis reactions between 1-hexene and 6-acetoxy-1-hexene, indicating that the BIAN ligand does not significantly alter the overall stereoselectivity of the metathesis process (Scheme 14).[46]

Scheme 14. Cross metathesis of 1-acetoxy-5-decene with 1-hexene.[a]



[a]See Experimental Section for details. "Recovery" value is the isolated yield of 1-acetoxy-5-decene at the end of the experiment. E:Z ratios are determined by GC analysis.

Of particular importance in the development of BIAN(H)(OBu^t) is the extension of the adduct methodology described in Part II of this chapter to NHC's that are sterically distinct from H_2IMes. The *tert*-butoxide adduct described herein incorporates many of

the same advantages of the H_2IMes chloroform adduct, namely, thermal, air-, and moisture-stability. For example, BIAN(H)(OBu^t) can be easily handled on the benchtop in air and stored for months (as a solid) at room temperature. In the presence of an appropriate metal precursor (such as the isopropoxychelate catalysts), BIAN(H)(OBu^t) is capable of generating free NHC and subsequently substituting another L-type ligand (in this case, a phosphine). In total, BIAN(H)(OBu^t) is a completely functional NHC adduct that can be readily scaled up (the synthesis has been performed on 20 g scales) for general catalyst synthesis.

The NHC adduct technology described in this chapter can therefore be successfully generalized to a variety of NHC's with differing steric bulk, and it has been performed on industrial scales (hundreds of grams of catalyst **6** have been produced from NHC adducts).[47] The problem set forth in the Introduction has therefore been successfully addressed: NHC adducts do offer easily handled alternatives to the free NHC's in catalyst design and synthesis. The original *tert*-butoxide-mediated synthesis of **6** has now been superceded by the implementation of the H_2IMes chloroform adduct technology described in Part II. This development in catalyst design has successfully increased the production of **6**, bringing the "next generation" of ruthenium-based olefin metathesis catalysts into the general synthetic laboratory.

Acknowledgements. The author thanks the National Institutes of Health for financial support of this research. Dr. Sharad Hajela is thanked for his continuous support of this research, in material, time, and effort. Dr. Melanie Sanford, Dr. Thomas Kirkland, Dr. Matthias Scholl, and Tina Trnka are thanked for helpful discussions and insight. Dr. Michael Ulman and Dr. Heather Maynard are gratefully acknowledged for

providing substrates described in Table 4. Dr. Richard Pedersen is also gratefully acknowledged for providing 1-acetoxy-5-decene.

Experimental Section. General. Anhydrous chloroform and toluene (obtained from Aldrich Chemical Company) are degassed by bubbling dry nitrogen gas throughout. Potassium hydroxide is obtained from EM Science and powdered by mortar and pestle. Sodium hydride is obtained as a 95% dry solid from Aldrich. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230–400 mesh) from EM Science. All other chemicals were purchased from the Aldrich or EM Science/Baker Chemical Companies, and used as delivered unless noted otherwise. All other solvents were purified by passage through a solvent column containing activated A-2 alumina. See: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520. NMR spectra were recorded on a Oxford Instruments 300 MHz instrument or a Varian Inova 500 MHz instrument. Deuterated solvents were dried over 4A molecular sieves and degassed prior to use. ^{1}H and ^{13}C NMR spectra were referenced to internal solvent, and ^{31}P spectra were referenced to an external standard (H_3PO_4).

Bis-(2,6-diisopropylphenyl)acenaphthalene diimine was prepared as described in van Asselt, R.; Elsevier, C. J.; Smeets, W. J.; Spek, A. L.; Benedix, R. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 88-98. [H_2IMes(H)][Cl] is synthesized and characterized in Arduengo, A. J. III; Krafczyk, R.; Schmutzler, R. *Tetrahedron*, **1999**, *55*, 14523-14534. [H_2IMes(H)][BF_4] was prepared by the route described in Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179.

$(PCy_3)(Cl)_2Ru{=}CH\text{-}o\text{-}OPr^iC_6H_4$ was prepared according to Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791-799.

2-Trichloromethyl-4,5-dihydroimidazolidine, $H_2IMes(H)(CCl_3)$, using KOH. Dry, degassed toluene (8.2 mL) was added to a flame dried 50 mL round-bottomed flask equipped with stirbar and reflux condenser. A large excess of powdered potassium hydroxide (> 10 mmol) was added to the flask, and the resulting suspension was rapidly stirred at room temperature. Chloroform (77 μL, 0.96 mmol) was added to this suspension by microsyringe. After 10 minutes, $[H_2IMes(H)][Cl]$ (100 mg, 0.29 mmol) was added, and the reaction mixture was then heated to 60°C for 75 minutes. The mixture was allowed to cool to room temperature, vacuum filtered, and concentrated *in vacuo* to a yellowish-white solid. This crude product was then purified by filtration through a silica gel plug, eluting with 9:1 hexanes:ethyl acetate. The product was further purified by recrystallization from boiling hexanes to give a white solid (110 mg, 88% yield). Characterization data for $H_2IMes(H)(CCl_3)$ are identical to those reported in Arduengo, A. J.; Calabrese, J. C.; Davidson, F.; Dias, H. V. R.; Goerlich, J. R.; Krafczyk, R.; Marshall, W. J.; Tamm, M.; Schmutzler, R. *Helv. Chim. Acta* **1999**, *82*, 2348-2364.

2-Trichloromethyl-4,5-dihydroimidazolidine, $H_2IMes(H)(CCl_3)$, using NaH. $[H_2IMes(H)][Cl]$ (10 g, 29 mmol) was dissolved in dry, degassed chloroform (250 mL) in a flame dried 1000 mL round-bottomed flask equipped with stirbar. Afterward, sodium hydride (dry powder, 695 mg, 29 mmol) was slowly added to the flask, and the resulting suspension was rapidly stirred at room temperature for 90 minutes. It was then vacuum filtered to remove NaCl, and concentrated *in vacuo* to a white solid. The product can be

further purified by recrystallization from boiling hexanes to give a white crystalline solid (11.7 g, 94% yield). Characterization data for $H_2IMes(H)(CCl_3)$ are identical to those reported in Arduengo, A. J.; Calabrese, J. C.; Davidson, F.; Dias, H. V. R.; Goerlich, J. R.; Krafczyk, R.; Marshall, W. J.; Tamm, M.; Schmutzler, R. *Helv. Chim. Acta* **1999**, *82*, 2348-2364.

Synthesis and characterization of $H_2IMes(H)(OBu^t)$: Method 1. Potassium *tert*-butoxide (28 mg, 0.25 mmol, 1.0 eq.) was added as a solid to a solution of $[H_2IMes(H)][BF_4]$ (100 mg, 0.3 mmol, 1.0 eq.) in dry THF (3 mL), previously prepared in a flame-dried 10 mL Schlenk flask. The colorless solution was stirred under a nitrogen atmosphere at room temperature for 10 minutes, and a persistent yellowish color developed after 1 minute. The solution was subsequently concentrated *in vacuo* to a yellowish solid. This crude product was washed with dry diethyl ether (5 mL) to produce a colorless semisolid product (approximately 50 mg, 51% yield) that decomposes by extrusion of *tert*-butanol at room temperature (observed in ^1H NMR (THF-d_8)). **Method 2:** A J. Young NMR tube was charged with 0.040 g (0.101 mmol) of $[H_2IMes(H)][BF_4]$, 0.011 g (0.101 mmol) $KOBu^t$, and 1 mL THF-d_8. ^1H and ^{13}C NMR were recorded after 6 hrs at room temperature. ^1H NMR (C_6D_6): δ 6.82 [s, 2H, m-CH_{Mes}], 6.81 [s, 2H, m-CH_{Mes}], 5.61 [s, 1H, CH], 3.74 [m, 2H, CH_2CH_2], 3.27 [m, 2H, CH_2CH_2], 2.46 [s, 6H, CH_3 of Mes], 2.34 [s, 6H, CH_3 of Mes], 2.20 [s, 6H, CH_3 of Mes], 1.11 [s, 9H, OBu^t]. ^{13}C NMR (C_6D_6): δ 139.69, 138.76, 137.83, and 134.96 [o-C_{Mes}, ipso-C_{Mes}, and p-C_{Mes}], 129.19 [CH_{Mes}], 128.50 [CH_{Mes}], 95.40 [N_2C], 70.81 [$OCMe_3$], 48.58 [CH_2CH_2], 28.03 [CH_3 on OBu^t], 20.06 [CH_3 on Mes], 19.02 [CH_3 on Mes], 18.08 [CH_3 on Mes]. This

solution was also subjected to HRMS analysis (EI) m/z: calcd for $C_{25}H_{36}N_2O$ [M^+] 380.2828, found 380.2831.

Synthesis of (H_2IMes)(PCy_3)Cl_2Ru=CHPh (6), using H_2IMes(H)(CCl_3). A flame-dried 50 mL Schlenk flask was charged with (PCy_3)$_2$(Cl_2)Ru=CHPh **1** (165 mg, 0.20 mmol, 1.0 eq.), H_2IMes(H)(CCl_3) (188 mg, 0.44 mmol, 2.2 eq.) and toluene (5 mL). The reaction mixture was heated to 60ºC for 90 minutes under a nitrogen atmosphere. The mixture was then allowed to cool to room temperature and was concentrated *in vacuo* to a brownish-pink semisolid. This crude product was washed with methanol (2 × 5 mL) and pentane (3 × 10 mL) and then dried *in vacuo* for 12 hours. The resulting reddish solid product (140 mg, 84% yield) can be further purified by column chromatography on TSI brand silica gel with gradient elution (7:1 hexanes:diethyl ether to 100% diethyl ether). Characterization data for **6** are identical to those reported in Sanford, M. S., Dissertation, California Institute of Technology, 2001.

NMR tube reactions of (H_2IMes)(PCy_3)Cl_2Ru=CHPh (6) with H_2IMes(H)(CCl_3). In the glovebox, an NMR tube equipped with Teflon septum is charged with (PCy_3)$_2Cl_2$Ru=CHPh **1** (16.5 mg, 20 μmol, 1 eq.) and C_6D_6 (0.25 mL). A separate vial, also equipped with Teflon septum, was charged with H_2IMes(H)(CCl_3) in C_6D_6 (0.25 mL). Both the NMR tube and the vial were sealed and removed from the glovebox, and the tube was equilibrated for 10 minutes at the reaction temperature in the NMR probe. The adduct solution is then added to the NMR tube via microsyringe and the NMR tube is carefully inverted once to mix the reagents. A ^{1}H NMR spectrum (8 scans) was

recorded every 15 seconds for 1 hour, and kinetics data were fit to a first order exponential with Varian VNMR software.

***Bis*-(2,6-diisopropylphenyl)acenaphthalene diamine.** *Bis*-(2,6-diisopropylphenyl)acenaphthalene diimine (10 g, 20 mmol, 1 eq.), sodium cyanoborohydride (7.5 g, 120 mmol, 6 eq.) and benchtop MeOH (200 mL) were added to a 500 mL round-bottom flask equipped with stirbar and gas inlet. The solution was stirred rapidly and concentrated HCl (10–15 mL) was added slowly until frothing ceased and purple color dissipated. The solution was allowed to stir for 4 hours, during which time the solution color became purple again. Another aliquot of concentrated HCl was added until the purple color dissipated (5 mL). The pH of the solution was measured to be 4–5 (by universal indicator pH paper). After another 4 hours of stirring at room temperature, the solution remained clear with white precipitate. The pH of the solution was raised to 12 with aq. NaOH (1 M, approximately 100 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organics were dried and concentrated *in vacuo* to produce a yellow, fluffy semisolid oil (0.26 g, quantitative yield).

Synthesis of [BIAN(H)][BF_4]. *Bis*-(2,6-diisopropylphenyl)acenaphthalene diamine (9.79 g, 19 mmol, 1 eq.) and ammonium tetrafluoroborate (2 g, 19 mmol, 1 eq.) were dissolved in triethylorthoformate (40 mL) and the resulting yellowish solution was refluxed for 3 hours under a nitrogen atmosphere. After this time the solution was vacuum filtered to remove precipitated solid product. This product was decolorized by

repeated washing with pentane, which produced a bright white semicrystalline salt (7.4 g, 65% yield).

Synthesis of BIAN(H)(OBu^t). A suspension of [BIAN(H)][BF_4] (4.22 g, 7 mmol, 1 eq.) in THF (85 mL) was prepared in a flame-dried 50 mL Schlenk flask equipped with stirbar. Potassium *tert*-butoxide (786 mg, 7 mmol, 1 eq.) was added in one portion as a solid to the reaction mixture, and the resulting suspension was rapidly stirred at room temperature under N_2 for 20 minutes. During this time the solution became slightly yellowish and the solid precipitate became more finely divided (typical of KBF_4 salt). The reaction mixture was concentrated to a sticky solid and then extracted repeatedly with Et_2O. Concentration of the combined Et_2O layer produced a yellow-orange fluffy solid product (2.84 g, 69% yield). The high solubility of this product in both polar and non-polar organics prevented crystal growth. Characteristic NMR data: ^{1}H NMR (C_6D_6): δ 5.62 (s, 1H, ipso proton), 1.25 (s, 9H, *tert*-butyl protons) ppm. HRMS (CI) showed only the cation [BIAN(H)]$^+$ at 513.3271 mu.

Synthesis of (BIAN)(Cl)$_2$Ru=CH-*o*-OPr^{i}C$_6$H$_4$. In the glovebox, a J. Young NMR tube was charged with (PCy_3)(Cl)$_2$Ru=CH-*o*-OPr^{i}C$_6$H$_4$ (10 mg, 17 μmol, 1 eq.), BIAN(H)(OBu^t) (50 mg, 85 μmol, 5 eq.) and C_6D_6 (1 mL). The tube was sealed and heated to 60°C for 14 hours, after which time complete conversion to product was observed. Pipet column chromatography with dichloromethane as eluent produced 14 mg of product as a yellowish solid (quantitative yield). The product identity was confirmed by a characteristic ^{1}H NMR resonance at δ 16.82 ppm in C_6D_6.

NMR tube synthesis of (IMes)(Cl)$_2$Ru=CH-*o*-OPr^{i}C$_6$H$_4$ from IMes free carbene. In the glovebox a solution of IMes free carbene (3 mg, 7.5 μmol, 1.5 eq.) in C_6D_6 (0.5 mL) was added by syringe to a solution of $(PCy_3)(Cl)_2Ru$=CH-*o*-OPr^{i}C$_6$H$_4$ (4 mg, 6.7 μmol, 1.0 eq.) also in C_6D_6 (0.5 mL). The yellow solution was sealed in a J. Young NMR tube and ^{1}H NMR spectra were recorded periodically. The production of the phosphine-containing intermediate was monitored by its characteristic signals in ^{1}H NMR (δ 20.61 ppm) and in ^{31}P NMR (δ 34.05 ppm). This intermediate was observed to convert to product, which was identified by its characteristic ^{1}H NMR peak (δ 16.84 ppm). Conversion to the product could be maximized by heating the solution to 55°C for 18 hours. After this time, the product could be isolated by pipet column chromatography with dichloromethane as the eluent. The final product was isolated from the NMR tube solution in approximately 70% yield as a yellowish brown solid. Characterization data are identical to those reported in Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179.

Attempted synthesis of (BIAN)(PPh$_3$)(Cl)$_2$Ru=CHPh. A flame-dried 100 mL Schlenk flask under N_2 was charged with $(PPh_3)_2(Cl)_2Ru$=CHPh (500 mg, 635 μmol, 1.0 eq.), BIAN(H)(OBu^t) (412 mg, 700 μmol, 1.1 eq.) and C_6D_6 (30 mL). The resulting brown solution was stirred under N_2 for 2.5 hours and subsequently concentrated *in vacuo* to a sticky brown solid. The solid was lyophilized from benzene and washed with pentane (3 × 2 mL). ^{1}H NMR of the brownish solid showed less than 40% desired alkylidene remained. Characteristic NMR data: ^{1}H NMR (C_6D_6): δ 20.15 ppm. ^{31}P NMR (C_6D_6): δ 35.0271 ppm.

Reaction of NHC-coordinated catalysts with malonate substrates. In the glovebox a screw cap NMR tube equipped with a Teflon septum was charged with malonate substrate (0.45 mmol, 1 eq.), NHC-coordinated catalyst (23 μmol, 5 mol %), and CD_2Cl_2 (1 mL, 0.45 M substrate). The tube was immediately sealed, the septum was punctured with a small (22 gauge) needle, and ^1H NMR spectra (8 scans) were recorded every 15 s for 30 minutes. Completion was monitored by noting the time when 3 half-lives had passed without a change in product integration that exceeded 5% of the total.

Cross metathesis of 1-acetoxy-5-decene and 1-hexene. In the glovebox a 10-dram vial is charged with 1-acetoxy-5-decene (40 mg, 0.2 mmol, E:Z = 80:20), catalyst (5 mol % relative to decene), and CH_2Cl_2 (1 mL). The vial is sealed with a cap containing a Teflon septum and removed from the box. The vial is placed under a nitrogen atmosphere and heated to 45°C for 12 hours. After this time, the starting material is reisolated by column chromatography and subjected to GC analysis for determination of its E:Z ratio.

References and Notes:

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[46] These substrates and cross metathesis conditions were generously provided by Dr. Richard Pedersen of Materia, Inc.

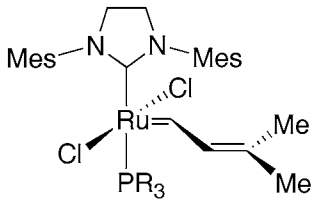
[47] Materia, Inc. has utilized the chloroform adduct technology described in Part II to synthesize **6** (and other similar catalysts) on kilogram scales.

Chapter 3. Improved Olefin Metathesis Activity of *N*-Heterocyclic Carbene-Coordinated Ruthenium Olefin Metathesis Catalysts I: Cross Metathesis[1]

Part I. Synthesis of Functionalized Olefins by Cross and Ring-Closing Metatheses[2]

The generation of olefins with electron-withdrawing functionality, such as α,β-unsaturated aldehydes, ketones, and esters, remains a difficult synthetic task. A practical method to approach this problem would involve olefin metathesis,[3] utilizing well-defined alkylidenes such as $((CF_3)_2MeCO)_2(ArN)Mo=CH(t\text{-}Bu)$ (**1**)[4] and $(PCy_3)_2Cl_2Ru=CHPh$ (**2**).[5] However, the generation of olefins with vinylic functionality through cross metathesis[6] (CM) has met with limited success. In one of the few reports of this reaction, Crowe and Goldberg[7] demonstrated that acrylonitrile participated in cross metathesis reactions with a variety of terminal olefins. Other π-conjugated olefins, such as enones and enoic esters, were not functional group compatible with alkylidene **1** and failed to react with **2**. Recently, the highly active ruthenium-based olefin metathesis catalyst **3**,[8] which contains a saturated carbene ligand, was found to efficiently catalyze the cross metathesis of 1,1-geminally disubstituted olefins (Figure 1).[9] In this section, we report the single-step synthesis of α-functionalized olefins by intermolecular cross metathesis using ruthenium alkylidene **3**.

Figure 1. *N*-heterocyclic carbene-coordinated metathesis catalyst **3**.

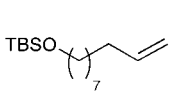
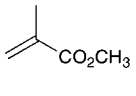
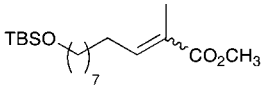
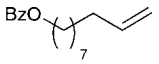
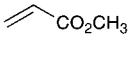
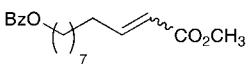
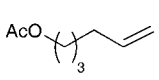
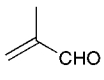
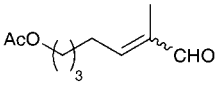
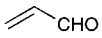
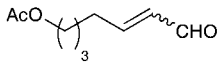
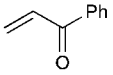
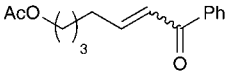
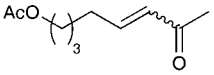


While exploring a variety of 1,1-geminally disubstituted olefins as substrates for CM, we discovered that methyl methacrylate **7** participates in CM with terminal olefin **4**

to generate the trisubstituted compound **13** in moderate yield with excellent stereoselectivity (Table 1, entry 1). This result led us to examine the cross metathesis of various α-carbonyl compounds (Table 1). Particularly noteworthy are the excellent yields

obtained with ketones and aldehydes (Table 1, entries 3 - 6). Extended reaction times

Table 1. Cross Metathesis Reactions with Esters, Aldehydes and Ketones[a]

entry	terminal olefin	α-functionalized olefin (equiv.)		product	isolated yield(%)	*E/Z*[b]
1	 **4**	 **7**	(0.5)	 **13**	62	>20:1
2	 **5**	 **8**	(2.0)	 **14**	91	>20:1
3	 **6**	 **9**	(0.5)	 **15**	92	>20:1
4	**6**	 **10**	(2.0)	 **16**	62	>20:1
5	**6**	 **11**	(2.0)	 **17**	99	>20:1
6	**6**	 **12**	(2.0)	 **18**	95	>20:1

[a] Reactions with 5 mol% of **3**. Reactions with geminally disubstituted olefins utilize the same stoichiometry as those reported in Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751-1753. [b] Ratio based on NMR spectra.

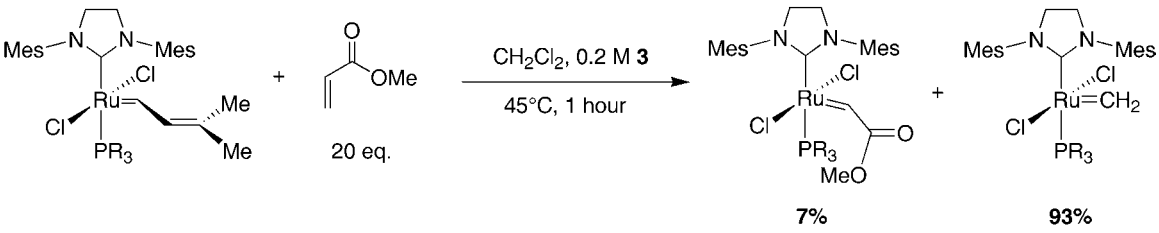
were necessary to ensure these high yields.[10] Recently this methodology has also been extended to α,β-unsaturated amides and carboxylic acids (62-99% yields, >20:1 E:Z) in CM reactions with terminal olefins.[11,12]

Choi et al. have shown that the homodimerization of α,β-unsaturated carbonyl compounds is slow relative to the cross metathesis of electron-rich or electron-neutral terminal olefins.[12] Additionally, our group has recently demonstrated that the CM of β-functionalized enoic esters does not proceed if the β-function is longer than a methyl group.[13] These results suggest that the cross products in Table 1 are the thermodynamically favored products, explaining their high yields. Specifically, the homodimers of the terminal olefins **4**-**6** are metathesis-active, meaning that they can reenter the catalytic cycle (and are therefore not the thermodynamic products). The cross products **13**-**18** do not readily reenter the cycle because their β-substituents are larger than methyl; these are kinetic and thermodynamic "traps" for the olefin substrates. Overall, it is clear that the success of functionalized olefin CM depends on the synergy between a substrate that remains metathesis-active upon dimerization (i.e., a terminal olefin) and one that does *not* (i.e., an α,β-unsaturated carbonyl compound, among others).[14]

Additionally, the efficiency of the reactions originally suggested that the highly unstable β-carbonyl-carbene species [Ru]=CH(C=O)R is not involved in the cross metathesis. It was recently shown that ester-carbene complexes (R = OR) decompose within a few hours at room temperature, in contrast to the long lifetime of catalyst **3** in cross metathesis.[15] The typically low degree of conversion to an ester-carbene, coupled with its instability, strongly suggests that these β-carbonyl-carbenes are not responsible

for the bulk of product formation.[16] However, Choi et al. have shown that β-carbonyl-carbenes do form under standard CM conditions and these species can dimerize α,β-unsaturated carbonyl species to the corresponding fumarates.[12] Additionally, the direct stoichiometric reaction of **3** with methyl acrylate results in the formation of β-carbonyl-carbene (in low conversion, 7%) observable by ^{1}H NMR (Scheme 1).[17] This species disappears rapidly (within seconds) if a terminal olefin cross-partner is added to the solution, suggesting that the β-carbonyl-carbene does in fact rapidly turn over to generate cross product. It is unclear without further kinetic study if this β-carbonyl-carbene pathway is the predominant product-generating pathway in a typical CM reaction.

Scheme 1. Stoichiometric reaction of compound **3** with methyl acrylate.



Overall, the stereoselectivities of the CM reactions in Table 1 are excellent, making these reactions synthetically practical. Although numerous factors control the stereochemistry of the final products, simple steric arguments provide a first level of analysis. Presumably the alkyl chain (from the terminal olefin) and the carbonyl group are well separated in metathesis intermediates leading to product formation. Adding a geminal methyl group (entries 1 and 3) radically amplifies this *trans* tendency.

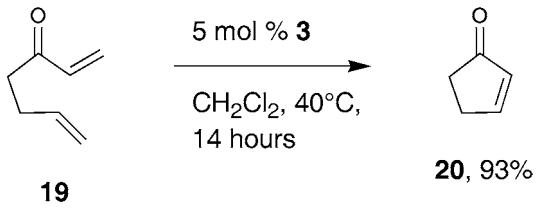
It should be noted that vinylic halides, pthalimides, acetates, ethers, and alkyltins were not reactive in cross metathesis with terminal olefins and **3**.[18] Some

homodimerization of terminal olefins **4-6** were observed in these reactions, but no significant amount of CM products were formed. This lack of reactivity may result from the sequestering of the catalyst in a stabilized Fischer-type carbene complex, which either rapidly decomposes or fails to react further.[19]

Other directly functionalized olefins do participate in cross metathesis reactions with terminal olefin substrates **5** and **6**. Butadiene monoxide and nonafluoro-1-(1,1,2-H)-hexene give moderate yields (34-38%) and stereoselectivities (2.3-5:1 E:Z) when reacted with **5**.[1] In these cases the remainder of the isolated material is homodimer of the functionalized olefin, suggesting that both substrate olefins are capable of efficient homodimerization. This situation does not follow the principle established above for efficient CM: it is necessary to have one substrate be *poor* at homodimerization so that the cross product is formed selectively.

In order to compare reactivities of intra- and intermolecular metathesis, RCM reactions of substrates bearing vinyl functional groups were performed. A demonstrative case is the formation of the cyclopentenone **20** from its α,β-unsaturated ketone precursor **19** (Scheme 2). Analogous cases of five, six, seven, and eight-membered cyclic enoic esters have been successfully formed under similar conditions.[1]

Scheme 2. Ring-closing metathesis of an α,β-unsaturated ketone.

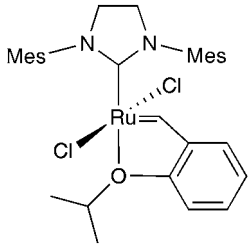


In conclusion, the cross metathesis of a variety of electron-deficient olefins employing ruthenium alkylidene **3** has been described. These findings further demonstrate the high activity and functional group compatibility of **3**, which significantly expands the range of olefins that can participate in the olefin metathesis reaction.

Part II. Development of a Practical and Efficient Ruthenium-based Catalyst for the Cross Metathesis of Acrylonitrile

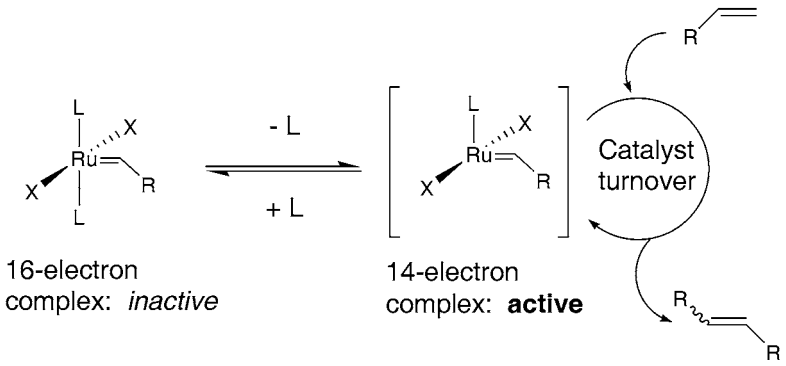
In spite of the well-established CM methodology developed in Part I, compound **3** remains a poor catalyst for the cross metathesis of acrylonitrile. Previously acrylonitrile CM has been successful only with Schrock's arylimido molybdenum alkylidene catalyst **1** and the ether-tethered ruthenium alkylidene derivative **21** described by Blechert, et al (Figure 2).[20,21] Attempts at acrylonitrile CM with phosphine-ligated ruthenium catalysts have produced poor results (< 30% yield).[1,22] The nature of the L-type ligands on the ruthenium catalyst is therefore critical to the overall success of this particular CM reaction.

Figure 2. Catalyst **21**, described in Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973.



Sanford et al. have implicated the importance of L-type ligands in their mechanism of olefin metathesis catalyzed by L_2X_2Ru=CHR complexes (Scheme 3).[23] The current model predicts that the catalysis proceeds through a 14-electron ligand-dissociated species. The 16-electron complexes **3** and **21** must therefore dissociate one L-type ligand in order to form the active catalytic species. Phosphine exchange studies have demonstrated that the L-type ligand that preferentially dissociates from **3** is the phosphine, rather than the *N*-heterocyclic carbene (NHC).[23(b,c)] In order for the catalyst to remain active, the equilibrium between the 16-electron and 14-electron species must be shifted toward the latter; the nature of the dissociated ligand may dramatically affect this equilibrium. A "stronger" ligand will naturally shift the equilibrium toward the 16-electron species, while a weaker ligand demonstrates the opposite behavior.[24] It is therefore desirable to have *weak* L-type ligands in the "precatalytic" 16-electron species.

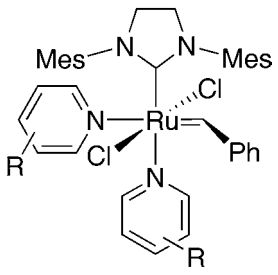
Scheme 3. Simplified mechanism of olefin metathesis catalyzed by L_2X_2Ru=CHPh complexes. Adapted from (a) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749-750. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543-6554.



This model may explain the success of **21** in effecting the CM of acrylonitrile with terminal olefins. The isopropoxystyrene ligand in **21** is a much weaker L-type

ligand than the phosphine in **3**, suggesting that the former catalyst remains active while the latter is rapidly "trapped" as the phosphine-associated 16-electron species. In order to test this hypothesis, a variety of NHC-coordinated catalysts containing weakly binding pyridine ligands were synthesized (**22**-**24**, Figure 3) and examined in the CM reaction between acrylonitrile and the terminal olefin allylbenzene (Table 2).

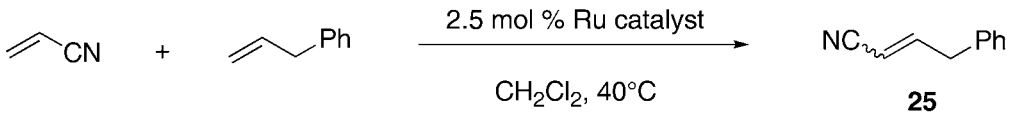
Figure 3. Pyridine-coordinated NHC metathesis catalysts.



22 (R = H)
23 (R = 4-Ph)
24 (R = 3-Br)

In these cases the pyridine ligands span the range from relatively electron-rich (R = H) to electron-poor (R = Br). As expected, the latter case is optimal, generating yields of CM product similar to those obtained with **21**. The electron-poor pyridines also offer synthetic advantages over the isoproxystyrene ligand in **21**: namely, these ligands are commercially available and can be substituted onto catalyst **3** in a single, high-yielding step that can be performed in non-purified benchtop solvents. In contrast, catalyst **21** requires multiple steps to synthesize and is generally only produced in low to moderate yields. The pyridine ligands therefore offer a reasonable, practical means of performing acrylonitrile CM reactions.

Table 2. Cross metathesis of acrylonitrile with allylbenzene.[a]



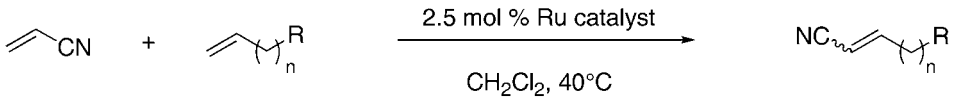
25

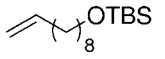
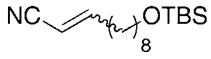
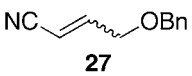
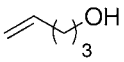
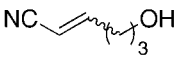
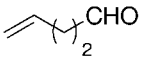
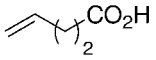
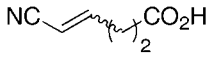
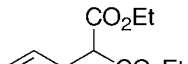
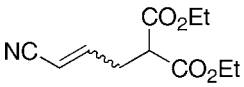
Ru catalyst	Isolated Yield(%)[b]	E:Z
21	**68**	1:1.9
22	26	1:1.2
23	29	1:1.8
24	**67**	1:1.8

[a]Conditions for CM: acrylonitrile plus 2.5 equivalents of allylbenzene, 0.2 M in CH_2Cl_2, 2.5 mol % ruthenium catalyst, 40°C for 12 hours. [b] Remainder of product is the homodimer of allylbenzene.

The similarity of catalysts **21** and **24** extends to a variety of terminal olefin cross partners (Table 3). Both concentrated and dilute conditions were employed in order to determine if acrylonitrile was deactivating the catalyst by coordination or other side reactions. The concentrated cases (entries 1 and 2) show similar yields to the dilute cases (entries 3-6)[25], suggesting that the catalyst remains intact at both concentrations. The reaction also appears to be insensitive to the identity of the limiting reagent; if either the terminal olefin or acrylonitrile is limiting, yields are nearly identical. Most notably, in every case catalyst **24** is capable of producing similar yields and stereoselectivities to **21**, within error. This result is not unexpected due to the similarity of the two catalysts; the 14-electron species generated from L-type ligand dissociation *is identical* in **21** and **24**. After a single catalytic turnover, these two catalysts are necessarily identical in the absence of a strongly binding L-type ligand.

Table 3. Comparison of acrylonitrile cross metathesis efficiencies.



Entry	Substrates		Complex **24**, conditions,[a,b] yield, *Z*:*E*	Complex **21**, conditions,[a,b] yield, *Z*:*E*
1	 2.5 eq	 **26**	A, 81%, 1:1.1	A, 78%, 1.1:1
2	 2.5 eq	 **27**	A, 71%, 1.7:1	A, 71%, 1.3:1
3	 0.5 eq		B, 77%, 3:1	B, 75%, 3:1
4	 0.5 eq		B, 80%, 3:1	B, 80%, 4:1
5	 0.5 eq		B, 70%, 2.5:1	B, 72%, 3:1
6	 0.5 eq		B, 80%, 2.5:1	B, 77%, 3:1

[a]A: 0.2 M, 12 h; B: 0.05 M, 2 h. [b]yields and *Z*:*E* selectivities are an average of two runs. [c]yields and *Z*:*E* selectivities are identical (within error) to those reported in Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430-432.

The development of catalyst **24** represents the first successful application of mechanistic principles to catalyst design. With the current understanding of metathesis mechanism, a rational solution to the long-standing problem of acrylonitrile CM has been proposed and executed. The continued cooperation between mechanistic study and catalyst design should allow rapid development of new and effective ruthenium-based olefin metathesis catalysts capable of expanding the boundaries of the field.

Acknowledgements. Support has been generously provided by the National Institutes of Health. The author thanks Arnab Chatterjee, Matthias Scholl, Thomas A. Kirkland, Helen E. Blackwell, Melanie S. Sanford, Tina M. Trnka, Steven D. Goldberg, and Daniel J. O'Leary for useful discussions and encouragement. The author also wishes to thank Richard Pederson for a generous supply of compound **6**.

General Experimental Section. NMR spectra were recorded on a JEOL GX-400, Varian Inova-500 or GE-300 NMR. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m). The reported ^{1}H NMR data refer to the major olefin isomer unless stated otherwise. The reported ^{13}C NMR data include all peaks observed and no peak assignments were made. High-resolution mass spectra (EI and FAB) were provided by the UCLA Mass Spectrometry Facility (University of California, Los Angeles).

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. All other chemicals were purchased from the Aldrich, Strem, VWR, or Nova Biochem Chemical Companies, and used as delivered unless noted otherwise. CH_2Cl_2 was purified by passage through a solvent column prior to use.[26] CD_2Cl_2 was dried by vacuum transfer from CaH_2 and degassed prior to use.

NMR scale experiments were performed in J. Young valve NMR tubes under an N_2 atmosphere with 20 equivalents of functionalized olefin to 1 equivalent of catalyst **3** in CD_2Cl_2.

Manipulation of organometallic compounds was performed using standard Schlenk techniques under an atmosphere of dry argon or in a nitrogen-filled Vacuum Atmospheres drybox ($O_2 < 2$ ppm), unless otherwise specified.

Abbreviations: PCy_3 = tricyclohexylphosphine; PCp_3 = tricyclopentylphosphine; H_2IMes = *N,N'*-dimesityl-4,5-dihydro-imidazolin-2-ylidene (the N-heterocyclic carbene).

Compound 3 $(H_2IMes)(PCp_3)(Cl)_2Ru=CH=C(Me)_2$. A 250-mL flame-dried round bottom flask equipped with a magnetic stirbar was charged with 1,3-dimesityl-4,5-dihydro-imidazolium tetrafluoroborate (3.08 g, 7.80 mmol, 1.6 equiv.) and dry THF (30 mL) under nitrogen atmosphere. A solution of potassium *tert*-butoxide (0.88 g, 7.80 mmol, 1.6 equiv.) in dry THF (30 mL) was slowly added at room temperature. The reaction mixture was allowed to stir for 1/2 hour and was then slowly transferred to a 500-mL flame-dried Schlenk flask containing a solution of $RuCl_2(=CH=C(CH_3)_2)(PCp_3)_2$ (3.50 g, 4.88 mmol, 1.0 equiv.) in dry toluene (200 mL). This mixture was stirred at 80°C for 15 min, at which point the reaction was complete as indicated by ^{1}H NMR. The reaction mixture was filtered through a glass frit under argon and all volatiles were removed under high vacuum. The residue was recrystallized three times from anhydrous methanol (40 mL) at –78°C to give **3** as a pinkish-brown microcrystalline solid (2.95 g) in 77% yield: ^{1}H NMR (C_6H_6, 400 MHz) δ 19.16 (d, J = 11 Hz, 1H), 7.71 (d, J = 11 Hz, 1H), 6.89 (s, 2H), 6.62 (s, 2H), 3.36-3.24 (m, 4H), 2.80 (s, 6H), 2.54 (s, 6H), 2.41-1.26

(br m, 27H), 2.20 (s, 3H), 2.02 (s, 3H), 1.06 (s, 3H), 0.90 (s, 3H); ^{31}P NMR (C_6H_6, 161.9 MHz) δ 28.05; HRMS (FAB) $C_{41}H_{61}Cl_2N_2PRu$ [M^+] 784.2993, found 784.2963.

Compound 13. 9-Decen-1(*tert*-butyldimethylsilane)-yl (330 μL, 1.0 mmol) and Methyl methacrylate (55 μl, 0.51 mmol) were added simultaneously *via* syringe to a stirring solution of **3** (21 mg, 0.026 mmol, 5.2 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2 x 10 cm), eluting with 9:1 hexane:ethyl acetate. A viscous oil was obtained (110 mg, 62% yield, *trans/cis* as determined by relative heights at 143.2 and 143.1 ppm of ^{13}C NMR spectra). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.75 (1H, m), 3.71 (3H, s), 3.57 (2H, t, J = 6.3 Hz), 2.14 (2H, m), 1.81 (3H, app s), 1.50 – 1.05 (12H, broad m), 0.87 (9H, s), 0.02 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 169.2, 143.2, 143.1, 128.0, 63.8, 52.1, 33.4, 30.0, 29.8, 29.2, 29.1, 26.5, 26.3, 18.9. 12.9. R_f = 0.81 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{19}H_{38}O_3Si$ [M+ H]$^+$ 343.2668, found 343.2677. Elemental analysis Calcd: C: 66.61, H: 11.18; Found: C: 66.47, H: 11.03.

Compound 14. 9-Decen-1-yl benzoate (145 ml, 0.52 mmol) and methyl acrylate (90 ml, 1.0 mmol) were added simultaneously *via* syringe to a stirring solution of **3** (17 mg, 0.022 mmol, 4.2 mol %) in CH_2Cl_2 (2.5 ml). The flask was fitted with a condenser and refluxed under nitrogen for 12 hours. The reaction mixture was then reduced in volume to 0.5 ml and purified directly on a silica gel column (2 x 10 cm), eluting with 9:1 hexane:ethyl acetate. A white crystalline solid was obtained (151.4 mg, 91% yield, 4.5:1

trans/cis as determined by relative integrations of ^{1}H peaks at 3.75 and 3.68 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.01 (2H, app d, J = 7.2 Hz), 7.50 (1H, m), 7.45 (2H, m), 6.93 (1H, dt, J = 15.9 Hz, 6.9 Hz), 5.78 (1H, app d, J = 15.9 Hz), 4.28 (2H, t, J= 6.6 Hz), 3.68 (3H, s), 2.15 (2H, m), 1.74 (2H, p, J = 6.6 Hz), 1.49 – 1.05 (10H, broad m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 167.5, 167.1, 150.0, 133.3, 131.1, 130.0, 128.8, 121.5, 65.5, 51.8, 32.7, 29.8, 29.5, 29.2, 28.5, 26.5. R_f = 0.40 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{19}H_{26}O_4$ $[M+ H]^+$ 319.1909, found 319.1914. Elemental analysis Calcd: C: 71.67, H: 8.23; Found: C: 71.31, H: 8.24.

Compound 15. A flame-dried round-bottomed flask equipped with reflux condenser was charged with 5-acetoxy-1-hexene (184 mg, 1.3 mmol, 2.5 eq.), methacrolein (35 mg, 0.5 mmol, 1.0 eq.), and dichloromethane (2.5 mL). Catalyst **3** (20 mg, 25 μmol, 0.05 eq.) was subsequently added as a solid, producing a light brown solution which was refluxed for 12 hours. The mixture was then concentrated *in vacuo* to a dark brown oil. Purification of this residue by silica gel chromatography (8:2 hexanes:ethyl acetate) allows isolation of 85 mg (0.46 mmol, 92%) of a clear oil (R_f = 0.44). This compound darkens rapidly (under one hour) in air at room temperature and/or in the presence of light, resulting in isomerization and production of uncharacterized polar side products. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.34 (1H, s), 6.43 (1H, t, J = 5.5 Hz), 4.02 (2H, t, J = 5.0 Hz), 2.34 (2H, t, J = 5.5 Hz), 1.99 (3H, s), 1.68 (3H, s), 1.65-1.50 (4 H, m). HRMS (EI) calcd. for $C_{10}H_{16}O_3$ $[M]^+$ 184.1099, found 184.1094.

Compound 16. A flame-dried round-bottomed flask equipped with reflux condenser was charged with 5-acetoxy-1-hexene (71 mg, 0.5 mmol, 1.0 eq.), acrolein (73 mt, 1.3

mmol, 2.6 eq.), and dichloromethane (2.5 mL). Catalyst **3** (20 mg, 25 μmol, 0.05 eq.) was subsequently added as a solid, producing a light brown solution which was refluxed for 12 hours. The mixture was then concentrated *in vacuo* to a dark brown oil. Purification of this residue by silica gel chromatography (9:1 hexanes:ethyl acetate) allows isolation of 52 mg (0.3 mmol, 62%) of a clear, colorless oil (R_f = 0.23). The title compound is produced as a mixture of isomers, *trans:cis* = 1.1:1 determined by integration of peaks at 9.50, 9.47, 7.03 and 6.83 ppm ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.50 (1H, s), 9.47 (1H, s), 7.03 (1H, dt, *J* = 7.1, 18 Hz), 6.83 (1H, dt, *J* = 6.8, 15.6 Hz), 6.1 (1H, qt, *J* = 1.5, 8.1 Hz), 5.82 (1H, dt, *J* = 1.5, 15.6 Hz), 4.05 (2H, dt, *J* = 4.5, 6.3 Hz), 2.38 (2H, q, *J* = 6.9 Hz), 2.24 (2H, q, *J* = 6.9 Hz), 2.03 (3H, s), 1.69-1.52 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 194.0, 171.2, 157.9, 151.1, 133.2, 121.0, 63.9, 32.1, 31.7, 28.0, 24.2, 22.6, 20.9, 14.0. HRMS (EI) calcd. for $C_9H_{14}O_3$ $[M]^+$ 170.0943, found 170.0878.

Compound 17. A flame-dried round-bottomed flask equipped with reflux condenser was charged with 5-acetoxy-1-hexene (32 mg, 0.2 mmol, 1.0 eq.), phenyl vinyl ketone (60 mg, 0.5 mmol, 2.5 eq.), and dichloromethane (1 mL). Catalyst **3** (7 mg, 8 μmol, 0.04 eq.) was subsequently added as a solid, producing a light brown solution which was refluxed for 12 hours. The mixture was then concentrated *in vacuo* to a dark brown oil. Purification of this residue by silica gel chromatography (7:3 hexanes:ethyl acetate) allows isolation of 49 mg (0.2 mmol, 99%) of a thin, clear yellow oil (R_f = 0.54). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.85 (1H, dd, *J* = 1.2, 6.9 Hz), 7.48 (2H, tt, *J* = 1.2, 7.2 Hz), 7.39 (2H, t, *J* = 7.5 Hz), 7.00 (1H, dt, *J* = 7.6, 15 Hz, *trans* isomer), 6.83 (1H, dt, *J* = 1.1, 15.6 Hz), 4.01 (2H, t, *J* = 6.3 Hz), 2.28 (2H, q, *J* = 6.9 Hz), 1.97 (3H, s), 1.64-1.49

(4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 190.4, 170.8, 148.6, 137.7, 132.4, 128.3, 126.1, 108.5, 63.8, 32.0, 27.9, 24.4, 20.6. HRMS (EI) calcd. For $C_{15}H_{18}O_3$ $[M]^+$ 246.1256, found 246.1255.

Compound 18. A flame-dried round-bottomed flask equipped with reflux condenser was charged with 5-acetoxy-1-hexene (71 mg, 0.5 mmol, 1.0 eq.), methyl vinyl ketone (91 mg, 1.3 mmol, 2.2 eq.), and dichloromethane (2.5 mL). Catalyst **3** (20 mg, 25 μmol, 0.05 eq.) was subsequently added as a solid, producing a light brown solution which was refluxed for 12 hours. The mixture was then concentrated *in vacuo* to a dark brown oil. Purification of this residue by silica gel chromatography (7:3 hexanes:ethyl acetate) allows isolation of 87 mg (0.47 mmol, 95%) of a clear, colorless oil (R_f = 0.33). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.68 (1H, dt, *J* = 6.9, 15.9 Hz), 5.97 (1H, dt, *J* = 1.5, 6 Hz), 3.96 (2 H, t, *J* = 6.6 Hz), 2.17 (2H, pentet, *J* = 1.5 Hz), 2.13 (3 H, s), 1.93 (3 H, s), 1.55-1.44 (4 H, broad multiplet). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 198.2, 170.8, 147.3, 131.3, 63.7, 31.7, 27.9, 26.6, 24.2, 22.4, 20.7. HRMS (EI) calcd. For $C_{10}H_{16}O_3$ $[M]^+$ 184.1099, found 184.1099.

Compound 20. Compound **19** (0.11 g, 0.18 mL, 1.0 mmol) was added via syringe to a homogenous, stirred solution of **3** (41 mg, 0.052 mmol, 5.2 mol. %) in CH_2Cl_2 (50 mL, 0.02 M). The resultant dark brown solution was refluxed under a nitrogen stream for 12 hours. The reaction mixture was then concentrated *in vacuo* and purified by silica gel column chromatography (6:4 ethyl acetate:hexanes, R_f = 0.55). The product, cyclopent-2-en-1-one, was isolated as a clear oil in 93% yield (81 mg, 0.98 mmol) which is identical in all respects to an authentic sample obtained from Aldrich Chemicals.

Compound 24 (H_2IMes)(3-Br-pyr)$_2$(Cl)$_2$Ru=CHPh. 3-bromopyridine (0.57 mL, 5.9 mmol) was added to commercially available (H_2IMes)(PCy_3)(Cl_2)Ru=CHPh (0.5 g, 0.59 mmol) in a 20 mL vial with a screw cap; no additional solvent is required. The reaction was stirred in air at room temperature for 5 minutes during which time a color change from red to bright green was observed. Room temperature pentane (20 mL) was added layered onto the green solution and a green solid began to precipitate. The vial was capped under air and cooled to ~5°C overnight (freezer). The green precipitate was vacuum-filtered, washed with 4 x 10 mL of room temperature pentane, and dried under vacuum to afford **24** as a green powder (0.46 g, 89% yield). Compounds **22** and **23** are prepared analogously.[1] ^{1}H NMR (CD_2Cl_2): δ 19.09 (s, 1H, CHPh), 8.79 (br. s, 2H, pyridine), 8.70 (br. s, 2H, pyridine), 8.09 (br. S, 2H, pyridine), 7.84 (br. S, 2H, pyridine), 7.65 (d, 2H, ortho CH, J_{HH} = 7.2 Hz), 7.47 (t, 1H, para CH, J_{HH} = 7.2 Hz), 7.08 (t, 2H, meta CH, J_{HH} = 7.2 Hz), 6.81 (br. s, 4H, Mes CH), 4.04 (br. s, 4H, NCH_2CH_2N), 2.57 (br. s, 6H, Mes CH_3), 2.28 (s, 12H, Mes CH_3). ^{13}C{^{1}H} NMR (CD_2Cl_2): δ 314.76 (m, Ru=CHPh), 216.70 (s, Ru-C(N)$_2$), 157.14, 154.93, 152.89, 152.09, 151.70, 148.55, 139.17, 138.71, 130.55, 130.32, 129.74, 128.52, 128.47, 128.26, 124.88, 51.82, 21.35, 20.43, 18.80.

General Procedure for Acrylonitrile Cross Metathesis. A solution of ($IMesH_2$)(3-Br-pyr)$_2$$Cl_2$Ru=CHPh **24** (18 mg, 25 μmol, 5 mol%) in CH_2Cl_2 (1.5 mL) was added by syringe to a stirring solution of terminal olefin substrate (1.3 mmol, 2.5 eq.) and acrylonitrile (27 mg, 0.50 mmol, 1.0 eq.) in CH_2Cl_2 (1.0 mL). The emerald green catalyst solution immediately turned brown upon addition to the olefin solution. The reaction

mixture was heated to reflux for 12 hours. The reaction was then allowed to cool to room temperature, concentrated *in vacuo*, and the residue was purified by column chromatography generating the products in good to excellent yields.

Compound 25. The product was isolated by column chromatography (4:1 hexanes:ethyl acetate) in 67% yield (48 mg, 0.33 mmol) as a yellowish oil. ^{1}H NMR, ^{13}C NMR, and IR data are identical to those reported in Inaba, S.; Matsumoto, H.; Rieke, R. D. *J. Org. Chem.* **1984**, *49*, 2093-2098 and Descotes, G.; Laconche, P. *Bull. Soc. Chim. Fr.* **1968** 2149. HRMS (CI) Calculated for $C_{10}H_9N$ (M^+): 143.0735; Found: 143.0729.

Compound 26. The product was isolated by column chromatography (9:1 hexanes:ethyl acetate) in 81% yield (120 mg, 0.41 mmol) as a clear oil (E:Z ratio = 1:1.1). IR (thin film): 2932.6, 2858.0, 2224.6, 1653.2, 1633.8, 1524.0, 1499.2, 1461.8, 1256.2, 1090.5, 910.6, 734.6 cm^{-1}. HRMS (CI) calculated for $C_{17}H_{34}NOSi$ ($M+H^+$): 296.2404; found: 296.2418. Elemental analysis calculated: C, 69.09; H, 11.25; N, 4.74; found: C, 69.30; H, 11.09; N, 4.86.

Compound 27. The product was isolated by column chromatography (9:1 hexanes:ethyl acetate) in 71% yield (87 mg, 0.36 mmol) as a cloudy white oil (E:Z ratio = 1.7:1). ^{1}H NMR, ^{13}C NMR, and IR data are identical to those reported in *Tetrahedron Lett.* **1996**, *37*, 2437-2440. HRMS (CI) Calculated for $C_{11}H_{12}NO$ ($M+H^+$): 174.0913; Found: 174.0923.

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[1] Parts of this chapter are published in: (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783-3784. (b) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem. Int. Ed.*, submitted.

[2] Note that the phrase "terminal olefin" refers to a mono-substituted olefin that contains a methylene group at the position α to the olefin (i.e., there is no α-functionality in conjugation with the olefin). Typical examples are compounds **4-6**.

[3] For a recent review of olefin metathesis see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450.

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[5] (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Eng.* **1995**, *34*, 2039-2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110. (c) Belderrain, T. R.; Grubbs, R. H. *Organometallics* **1997**, *16*, 4001-4003.

[6] Recent developments in cross metathesis include: (a) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998-10999. (b) Crowe, W. E., Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117-2120. (c) Brummer, O.; Ruckert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441-446. (d) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427-7430. (e) O'Leary, D. J.; Blackwell,

H. E.; Washenfelder, R. A.; Miura, K.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 1091-1094. (f) Roy, R.; Dominique, R.; Das, S. K. *J. Org. Chem.* **1999**, *64*, 5408-5412. (g) Huwe, C. M.; Woltering, T. J.; Jiricek, J.; Weitz-Schmidt, G.; Wong, C.-H. *Bioorg. Med. Chem.* **1999**, *7*, 773-788. (h) Oguri, H.; Sasaki, S.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 5405-5408. (i) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58-71.

[7] Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162-5163.

[8] Scholl, M.; Ding, S.; Lee C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956. The dimethylvinyl carbene **3** is prepared by analogy to the synthesis of the benzylidene reported therein.

[9] Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751-1753.

[10] In entry 3 (Table 1), productive CM was still observed (^{1}H NMR) to occur after 8 hours. This result is also consistent with previous experiments which indicate that the propagating species, the methylidene derivative of **3**, has a lifetime in excess of 12 hours: Ulman, M.; Grubbs, R. H. Unpublished results.

[11] Choi, T. L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1277-1279.

[12] Choi, T. L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417-10418.

[13] Morrill, C.; Grubbs, R. H. Unpublished results.

[14] Chatterjee, A. K. Dissertation, California Institute of Technology, 2002.

[15] Ulman, M.; Belderrain, T. R.; Grubbs, R. H. Manuscript in preparation.

[16] NMR scale experiments were performed in J. Young valve NMR tubes under an N_2 atmosphere, with 20 equivalents of functionalized olefin to 1 equivalent of **3** in CD_2Cl_2.

[17] Characteristic ^1H NMR (300 MHz, C_6D_6): 17.329 ppm. This species decomposes rapidly (within 4 hours).

[18] Recently the cross metathesis of L_2X_2Ru-Fischer carbenes has been reported. See: Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153-2164.

[19] For typical experimental conditions in NMR reactions, see reference 16. For 9-vinylcarbazole reaction with **3**, the new Fischer carbene species has the following characteristic resonances: ^1H NMR: 16.64 ppm; ^{31}P NMR: 30.06 ppm. After 40 minutes at 45°C, all **3** has been consumed. For ethyl vinyl ether, the new Fischer carbene has characteristic resonances: ^1H NMR: 13.62 ppm; ^{31}P NMR: 27.07 ppm. Even after 4.5 hours at 45°C, some **3** remains visible by ^1H NMR.

[20] (a) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162-5163. (b) Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117-2120. (c) Brümmer, O.; Rückert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441-446.

[21] (a) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430-432. (b) Randl, S.; Buschmann, N.; Cannon, S. J.; Blechert, S. *Synlett* **2001**, 1547-1550. (c) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973-9976.

[22] (a) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *624*, 327-332. (b) Wright, D. L.; Usher, L. C.; Estrella-Jimenez, M. *Org. Lett.* **2001**, *3*, 4275-4277. (c) Blanco, O. M.; Castedo, L. *Synlett* **1999**, 557-558.

[23] (a) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749-750. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543-6554. (c) Sanford, M. S. Ph.D. Dissertation, California Institute of Technology, **2001**.

[24] Here "strong" ligands are either kinetically inert to dissociation or substitution by another L-type ligand.

[25] Products are described and characterized in Reference 21.

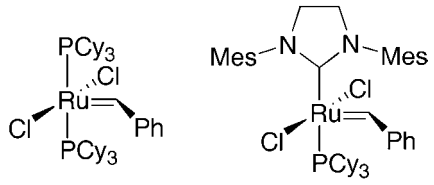
[26] The solvent columns are composed of activated alumina (A-2) and supported copper redox catalyst (Q-5 reactant). See: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

Chapter 4. Improved Olefin Metathesis Activity of *N*-Heterocyclic Carbene-Coordinated Ruthenium Olefin Metathesis Catalysts II: Ring-Opening Cross Metathesis[1]

Introduction

The flexibility of the olefin metathesis reaction allows the efficient production of highly functionalized, unsaturated polymers and small molecules.[2] Many synthetically relevant applications that involve multiple metathesis transformations utilize the most common ruthenium catalysts **1** and **2** (Figure 1).[3] For example, the combination of ring-opening metathesis polymerization (ROMP) and cross metathesis (CM) produces unique telechelic and multiple-block copolymers with novel properties.[4] For the synthesis of small molecules, ring-opening ring-closing metathesis "tandem" sequences (ROM-RCM) allow the rapid construction of multiple ring systems, including those in natural products.[5,6] In all these cases, the product of one metathesis event is directly available for the next, which permits the rapid generation of complexity in a single reaction.[7]

Figure 1. Ruthenium-based olefin metathesis catalysts.

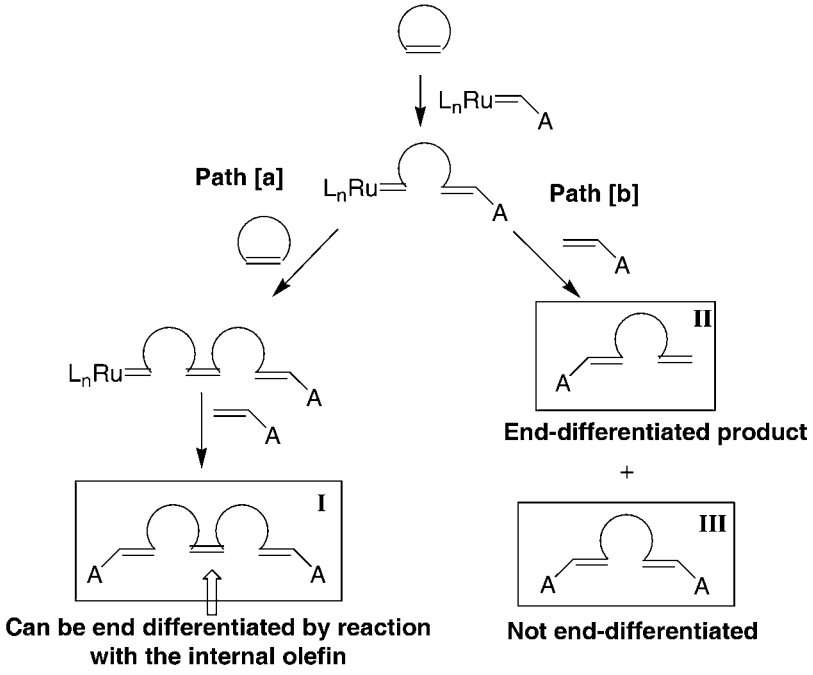


1 **2**

An important variation on this theme is ring-opening cross metathesis (ROCM, Scheme 1).[8,9,10] In this tandem sequence, a cycloolefin is opened and other alkenes are crossed onto the newly formed terminii. Ideally, the product olefins should be electronically or sterically orthogonal, to allow subsequent elaboration in a straightforward manner. Two approaches to end-differentiation of alkenes are shown in Scheme 1 (paths [a] and [b]). After the initial ring-opening event, the ruthenium-bound

intermediate has two options: reaction with another cycloolefin (path [a]) or reaction with the cross partner (path [b]). In the first case, the ring-opening of the cycloolefin is fast relative to the rate of cross metathesis. The resulting dimeric intermediate can then react with the cross partner to form a symmetrically capped product **I**.[11] A subsequent cross metathesis reaction on the internal olefin can differentiate the two ends of **I**, thereby achieving ROCM selectivity in two steps.

Scheme 1. Ring-opening cross metathesis (ROCM).



The second case (path [b] in Scheme 1) allows end-differentiation in a single reaction. This path will be followed if the cross metathesis step is faster than the ring-opening of another cycloolefin. Two products are possible from this cross metathesis: the desired end-differentiated product **II** and the symmetrically capped product **III**.

Selectivity for product **II** is therefore highly dependent on the nature of both the substrates and the catalyst.

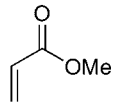
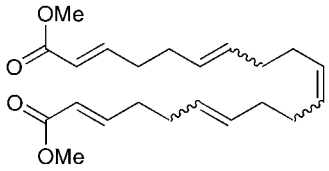
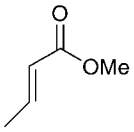
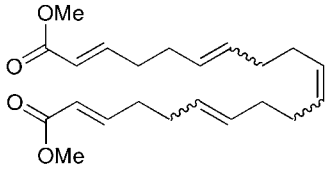
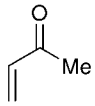
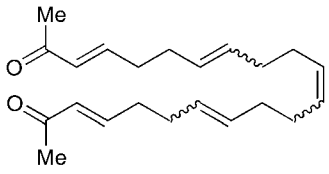
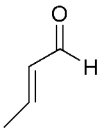
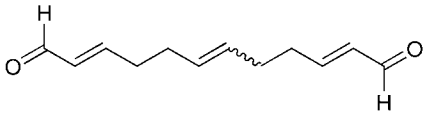
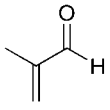
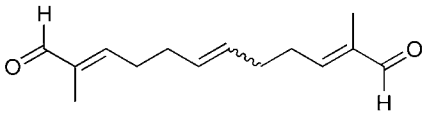
In particular, catalyst **2** is well suited to these selective ROCM reactions due to its combination of tunable activity and expanded substrate scope. The ability of **2** to react with both electron-poor acrylates and electron-rich cycloolefins makes it ideal for electronic end-differentiation in ROCM. In the following, we describe both stepwise and one-pot selective ROCM reactions using catalyst **2**.

Results and Discussion

Promising initial efforts toward ROCM along path [a] focused on the readily polymerizable substrate 1,5-cyclooctadiene (COD, Table 1).[12] High yields of ROCM dimers analogous to **I** can be achieved under typical reaction conditions.[13] A comparison of entries 1 and 2 reveals that the presence of a β-methyl group has little effect on product structure; the same dimer is formed in both cases. A similar product, containing three internal olefins, predominates for methyl vinyl ketone (entry 3). In contrast, crotonaldehyde and methacrolein result in monomeric species containing only one internal olefin (entries 4 and 5). Apparently the cross metathesis of an α,β-unsaturated aldehyde can most efficiently compete with the ring-opening of another cycloolefin.

The critical step in end-differentiation of the dimeric products lies in the selective manipulation of the internal, electron-rich olefins. Bisphosphine catalyst **1** is ideal for this selective cross metathesis of the dimers at the desired positions (Scheme 1).[12] The fact that **1** does not significantly react with acroyl species ensures that the acroyl cap remains untouched throughout this metathesis reaction.[14] Catalyst choice can therefore be important in the selective manipulation of ROCM products.

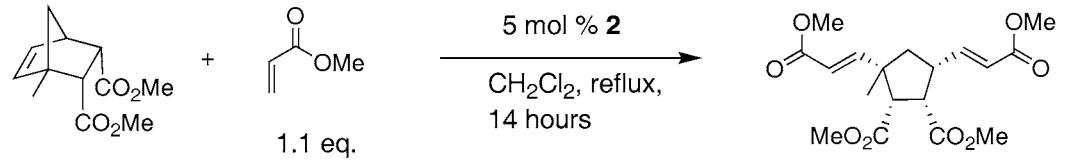
Table 1. Ring-opening cross metathesis of cyclooctadiene with various acroyl species.

Entry	Substrates		Products	Isolated yield
1	 COD			**80%**
2	COD			**75%**
3	COD			**40%**
4	COD			**95%**
5	COD			**19%**

[a]All reactions are performed in refluxing CH_2Cl_2, at 0.2 M concentration of cycloalkene and 5 mol% catalyst **2**. The relative stoichiometry is 1:1.2 cycloolefin:acroyl species, except for entry 5, in which methacrolein is used as solvent. All acroyl alkenes are predominantly trans, by ^{1}H NMR analysis. The stereochemistry of all other internal olefins is approximately 3-4:1 E:Z by 500 MHz ^{1}H NMR analysis.

A more efficient route to selective ROCM would involve the generation of end-differentiated products in a single metathesis reaction (Scheme 1, path [b]). In order to suppress dimer formation (path [a]), cycloolefins with a reduced tendency to dimerize must be chosen. *Endo*-substituted norbornenes, such as **3**, fall into this category because they cannot readily coordinate to the ruthenium center (Scheme 2). Both olefin faces are prevented from coordination: the bottom face is sterically encumbered by the *endo* substitutents and the top face by the methylene bridgehead. Dimerization is therefore dramatically suppressed in these substrates. These compounds are often used as high ring-strain olefins in ROCM due to this lowered reactivity relative to less sterically hindered unsubstituted or *exo*-substituted norbornenes.[8]

Scheme 2. ROCM of an *endo*-substituted norbornene substrate containing allylic substitution.



Compound 3, 100% *endo*, racemic

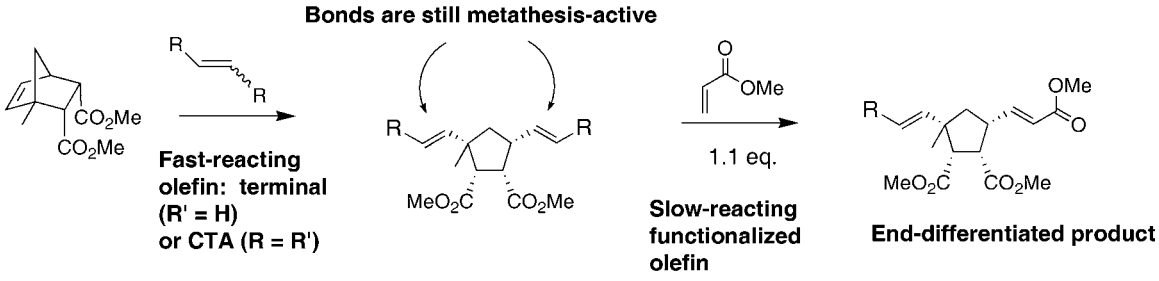
Compound 4, Approximately 60% yield by ^{1}H NMR, GC

An additional aspect of substrate **3** is its overall lack of C_s symmetry, unlike COD (Table 1). If the two olefin termini in a ROCM substrate can be sterically differentiated by this asymmetric substitution, a single metathesis reaction may directly generate a regioselectively functionalized product. In this way one of the termini will be more reactive toward CM and will preferentially react with the cross partner (e.g., methyl acrylate). Substrate **3** exemplifies this differentiation: one of the olefin termini is

proximal to a quaternary center and should be largely blocked from reaction with the ROCM partner.

Unfortunately, in a standard ROCM reaction between substrate **3** and methyl acrylate, **3** is approximately 60% converted to the doubly capped, undifferentiated product **4** (Scheme 2).[15] This result suggests that the CM reaction between ring-opened norbornene and methyl acrylate is more facile than the ring-opening event itself. It was therefore desirable to introduce another component into the system that would rapidly open the monomer prior to the eventual cross metathesis reaction (Scheme 3). Under the proposed conditions, the third component would end up crossed on to the more reactive terminus of the product.

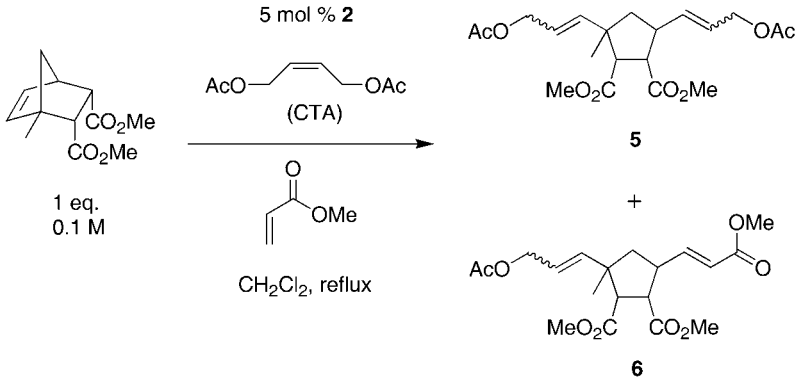
Scheme 3. Original model for the three-component ROCM reaction.



The obvious choice for this third component would be ethylene (R = R' = H in Scheme 3): this olefin would then ring-open **3** to the *bis*-terminal olefin product, and the methyl acrylate could then be crossed onto the less substituted terminus. Sanford et al. have suggested, however, that the methylidene $(H_2IMes)(PR_3)(Cl)_2Ru{=}CH_2$ (which *must* be formed in the metathesis of ethylene) is *significantly* less reactive than an alkyl or phenyl-substituted alkylidene.[16] This observation makes ethylene inoptimal for the third component.

Alternatively a more reactive olefin (such as a terminal olefin or a chain-transfer agent, CTA)[17] would make a better choice: it would be capable of rapidly converting **3** to the ring-opened, doubly capped species which could then re-enter the catalytic cycle. Eventually the less reactive functionalized cross partner (here, methyl acrylate) would then be crossed onto the less substituted, more reactive terminus. A standard CTA, butenediol diacetate, was chosen for this study, and the results are presented in Table 2.

Table 2. Regioselective three-component ROCM reaction optimization. Product distribution and conversion were determined by ^{1}H NMR.

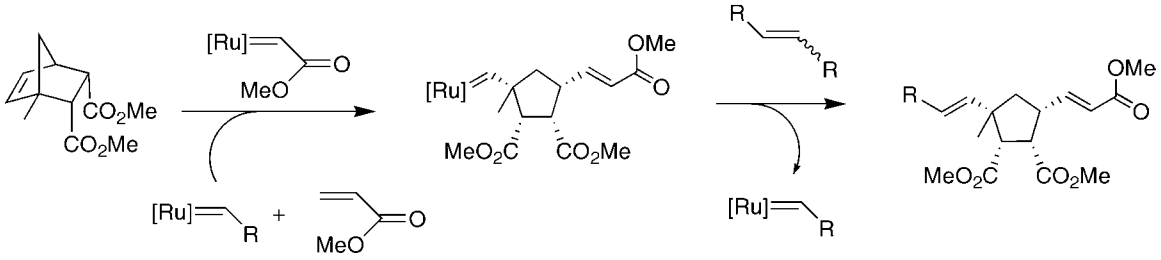


entry	equiv. acrylate	equiv. acetate	reaction conditions	product distribution (**5**:**6**)
1	0.6	1.2	Standard	**4 : 1**
2	1.2	1.2	Standard	**2.3 : 1**
3	1.2	3	Standard	**1 : 1**
4	1.2	3	CTA, then acrylate after 2.5 hours	**All 5 (68%)**
5	1.2	10	Standard	**1 : 2.6**
6	1.2	50	Standard	**1 : 5**

With acrylate as the limiting reagent (entry 1), the *bis*-acetate capped product **5** predominates (as expected). However **5** continues to predominate when equal stoichiometry is used (entry 2). Increasing acrylate stoichiometry did result in increased amounts of the desired end-differentiated product **6**. Continued increase in acrylate stoichiometry results in a corresponding increase in **6** up to an observable maximum **5**:**6** ratio of 1:5 at 50 equivalents of acrylate (entry 6). Although these products were not isolated, full conversion to ring-opened products was observed in the NMR tube, suggesting that the potential yield of **6** in entry 6 is approximately 83%, a synthetically useful result.

Entry 4 presents an unexpected result: addition of acrylate after the reaction has proceeded for 2.5 hours does not produce **6** at all. This result suggests that the proposed model is actually incorrect, implicating potential involvement from an ester-carbene (Scheme 4).[18] If the ester-carbene is responsible for ring-opening, the standard metathesis metallocyclobutane model indicates that the ruthenium catalyst is crossed onto the more-substituted olefin terminus of the substrate. The catalyst is subsequently exchanged with the more reactive olefin (the CTA), leading to the end-differentiated product. All three substrates must therefore be simultaneously present in the reaction to generate end-differentiated products by this mechanism.

Scheme 4. Modified pathway for three-component ROCM reactions.

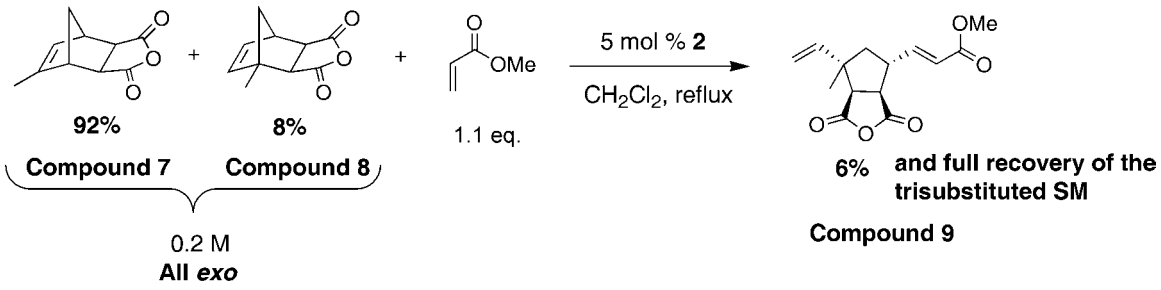


It is noteworthy that **6** is the only end-differentiated product that is generated – there is no indication of acrylate on the more substituted terminus. Doubly capped acrylate product **4** is also not generated under these reaction conditions. Presumably the product regioselectivity arises from the ester-carbene model (*vide supra*) although this mechanistic model remains largely unsupported.

An alternative route to end-differentiated ROCM products involves the direct ring-opening of trisubstituted olefins. These substrates represent the largest degree of steric differentiation between the olefin termini; the monosubstituted terminus should be more reactive toward CM after the initial ring-opening event. In order to test this hypothesis a trisubstituted norbornene monomer **7** was subjected to standard ROCM conditions with methyl acrylate (Scheme 5). The sample of **7** was unavoidably contaminated with a small amount of **8**, a disubstituted norbornene analogous to **3**, that could not be separated by either distillation or column chromatography. The reaction of the **7**/**8** mixture with methyl acrylate resulted in the ROCM of the minor component **8** with full recovery of intact trisubstituted **7**. Although the trisubstituted norbornene did not react, the recovered product **9** was in fact end-differentiated, once again with the acrylate present on the less-substituted terminus. In contrast to this result, successful

ROCM of lower ring-strain trisubstituted cycloolefins (such as cyclopentanes and cyclohexenes) has been reported[1] and is currently being applied to a total synthesis.[19]

Scheme 5. Modified pathway for three-component ROCM reactions.



In summary, substrate and catalyst control in ROCM make this reaction a potentially powerful means to rapidly and efficiently synthesize highly functionalized, end-differentiated alkenes. Application of both stepwise and one-pot methods to general problems will require the continued development of predictable substrate-product relationships described herein.

Acknowledgements. The author thanks the National Institutes of Health for financial support of this work. The author also thanks Daniel P. Sanders, Tina M. Trnka, Dr. Jennifer Love, Dr. Arnab K. Chatterjee, Tae-Lim Choi, Dr. F. Dean Toste, and Dr. Steven D. Goldberg for helpful suggestions and insight. Daniel P. Sanders is acknowledged for generously supplying compounds **3** and **7**/**8**.

General Experimental Section. NMR spectra were recorded on either an Inova 500 MHz or 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. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m). The reported ^{1}H NMR and ^{13}C NMR data refer to the major olefin isomer unless stated otherwise, and no peak assignments were made for the latter. High-resolution mass spectra (EI and CI) were provided by the University of California, Los Angeles Mass Spectrometry Facility. Product ratios were in part determined by gas chromatography/mass spectrometry using a Hewlett-Packard 5890 Gas Chromatograph interfaced with a HP 5970 series mass detector running HP ChemStation Software. Molecular mass calculations were performed with ChemDraw Ultra (Cambridge Scientific) or ChemIntosh Molecular Mass Calculator, version 1.3.

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 either standard *p*-anisaldehyde or potassium permanganate stains. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. Catalyst **2** was prepared as described in Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956. All other chemicals were purchased from the Aldrich, Strem, TCI America, and ChemSampCo Chemical Companies, and used as obtained unless noted otherwise. CH_2Cl_2 was purified and dried by passage through a solvent column[20] and subsequently degassed (by N_2 purge) prior to use. Compound **3** was originally prepared as described in Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843-862.

General procedure for ring-opening cross metathesis of cyclooctadiene with various acroyl species. Entry 1. A flame-dried round-bottomed flask equipped with reflux condenser was charged with 1,5-cyclooctadiene (43 mg, 0.4 mmol, 1.0 eq.), methyl acrylate (43 mg, 0.5 mmol, 1.3 eq.), and dry dichloromethane (1.0 mL). A solution of catalyst **2** (20 mg, 24 μmol, 0.05 eq.) in dichloromethane (1.0 mL) was subsequently added via cannula, producing a brick red solution, which was refluxed for 14 hours. The mixture was passed through a pipet plug of silica gel to remove the catalyst, and subsequently concentrated *in vacuo* to a yellow-brown oil. Purification of this residue by silica gel chromatography (7:3 hexanes:ethyl acetate) allows isolation of 56 mg of a clear yellow oil (0.16 mmol, 78%, $R_f = 0.36$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.96 (dt, J = 6.6, 15.6 Hz, 2 H), 5.82 (dm, J = 2.7, 15.6 Hz, 2 H), 5.40 (m, J = 2.4, 3 Hz, 6 H), 3.72 (s, 6 H), 2.24 (t, J = 7.8 Hz, 4 H), 2.15 (t, J = 4.8 Hz, 4 H), 2.03 (m, J = 1.5 Hz, 8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 167.1, 148.7, 131.0, 129.8, 128.8, 121.2, 51.4, 32.1, 31.6, 30.91, 30.86. HRMS (EI) calcd. for $C_{22}H_{33}O_4$ $[M+H]^+$ 361.2378, found 361.2382. The E:Z ratio of the internal olefins is determined by comparison of the multiplet at 5.40 ppm to the data reported for similar compounds (5.40 ppm for cis, 5.44 ppm for trans as reported in Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron* **1986**, *42*, 2855-2862).

Table 1, entry 2. Relative stoichiometry is 1,5-cyclooctadiene (43 mg, 0.4 mmol, 1.0 eq.), methyl crotonate (50 mg, 0.5 mmol, 1.3 eq.), and catalyst **2** (20 mg, 24 μmol, 0.05 eq.), in dichloromethane (2.0 mL). The crude product was purified by column chromatography (9:1 hexanes:ethyl acetate, $R_f = 0.43$) resulting in 54 mg of a yellow oil

(0.15 mmol, 75%). ^{1}H and ^{13}C NMR data are identical to those reported for Table 1, entry 1. HRMS (EI) calcd. for $C_{22}H_{33}O_4$ $[M+H]^+$ 361.2378, found 361.2379.

Table 1, entry 3. Relative stoichiometry is 1,5-cyclooctadiene (43 mg, 0.4 mmol, 1.0 eq.), methyl vinyl ketone (36 mg, 0.5 mmol, 1.3 eq.), and catalyst **2** (20 mg, 24 μmol, 0.05 eq.), in dichloromethane (2.0 mL). The crude product was purified by column chromatography (55:45 hexanes:ethyl acetate) resulting in 26 mg of a yellow oil corresponding to dimeric product (0.08 mmol, 39%, $R_f = 0.75$) and 8 mg of a brownish yellow oil corresponding to terminal olefin product (0.04 mmol, 12%, $R_f = 0.55$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.78 (dt, J = 6.6, 15.9 Hz, 2 H), 6.07 (dm, J = 1.2, 15.9 Hz, 2 H), 5.41 (m, J = 2.4, 5.7 Hz, 6 H), 2.27 (m, J = 1.5, 6.6 Hz, 8 H), 2.23 (s, 6 H), 2.17 (m, J = 1.8, 6.6 Hz, 8 H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 198.7, 147.9, 131.6, 131.3, 128.9, 32.8, 32.7, 31.3, 27.1, 23.0. HRMS (EI) calcd. for $C_{22}H_{33}O_2$ $[M+H]^+$ 329.2480, found 329.2477.

Table 1, entry 4. Relative stoichiometry is 1,5-cyclooctadiene (43 mg, 0.4 mmol, 1.0 eq.), crotonaldehyde (35 mg, 0.5 mmol, 1.3 eq.), and catalyst **2** (20 mg, 24 μmol, 0.05 eq.), in dichloromethane (2.0 mL). The crude product was purified by column chromatography (7:3 hexanes:ethyl acetate, $R_f = 0.43$) resulting in 46 mg of a yellow oil (0.24 mmol, 95%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 9.53 (d, J = 14.5 Hz, 2 H), 6.83 (dt, J = 7.5, 15.6 Hz, 2 H), 6.17 (dd, J = 12.5, 25.5 Hz, 2 H), 5.48 (m, J = 2.5, 3.5 Hz, 2 H), 2.43 (m, J = 6.5 Hz, 4 H), 2.25 (m, J = 3.5, 14 Hz, 4 H). ^{13}C NMR (125 MHz,

$CDCl_3$, ppm): δ 133.9, 157.6, 133.3, 129.7, 32.4, 30.6. HRMS (EI) calcd. for $C_{12}H_{15}O_2$ $[M-H]^+$ 191.1071, found 191.1073.

Table 1, entry 5. Relative stoichiometry is 1,5-cyclooctadiene (43 mg, 0.4 mmol, 1.0 eq.) and catalyst **2** (20 mg, 24 μmol, 0.05 eq.) in methacrolein (2.1 mL). The crude product was purified by column chromatography (9:1 hexanes:ethyl acetate, $R_f = 0.18$) resulting in 17 mg of a yellow oil (0.07 mmol, 19%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 9.38 (s, 6 H), 6.46 (td, J = 1.5, 7.5 Hz, 2 H), 5.48 (m, J = 1.8, 2.1 Hz, 2 H), 2.40 (m, J = 6.9 Hz, 4 H), 2.21 (m, J = 1.2, 5.1, 6.6 Hz, 2 H), 1.73 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 195.2, 153.6, 139.6, 130.0, 31.1, 28.8. HRMS (EI) calcd. for $C_{14}H_{19}O_2$ $[M-H]^+$ 219.1384, found 219.1383.

Schemes 3, 5 and Table 2 vial reactions. A typical reaction setup is as follows: a 10 dram vial with a Teflon septum is charged with norbornene substrate (0.24 mmol, 1.0 eq.) and degassed CD_2Cl_2 (1.2 mL) under a steady nitrogen flow. For the reactions reported in Schemes 3 and 5, methyl acrylate (0.29 mmol, 1.2 eq.) is added to the reaction by syringe. For the reactions reported in Table 2, relative stoichiometries of methyl acrylate and *cis*-butenedioldiacetate were added to the vial by syringe, keeping the concentration of norbornene substrate constant. A solution of **2** (10 mg, 12 μmol) in CD_2Cl_2 (1.2 mL) was subsequently added to the reaction solution *via* syringe. The resulting reddish brown solution was heated to 50°C for approximately 14 hours under a nitrogen atmosphere. ^{1}H NMR spectra of aliquots (removed every 2-4 hours) and GC/MS analysis provided conversions and product identities.

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[3] (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039-2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110. (c) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett*. **1999**, *1*, 953-956.

[4] (a) Chung, T. C.; Chasmawala, M. *Macromolecules* **1992**, *25*, 5137-5144. (b) Hillmyer, M. A.; Nguyen, S. T.; Grubbs, R. H. *Macromolecules* **1997**, *30*, 718-721. (c) Maughon, B. R.; Morita, T.; Bielawski, C. W.; Grubbs, R. H. *Macromolecules* **2000**, *33*, 1929-1935. (d) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 2903-2906. (e) For a review on telechelic polymers, see Goethals, E. J. *Telechelic Polymers: Synthesis and Applications*; CRC: Boca Raton, FL, **1989**.

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[6] For the synthesis of chromenes by ROM-RCM, see: (a) Harrity, J. P.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488-1489. (b) Harrity, J. P.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343-2351.

[7] For reviews on the applications of tandem metathesis sequences, see: (d) Schuster, M.; Blechert S. *Chem. Unserer Zeit* **2001**, 35, 24-29. (e) Fürstner, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3013-3043. (f) Naota, T.; Takaya, H.; Murahashi, S. I. *Chem. Rev.* **1998**, *98*, 2599-2660 and references therein.

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[9] For examples of selective ROCM with chiral alkylidenes, see: (a) La, D. S.; Ford, J. G.; Sattely, E. S.; Bonitatebus, P. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 11603-11604. (b) La, D. S.; Satteley, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2001**, *123*, 7767-7778.

[10] For examples of the ROCM of low-strain cycloolefins, see: (a) Stüer, W.; Wolf, J.; Werner, H.; Schwab, P.; Schulz, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3421-3423. (b) Randl, S.; Connon, S. J.; Blechert, S. *Chem. Commun***. 2001**, 1796-1797.

[11] Alternatively, **I** may form from the depolymerization of a ROMP oligomer that is rapidly formed during the ROCM of a readily polymerizable monomer.

[12] Cyclooctene generally results in lower yields, presumably due to its lower ring strain relative to cyclooctadiene. The methyl ketone dimer substrate in Scheme 2 can be produced in low yield from cyclooctene ROCM.

[13] If the stoichiometry of the acroyl species is reduced relative to COD, a range of multiple oligomers that contain 4-10 internal alkenes predominates in the product mixtures.

[14] Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58-71.

[15] All methyl acrylate is consumed in the reaction; the remainder of substrate **3** remains unopened at the end of the reaction.

[16] (a) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543-6554. (b) Sanford, M. S. Ph.D. Dissertation, California Institute of Technology, **2001**.

[17] As defined, "terminal olefin" refers to a mono-substituted olefin with a methylene unit in the position α to the olefin. "Chain-transfer agent" or "CTA" refers to a disubstituted olefin that is typically used to terminate polymer chains in ring-opening metathesis polymerization (ROMP). Here, CTA refers to a disubstituted olefin that is highly metathesis-active.

[18] See Chapter 3 of this work for a more complete discussion of the reactivity of ester-carbenes and β-carbonyl carbenes.

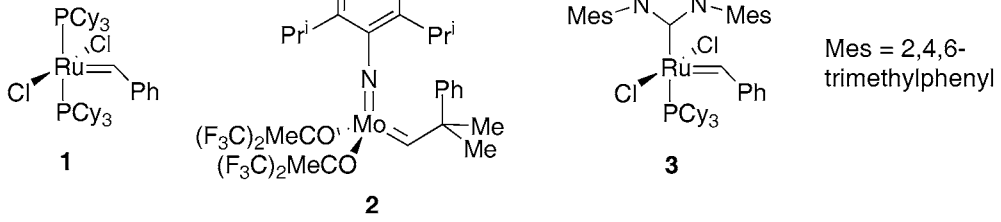
[19] Morrill, C.; Grubbs, R. H. Unpublished results.

[20] The solvent columns are composed of activated alumina (A-2) and supported copper redox catalyst (Q-5 reactant). See: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

Chapter 5. Activation of Ruthenium-based Olefin Metathesis Catalysts by Phosphine Ligand Scavenging[1]

Part 1: In situ Preparation of an N-Heterocyclic Carbene-Coordinated Olefin Metathesis Catalyst and Its Activation by Phosphine Scavenging

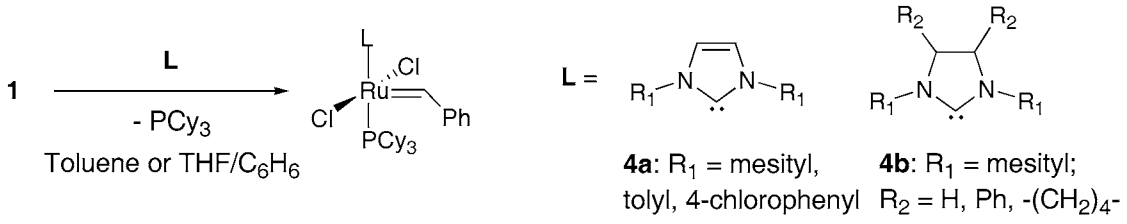
Olefin metathesis with well-defined alkylidene complexes has recently become a widely used carbon-carbon bond forming method in organic synthesis.[2] In particular, complexes **1**[3] and **2**[4] are now routinely employed in synthesis as both ring-closing (RCM) and cross metathesis (CM) catalysts. Although catalyst **1** exhibits excellent functional group compatibility, the range of substrates amenable to metathesis has been limited to electronically rich alkenes that are relatively removed from heteroatom functionality. The recent advent of *N*-heterocyclic carbene-coordinated catalysts,[5] such as ruthenium benzylidene **3**, has dramatically alleviated this limitation by performing the metathesis of vinyl siloxanes, fluorinated alkenes, and α,β-unsaturated carbonyl substrates.[6] Catalyst **3** has permitted significant reduction in catalyst loadings and reaction times compared to the parent complex **1**. In essence, **3** demonstrates the high activity of **2** while maintaining the functional group tolerance of **1**.



Currently, the widespread use of **3** is limited due to its relatively difficult preparation. Initial syntheses have utilized the free carbenes of type **4**, which are extremely air and moisture sensitive (Scheme 1).[7] Recent investigations by our group[5d,e] and subsequently by others[8] have demonstrated that the free carbenes can be generated

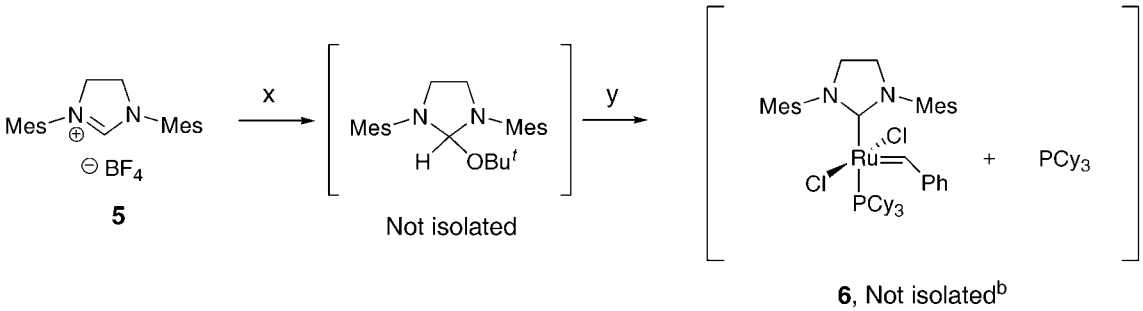
and directly trapped by **1**. In spite of this simplified ligand preparation, the isolation of these new catalysts usually requires air-free, anhydrous conditions and multiple purifications to remove free phosphine generated in the synthesis. It would be highly desirable to obtain a catalyst that has comparable activity to **3** but does not require extensive purification under rigorously air- and moisture-free conditions.

Scheme 1. Synthetic scope of *N*-heterocyclic carbene-coordinated ruthenium olefin metathesis catalysts.



A potential solution to the purification problem would be the production and use of **3** *in situ*. Although a majority of organometallic reagents are generated *in situ*, olefin metathesis catalysts prepared in this way are not commonly used by organic chemists.[9] Complexes of high purity are required because productive metathesis using **1** or **3** is inhibited by an excess of free phosphine.[5c,10a] A simple combination of **1** and an *N*-heterocyclic carbene (or the corresponding alkoxide adduct) is therefore not expected to produce a highly active catalyst, because one equivalent of free phosphine is generated (Scheme 2).

Scheme 2. *In situ* catalyst synthesis by the alkoxide route.[a]



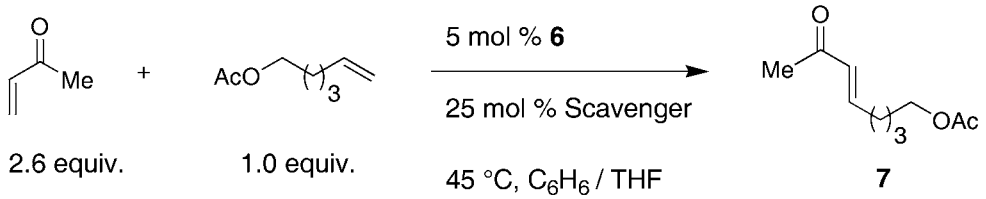
[a]Key: (x) $KOBu^t$, THF, less than 1 min. at 25°C; (y) catalyst **1**, 80°C, 30 min. [b] **6** refers to the mixture of **3** and 1 equiv. of PCy_3.

In order to overcome potential phosphine inhibition in the *in situ* generation of **3**, the use of phosphine scavengers is an attractive possibility. Previously studied in our group for **1**,[10a] scavengers are believed to activate the catalyst by removing free phosphine from solution and abstracting bound phosphine from the ruthenium metal center. In order to probe the efficacy of these processes, a variety of scavengers has been screened in the *in situ* cross metathesis of methyl vinyl ketone and an unfunctionalized terminal olefin (Table 1). This test reaction was chosen because catalyst **1** only produces homodimer of the terminal olefin; thus no "background" cross metathesis (from unconverted catalyst) will be observed. Additionally, high conversion is obtained at long reaction times even in the absence of a phosphine scavenger (entry 1). The addition of ethereal HCl (entry 2) provides yields and reaction times typical of isolated **3** (i.e., 95% after 14 hours for the identical reaction with pure **3**).[6a]

Other phosphine scavengers are much less effective. The generally slow formation of insoluble phosphine-copper adducts may explain the lower yields obtained with copper salts (entries 3-4). Another common phosphine scavenger, $B(C_6F_5)_3$, was also ineffective in driving the reaction to desirable yields (entry 5). Using $Ni(COD)_2$

(entry 6) produced a paramagnetic species (as determined by NMR), completely shutting down the reaction. Only the last additive ($AlCl_3$) and HCl provide acceptable metathesis activity.[11]

Table 1. Effect of phosphine scavenger on the cross metathesis of methyl vinyl ketone.[a]



2.6 equiv. 1.0 equiv. **7**

entry	scavenger	% yield[b]	time (h)
1	none	92	48
2	HCl/ether	90	14
3	$CuCl_2$	12	14
4	CuCl	42	24
5	$B(C_6F_5)$	47	14
6	$Ni(COD)_2$	NA[c]	<1
7	$AlCl_3$	67	14

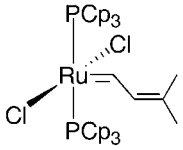
[a] **6** represents the in situ catalyst preparation described in Scheme 2. COD = cyclooctadiene. See chapter references for full experimental procedure. E/Z ratios = 14:1. [b]Isolated yields. [c] Yield is negligible; paramagnetic line broadening in ^1H NMR.

In order to ascertain the overall effectiveness of HCl as a phosphine scavenger, NMR-scale experiments were performed.[12] Under the conditions of Table 1, catalyst **1**

was observed to completely convert to catalyst **3** and generate one equivalent of free phosphine. Addition of ethereal HCl (25 mol%) to the NMR sample immediately converted the free phosphine to its phosphonium salt without decomposing **3** (as determined by ^{31}P NMR spectroscopy).

Further optimization of the reaction temperature, loading of HCl, and ruthenium source was then performed (Table 2). Raising the temperature results in catalyst deactivation (entry 1). Lowering the HCl loading dramatically reduces the yield, although the amount of acid used in this case remains greater than twice that of the catalyst (entry 2).[13]

Table 2. Variation of reaction parameters for the **6**/HCl *in situ* system in the production of **7**.[a]

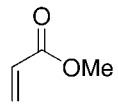
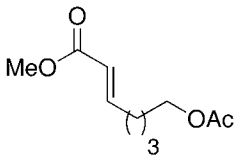
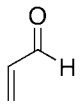
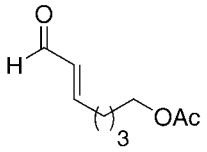
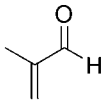
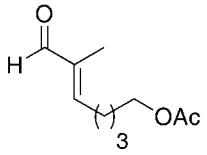
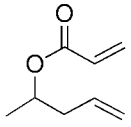
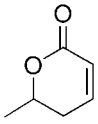
entry	temperature (°C)	mol % HCl	Ru source	% yield of **7**[b]
1	80[c]	25	**1**	trace
2	45	12	**1**	34
3	45	25	 **8**	24

[a] All unspecified conditions are identical to those in entry 2 of Table 1. [b]Isolated yields. [c]Toluene/THF was used as solvent.

Switching to the dimethylvinyl carbene **8** as the ruthenium source resulted in reduced yields, apparently arising from the slower initiation of **8** relative to **1**. The most active system is therefore prepared from **1**, **5**, and 25 mole percent ethereal HCl at 45°C.

Preliminary work on a range of CM and RCM substrates indicates that **3** and the **6** + HCl system behave similarly (Table 3).[6a,14] Unsaturated esters and aldehyes readily participate in CM with unfunctionalized terminal olefins (entries 1-2). Even a challenging trisubstituted case (entry 3) and a RCM (entry 4) are successful with this *in situ* catalyst system. In each case only small reductions in yield are observed relative to those obtained with pure **3** (Chapter 3).

Table 3. Substrate scope for the **6** + HCl *in situ* system.[a]

entry	substrate	product	% yield[b]	E:Z
1			98	> 20:1
2			52	>20:1[c]
3			82	> 20:1
4			83	---

[a] Conditions are identical to entry 2 of Table 1. [b]Isolated yields. [c]The compound originally characterized as the Z isomer in Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783-3784 was later found to be the autoxidized E isomer.

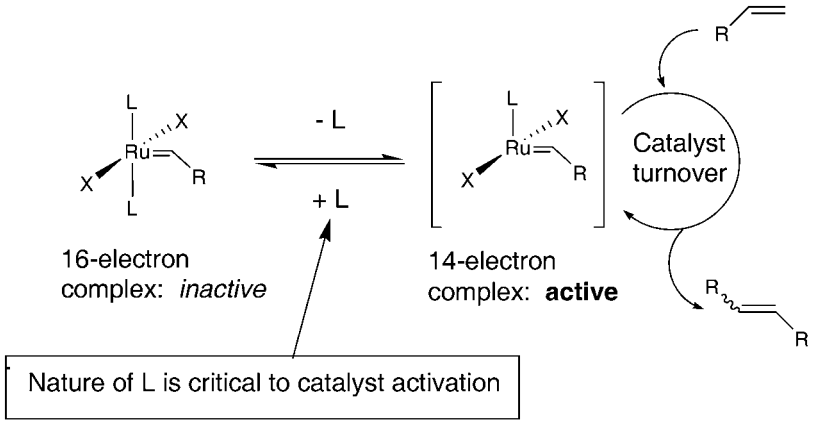
For many applications the **6** + HCl system offers an advantage over isolated **3**. No organometallic isolation is required. All of the reagents, including the imidazolium salt and the ruthenium benzylidene **1**, are easily obtained and are air stable as solids.[15] The reaction is therefore easily scalable, allowing *in situ* metathesis to be applied to the early stages of preparative scale syntheses.

In summary, generating **3** *in situ* and in the presence of HCl is a viable method for achieving high activity similar to that obtained with pure **3**. Further work on *N*-heterocyclic carbene ligands for *in situ* catalysis is currently underway.

Part II. Carboxylic Acids as Mild, Organic Phosphine Scavengers for the Activation of an N-Heterocyclic Carbene-Coordinated Ruthenium Methylidene

The currently established model of ruthenium-catalyzed olefin metathesis developed by Sanford et al. predicts that catalyst activity is highly dependent on the presence and nature of a given L-type ligand (Scheme 3).[16] As discussed in Chapter 3, any perturbation to the system that shifts the catalytic equilibrium toward a 14-electron species "activates" the catalyst. In that chapter, the method of choice for shifting this equilibrium was the careful selection of weakly binding L-type ligands (pyridines). Although this method has solved a relevant problem for the cross metathesis of acrylonitrile, practicality remains at issue; the pyridine complexes do require some (albeit relatively straightforward) synthesis. An appealing alternative to this route involves the direct scavenging of phosphine from commercially available 16-electron complexes.

Scheme 3. Simplified mechanism of olefin metathesis catalyzed by $L_2X_2Ru=CHPh$ complexes. Adapted from (a) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749-750. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543-6554.



Current methods for phosphine scavenging in these ruthenium systems involve the use of phosphorophilic transition metals (such as copper) or strong mineral acids. Copper (I) salts have been observed to form polymeric phosphine adducts that have reduced solubility in organics.[17] Unfortunately there exists no structural data on these polymeric copper-phosphine complexes; in solution they are predicted to dynamically swap phosphines between metal centers. This behavior prevents the establishment of exact stoichiometries of copper additive, and different phosphines form copper-phosphine complexes at differing rates and with differing solubilities. Additionally copper(I) is nitrophilic and Lewis acidic, preventing its use with delicate and/or highly functionalized organic substrates.

Alternatively, strong acid presents its own set of problems. In particular many protecting groups remain sensitive to strong mineral acids, once again preventing the use of phosphine scavenging in delicate situations. Additionally Lynn et al. suggest that acid may catalyze the ruthenium alkylidenes to undergo rearrangement to ruthenium carbyne

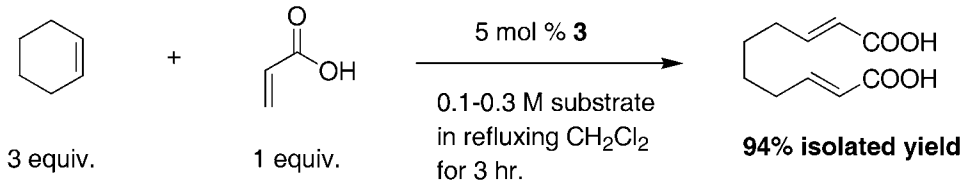
species.[18] Strong acids may therefore decompose both the substrate and the catalyst under a variety of reaction conditions.

A gentler method for scavenging phosphine would therefore combine many desirable characteristics: it would be easily carried out in the organic chemistry laboratory (with known procedures and stoichiometries), and it would preferentially decompose neither substrate nor catalyst. Because the pK_a of protonated trialkylphosphines is approximately 9 in H_2O,[19] a variety of protonated organic species that are much weaker than mineral acids are predicted to meet these specifications.

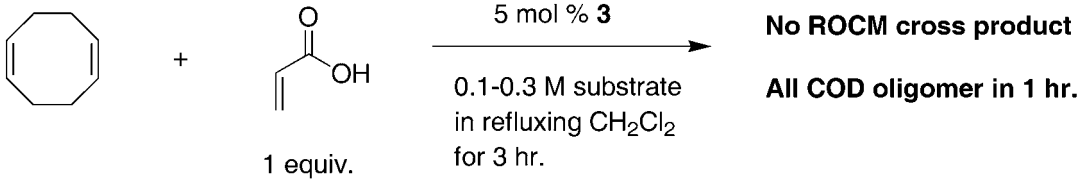
A promising lead came to our attention during the ROCM work discussed more fully in Chapter 4. Choi et al. had successfully utilized acrylic acid as a cross partner in the ROCM of cyclohexene (Scheme 4a).[20] This reaction was more facile than other ROCM reactions involving cyclohexene because the product was largely insoluble in the reaction solvent, thereby driving the overall process toward ROCM product. When similar conditions were attempted with COD as the cyclic precursor, no ROCM product was observed, but all COD was observed to rapidly oligomerize (within 1 hour, Scheme 4b). Even after long reaction times no acrylic acid moieties were detected by ^1H NMR in the growing polymer chain. Other ROCM reactions using COD as cycloolefin (Chapter 4, Table 1) demonstrated similar reactivity (i.e., polymerization over short reaction times), but the polymers were eventually cleaved into small molecules by the slower cross metathesis of the α,β-unsaturated olefin. Ultimately at equilibrium, only the small molecule products in Chapter 4, Table 1 were observed (essentially no polymer was present). The lack of incorporation of acrylic acid suggested that this substrate was not behaving as a typical cross metathesis partner, but rather as an "activator." The

possibility of utilizing other carboxylic acids as phosphine scavengers was then investigated.

Scheme 4(a). Ring-opening cross metathesis of cyclohexene with acrylic acid. Reported in Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am . Chem. Soc.* **2001**, *123*, 10417-10418.



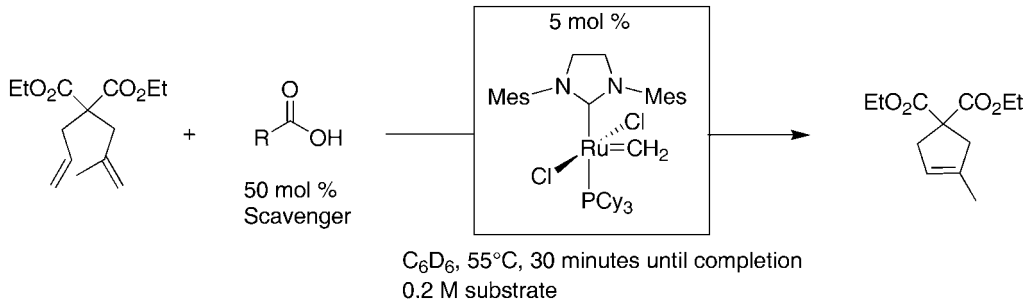
Scheme 4(b). Attempted ROCM of COD with acrylic acid.



In order to screen various carboxylic acids, a suitable "test reaction" had to be designed (Scheme 5). The choice of methylidene as precatalyst is twofold: first, this catalyst is the least effective of the NHC-coordinated ruthenium alkylidenes, and second, the overall reaction is degenerate from the catalyst point-of-view. Sanford et al. have evidence that the methylidene is a kinetic "trap," slowing down reactions during which it is formed.[16] A scavenger that can accelerate methylidene catalysis should therefore have even more dramatic effects on the more active benzylidene or alkylidene members of the catalyst family. Secondly, the overall reaction must be degenerate in catalyst so that both the activity and decomposition of the catalyst can be readily monitored. If different alkylidenes formed during the reaction, the overall reaction rates would be dependent on

multiple species. The effect of phosphine scavenger may thus be different for each alkylidene species formed, preventing a simple assessment of the scavenger's efficacy.

Scheme 5. Test reaction for phosphine scavenging.



The choice of substrate is also reflective of reaction rate. The substrate 4,4-dicarboethoxy-2-methyl-1,6-heptadiene undergoes metathesis sufficiently slowly to permit monitoring by ^{1}H NMR kinetics ($t_{1/2}$ is approximately 10-20 minutes at 40°C). Additionally the resonances for the substrate and ring-closed product are baseline separated and easily distinguishable in a 300 MHz ^{1}H NMR spectrum. A drawback to the use of this substrate is the generation of ethylene gas as the reaction proceeds; at periodic intervals (every 3 minutes) this byproduct gas was directly released from the J. Young NMR tube. Some scatter (generally less than 5 s) was generated in the kinetics time course data due to this drawback.

An additional concern is one of protonation chemoselectivity; the carboxylic acid may protonate the substrate ester groups rather than the free phosphine. This ester protonation is not predicted to accelerate the catalysis because the ester groups are electronically and spatially removed from the reacting olefin groups in the substrate. More importantly, the stronger phosphine base should fully sequester the protons from

the protonated esters, rendering the question of protonation moot. The phosphine remains the strongest base in solution in every case studied and will therefore be preferentially converted to phosphonium ions in the presence of the carboxylic acid scavengers.

For this study, the phosphine scavengers are limited to carboxylic acids. Although ammonium species and phenols have suitable pK_a values (8-11 in H_2O), these molecules are inappropriate for use as phosphine scavengers. If these acidic species protonate the phosphine (thereby "scavenging" it), they generate conjugate bases (amines, phenolates) that may coordinate to the catalyst and alter its reactivity. In contrast, Dias et al. have demonstrated that free carboxylates (i.e., not metal-bound) do not readily displace phosphines in ruthenium alkylidenes.[21] Instead a transmetallation from thallium(I) carboxylates is necessary for successful phosphine displacement. This result suggests that carboxylates are in fact "weak" ligands for the ruthenium center and will not interfere in the catalysis.

Benzene was chosen as the reaction solvent due to its non-coordinating nature and relatively high boiling point, allowing the reactions to be performed at 55°C. Not all of the studied phosphine scavengers are soluble in warm non-polar organics, preventing a complete comparison of all species. Additionally, the ruthenium catalysts themselves show dramatically reduced activity in more polar solvents such as DMF/DMSO. For this reason, two independent comparisons were made: those phosphine scavengers that remained soluble were differentiated from those that were insoluble in warm benzene.

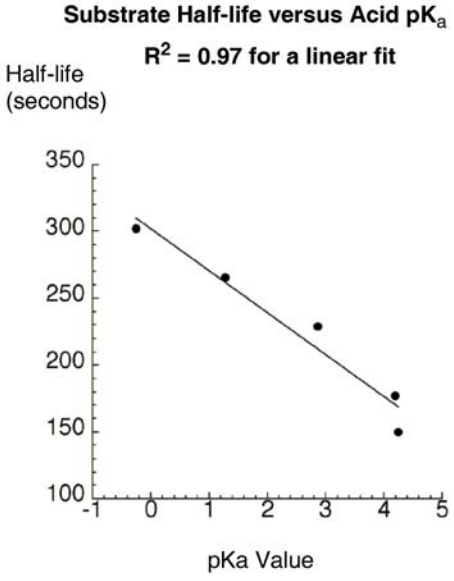
The half-lives for substrate consumption and methylidene decomposition are depicted numerically and graphically in Table 4. An internal anthracene standard (5 mol %) was used to monitor the disappearance of the methylidene α-proton. Only those

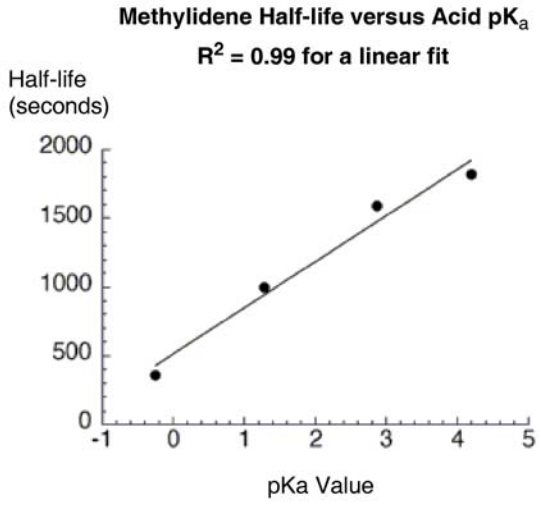
values whose error is lower than 5% of the experimental value is plotted on the graphs (e.g., benzoic acid and acrylic acid trials were discarded from the methylidene decomposition graph due to large errors). Although the linear fits have good R^2 statistics, their presence is merely suggestive: the linear fits are meant to emphasize the relationships between pK_a and rate, never to demonstrate a linear relationship. ^{31}P NMR experiments do not show free phosphine in any of the experiments so the degree of "scavenging" could not be directly assessed.

Table 4. Soluble carboxylic acid phosphine scavengers.[a]

Phosphine Scavenger	pK_a (H_2O)	Half-life (seconds) of substrate[b]	Half-life (seconds) of methylidene[c]
Control (no scavenger)	---	595 ± 12	922 ± 71
Trifluoroacetic	-0.25	302 ± 7	358 ± 7
Trichloroacetic	0.65	Hydride forms	Hydride forms
Dichloroacetic	1.29	265 ± 4	999 ± 40
Chloroacetic	2.86	229 ± 3	1587 ± 97
Methacrylic	approx. 4.2	207 ± 4	1820 ± 143
Benzoic	4.2	177 ± 6	945 ± 278
Acrylic	4.25	150 ± 9	531 ± 207

[a]Each experiment was repeated three times and the average is reported. Conditions: 1 eq. diethylallylprenylmalonate, 50 mol % scavenger, 5 mol % methylidene in C_6D_6. Trials in which the error is greater than 5% of the experimental value are not plotted below. [b]Measured by disappearance of ^1H NMR (300 MHz, C_6D_6) resonance at δ 2.86 ppm. [c]Measured by disappearance of ^1H NMR(300 MHz, C_6D_6) resonance at δ 18.23 ppm.





The data do suggest both expected and unexpected trends. As expected, the methylidene half-life increases with increasing pK_a. Less acidic phosphine scavengers should decompose the catalyst less readily, thereby increasing catalyst half-life. Conversely, an increase in scavenger pK_a decreases the substrate half-life, suggesting that less acidic phosphine scavengers are *more* effective at promoting the ring-closing reaction. Two rationales may be proposed to explain this behavior. The first is related to methylidene half-life: higher pK_a translates into less decomposed catalyst, subsequently producing a faster rate. This behavior may be inconsistent with the data because catalyst half-lives are significantly longer (in general) than the total time for substrate consumption (approximately 300-400 s). This observation suggests that the majority of the catalyst remains "alive" throughout the entire reaction and that decomposition does not play a major role in reduced rates of substrate consumption.

Another possible explanation for the efficacy of higher pK_a scavengers is a "buffering" effect. A higher pK_a scavenger will buffer the reaction by releasing fewer protons into solution. This phenomenon would result in lower solution polarity and a more active catalyst. Lynn and coworkers have demonstrated that ruthenium alkylidenes are less active in highly polar solvents that potentially contain ionized species, such as water and methanol.[18(b)] This observation is also supported by Sanford et al. who suggest that *non-ionizing* solvents of higher dielectric constant result in faster reaction rates (also compare to results in Chapter 2 of this thesis).[22] Therefore the absence of ionized species is critical to catalyst activity and stability.

In either case the success of higher pK_a scavengers is advantageous to the field of synthetic chemistry. The ability to scavenge phosphine more effectively with weaker acids in particular is beneficial for more sensitive organic substrates. Use of mineral

acids and copper sources may now be effectively eliminated, for the scavenging ability of benzoic acid is comparable to both CuCl and HCl/Et_2O (Table 5). Although CuCl remains the "best" phosphine scavenger, the rate of catalyst decomposition under these conditions makes its use prohibitive. In contrast, HCl is apparently the mildest scavenger with respect to catalyst decomposition, but its ability to promote the ring closure is lower. The use of benzoic acid as phosphine scavenger combines the best aspects of both "traditional" scavengers in that it accelerates the rate of ring closure by a factor of four without significantly increasing the decomposition rate of the catalyst.

Table 5. Comparison of reaction rates for both traditional and carboxylic acid phosphine scavengers for the reaction detailed in Scheme 5.[a]

Phosphine Scavenger	Rate of Ring Closure to trisubstituted olefin (k_{obs} X 10^3, s^{-1})	Rate of Methylidene Decomposition (k_{decomp} X 10^3, s^{-1})
None	1.68 ± 0.03	1.17 ± 0.02
CuCl (10 eq.)	7.58 ± 0.29	8.55 ± 0.93
HCl/Et_2O	4.74 ± 0.27	0.18 ± 0.01
Acetic Acid	4.08 ± 0.14	2.04 ± 0.63
Acrylic Acid	6.67 ± 0.38	1.88 ± 0.52
Benzoic Acid	5.65 ± 0.19	1.06 ± 0.24

[a]All reaction rates are averages of three independent experiments. Both rates and error is determined by the curvefitting program in Varian VNMR software. Experimental conditions are described in Scheme 5.

The only foreseeable drawback to the widespread use of soluble phosphine scavengers is their cleanup from reaction mixtures upon completion of the reaction. The removal of 10 equivalents of scavenger (relative to catalyst) is not necessarily trivial on

the large preparative scale. The use of carboxylic acids as scavengers offers a potential solution: the water solubility of these acids should allow their separation by a simple aqueous wash. A more practical alternative would involve the use of insoluble and/or polymeric phosphine scavengers that could be easily filtered away from the reaction upon completion. An additional benefit comes from the potential reuse, or "recycling," of these insoluble scavengers in future reactions.

Unfortunately the activity of insoluble carboxylic acid scavengers is not readily predictable (Table 6). These trials do not show the same general trends as the soluble scavengers, suggesting that the relative solubilities of each scavenger may be critical to their efficacy. Under such conditions the prediction of general trends is impossible, and remains an empirical process. In spite of this observation, certain insoluble scavengers such as anisic acid (or *m*-nitrobenzoic acid) are comparable to the best soluble carboxylic acids in either their ability to promote the ring closure or their compatibility with the catalyst. These compounds may therefore be the "best" options overall, combining good rate accelerations and easy workup.

As opposed to the use of monomeric, insoluble carboxylic acids, poly-acrylic acid was tested as a potential phosphine scavenger. The success of acrylic acid (*vide supra*) suggested that lower polymer loadings of poly-acrylic acid may be a sufficiently effective alternative. However the methylidene NMR resonances were observed to rapidly disappear in the presence of poly-acrylic acid, suggesting that rapid decomposition had occurred. In addition no ring-closed product was observed, further supporting the decomposition hypothesis.

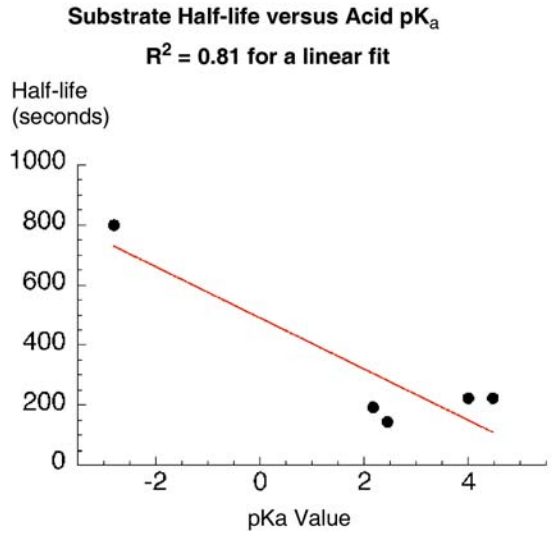
Overall, soluble carboxylic acids offer an attractive alternative to the mineral acids as "activators" of ruthenium alkylidenes. For small preparative scale applications,

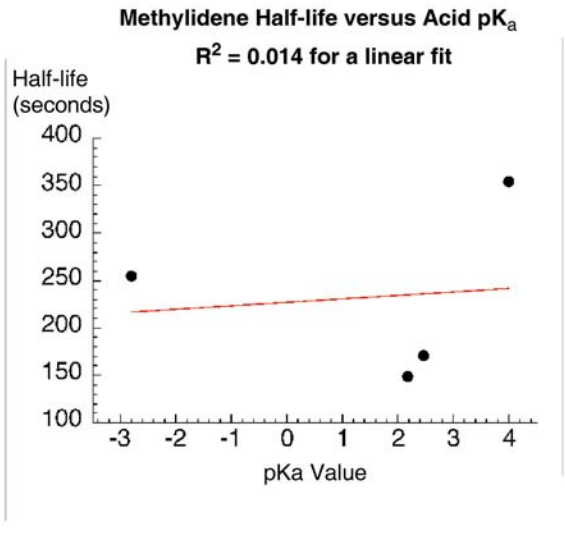
the use of these acids is operationally straightforward and may significantly increase reaction rates. Workup is typically limited to a neutral or slightly basic aqueous wash that should be amenable to a variety of sensitive organic functionalities. Finally, these scavengers are cheap, commercially available materials that are common in many laboratories and are easily obtained and stored. A new level of reactivity may be readily reached if *in situ* synthetic methods (described in Part I of this chapter) and phosphine scavenging are used in tandem to generate active olefin metathesis preparations.

Table 6. Insoluble carboxylic acid phosphine scavengers.[a]

Phosphine Scavenger	pK_a (H_2O)	Half-life (seconds) of substrate[b]	Half-life (seconds) of methylidene[c]
Control (no scavenger)	---	595 ± 12	922 ± 71
Tosic acid	-2.8	798 ± 22	254 ± 15
o-nitrobenzoic	2.17	191 ± 5	149 ± 6
m-nitrobenzoic	2.45	145 ± 3	171 ± 17
p-nitrobenzoic	3.44	3280 ± 310	N. D.
p-chlorobenzoic	3.99	221 ± 7	354 ± 24
p-anisic	4.47	225 ± 4	4620 ± 1220

[a]Each experiment was repeated three times and the average is reported. N. D. = not determined. Conditions: 1 eq. diethylallylprenylmalonate, 50 mol % scavenger, 5 mol % methylidene in C_6D_6. Most scavengers did not visibly dissolve in the reaction medium. Trials in which the error is greater than 5% of the experimental value itself are not plotted below. [b] Measured by disappearance of ^1H NMR (300 MHz, C_6D_6) resonance at δ 2.86 ppm. [c]Measured by disappearance of ^1H NMR(300 MHz, C_6D_6) resonance at δ 18.23 ppm.





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methyl-1,6-heptadiene (Scheme 5 substrate). Drs. Choon Woo Lee, Jennifer Love, Melanie Sanford, and Arnab Chatterjee are also acknowledged for helpful discussions and suggestions.

Experimental Section. C_6D_6 was obtained from Cambridge Scientific and dried over activated 4Å molecular sieves. 4,4-Dicarboethoxy-2-methyl-1,6-heptadiene was generously provided by Dr. Michael Ulman. ^{1}H NMR spectra were recorded on an Oxford Instruments 300 MHz instrument running Varian VNMR software, which was also used to record and curvefit kinetics data. NMR spectra were referenced to residual solvent (7.15 ppm for C_6D_6). For phosphine scavenging experiments, all phosphine scavengers were obtained from Aldrich Chemical Company and used as received. $(IMesH_2)(PCy_3)(Cl)_2Ru{=}CH_2$ (hereafter referred to as "methylidene") was synthesized by a procedure detailed in Sanford, M. S., Dissertation, California Institute of Technology, 2001. All samples were prepared in a nitrogen-filled Vacuum Atmospheres glovebox (O_2 < 1 ppm) or using standard Schlenk techniques (where noted).

General procedure for phosphine scavenging experiments. In the glovebox, methylidene (5.4 mg, 7 μmol, 5 mol %) was dissolved in C_6D_6 (0.7 mL), and the mixture was transferred to a screw-cap NMR tube containing a Teflon septum. At this point insoluble phosphine scavengers (70 μmol, 50 mol %) were directly added to the tube as solids. The tube cap was then sealed with Parafilm and removed from the glovebox. The tube was equilibrated for 10 minutes at 55°C in the NMR instrument. After this time the tube was removed and placed in a 55°C oil bath during which time diethylprenylmalonate (36 μL, 140 μmol, 1 eq.) and soluble phosphine scavenger (70

μmol, 50 mol %) were sequentially added by syringe. Immediately after addition of the phosphine scavenger the tube was replaced in the NMR instrument and kinetic data were recorded (spectra were recorded every 15 s, 4 scans per spectrum, 45 minutes total recording time). Kinetics data were fit using the exponential curve-fitting program in the Varian VNMR software. Each experiment was performed 3 times and the average of all runs is reported in Tables 4-6. Reported errors are the largest values obtained during any single given experiment as estimated by the curvefitting program. Substrate consumption was monitored by the disapperance of the ^{1}H NMR resonance at δ 2.86 ppm and methylidene decomposition was monitored by the disappearance of the ^{1}H NMR resonance at δ 18.23 ppm.

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[9] In this work, the phrase "*in situ* catalyst" refers to a catalyst system that is constructed from many distinct components and then used in the same reaction vessel. It does not refer to single-component catalysts (i.e., allenylidenes) which are thermally or

photochemically activated *in situ*. For the latter cases, see: (a) Picquet, M.; Touchard, D.; Bruneau, C.; Dixneuf, P. H. *New J. Chem.* **1999**, *23*, 141-143. (b) Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1998**, 2249-2250.

[10] (a) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887-3897. For the use of HCl as phosphine scavenger, see: (b) Lynn, D. M.; Mohr, B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 1627-1628. (c) Lynn, D. M.; Mohr, B.; Grubbs, R. H.; Henling, L. M.; Day, M. W. *J. Am. Chem. Soc.* **2000**, *122*, 6601-6609.

[11] For a related discussion of HCl, $AlCl_3$, and other Lewis acids as potential phosphine scavengers, see: (a) Sanford, M. S.; Henling, L. M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 5384-5389. (b) Katayama, H.; Yoshida, T.; Ozawa, F. *J. Organomet. Chem.* **1998**, *562*, 203-206.

[12] NMR tube reactions were prepared under dry nitrogen atmosphere in a Vacuum Atmospheres glove box and sealed in a J. Young NMR tube. THF-d_8 and C_6D_6 were dried and degassed prior to use and stored over molecular sieves. The concentration of all reagents was identical to those used in the experiments of Table 1. NMR spectra were recorded with Varian VNMR software on an Oxford 300 MHz instrument.

[13] The excess HCl is required to fully protonate the free phosphine. In addition this strong acid may protonate the carbonyl substrates to provide a rate acceleration. A highly oxophilic Lewis acid such as $AlCl_3$ may also play a similar role. For a related example of Lewis acid activation of carbonyl-containing substrates, see: Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130-9136.

[14] A typical experimental procedure is as follows. A suspension of tetrafluoroborate salt **5** (14 mg, 35 μmol) in dry THF (1 mL) was prepared in a flame-dried Schlenk flask

under nitrogen. Potassium *tert*-butoxide (4 mg, 35 μmol) was added to the rapidly stirred suspension at room temperature, resulting in the immediate dissolution of **5** to form a yellow solution. After 5 minutes, a solution of **1** (21 mg, 25 μmol) in dry benzene (2 mL) was added via cannula. The mixture was heated to 80°C for 35 minutes and subsequently cooled to room temperature. Methyl vinyl ketone (100 μL, 1.3 mmol), 5-hexenylacetate (84 μL, 0.5 mmol), and HCl (2.0 M in diethyl ether, 60 μL, 120 μmol) were added to the cooled solution via syringe. The reaction mixture was then heated to 45°C for 14 hours, followed by concentration *in vacuo* to a brown residue. Purification by silica gel chromatography (9:1 hexanes:ethyl acetate) yielded 90% of **6** (84 mg, 0.45 mmol) as a clear, yellowish oil.

[15] Catalyst **1** (1g: $55.00 USD) and the imidazolium tetrafluoroborate salt **5** (1g: $70.00 USD) are currently available from Strem Chemicals, Inc.

[16] (a) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749-750. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543-6554.

[17] Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887-3897 and references therein.

[18] (a) Lynn, D. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 3187-3193. (b) Lynn, D. M. Dissertation, California Institute of Technology, 1999.

[19] pK_a values are obtained from the website of Professor David Evans at the Harvard University Department of Chemistry and Chemical Biology. Address: http://daeiris.harvard.edu/DavidEvans.html

[20] Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417-10418.

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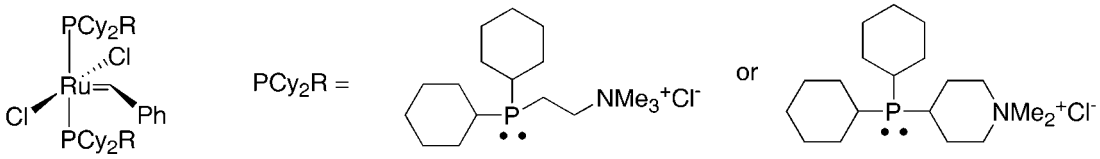
Chapter 6. Conclusions and Perspectives on *N*-Heterocyclic Carbene Chemistry

The extension of *N*-heterocyclic carbene technology to olefin metathesis catalysis is the marriage of two rapidly developing fields in organometallic and organic chemistry. The rich ligand chemistry of NHC's has enjoyed a recent resurgence, as these versatile ligands are widely applied as phosphine "mimics."[1] The fortuitous application of this ligand set to ruthenium-based olefin metathesis catalysts has produced systems with unexpectedly high activity.[2] As is often the case, combination of known synthetic technology sheds light upon the areas that remain unexplored. It has been a goal of the preceding work to demonstrate a few of these active research areas. The following discussion is designed to expand upon other areas of the work that have recently emerged. Each of these areas remains in the developmental stages and may become future fields of active inquiry.

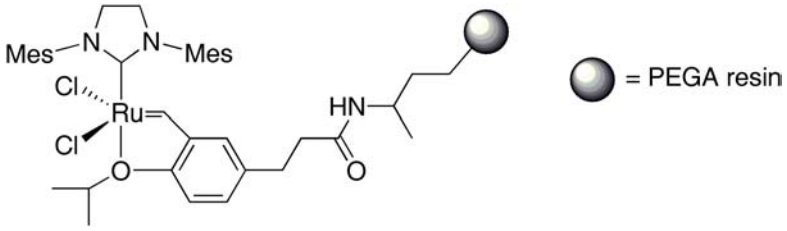
Of particular recent interest to olefin metathesis researchers is the question of metathesis in partially or fully aqueous environments. Although Novak and Grubbs successfully polymerized water-soluble monomers in emulsion, their initial catalyst systems were largely undefined and were consequently difficult to study.[3] Lynn and Grubbs addressed this problem with their development of well-defined, single component, water-soluble ruthenium-based olefin metathesis catalysts.[4] Their initial strategy focused on water-soluble phosphines (Figure 1), and the catalysts coordinated with these phosphines were active in both ROMP and RCM in protic solvents (including water).[5] Unfortunately these catalysts demonstrated poor stability in water, especially when methylidene ($Ru{=}CH_2$) species were formed.

Figure 1. Water-soluble *bis*-phosphine olefin metathesis catalysts described in Lynn, D. M. Dissertation, California Institute of Technology, 1999.



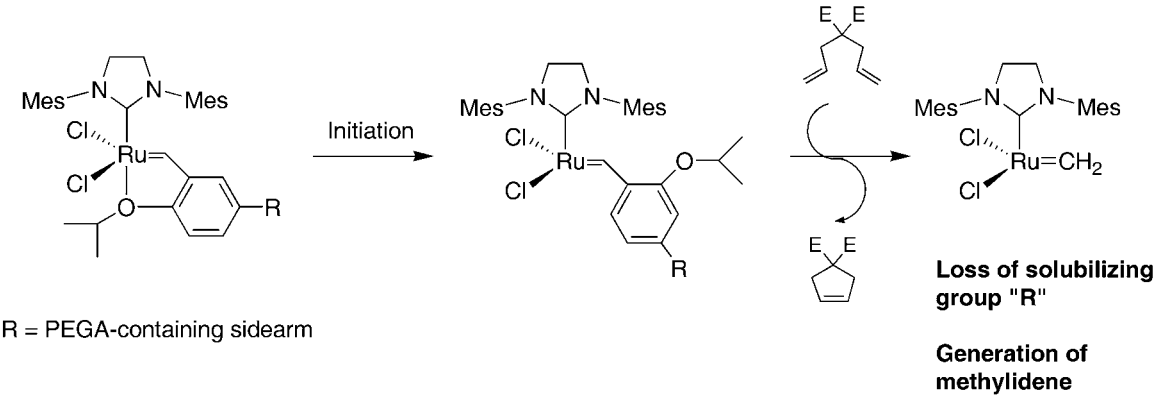
Vinylidene ($Ru=C=CR_2$) systems coordinated with water-soluble phosphines have also been prepared, although the precedented low activity of these systems in RCM or cross metathesis makes these catalysts less desirable.[6] In order to circumvent these activity and stability problems, a more stable ligand system than the water-soluble phosphines needed to be developed. The higher stability conferred by NHC coordination makes these ligands a natural choice for water-soluble catalysts. Recently NHC-coordinated ruthenium alkylidenes have been prepared and covalently linked to a resin that swells in protic solvents (Figure 2).[7] The resulting catalysts are mildly active for RCM and cross metathesis in water, but they remain much less efficient in water than in other organic solvents. The reduced activity may be a result of the hydrophobicity of the catalyst; upon initiation the resin is separated from the active catalytic 14-electron species (Scheme 1). A more efficient solution to the activity problem would involve the development of an NHC ligand that is water-soluble. Upon initiation, the NHC would remain coordinated to the catalyst and the active 14-electron species would also remain fully soluble.

Figure 2. *N*-heterocyclic carbene-coordinated metathesis catalyst bound to a hydrophilic solid support. PEGA = polyethyleneglycolamide. See: Connon, S. J.; Blechert, S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1873-1876.



Gallivan, Jordan, and Grubbs have successfully realized this goal with a PEG-bound NHC catalyst (Figure 3).[8] This catalyst is particularly active for ROMP in protic solvents, but its polymeric nature makes this ruthenium alkylidene difficult to characterize. Non-polymeric, water-soluble catalysts should help alleviate these problems. In pursuit of this goal, a sulfonated NHC was developed as an alternative, easily synthesized ligand for ruthenium olefin metathesis catalysts.

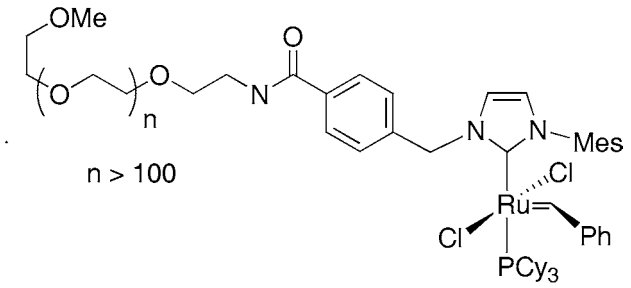
Scheme 1. Initiation and first turnover of resin-bound catalyst ejects the resin, leading to catalyst decomposition in a protic environment.



The synthesis of the desired ligand is detailed in Scheme 2. A standard alkylation reaction of mesitylimidazole with the commercially available sodium salt of 1-

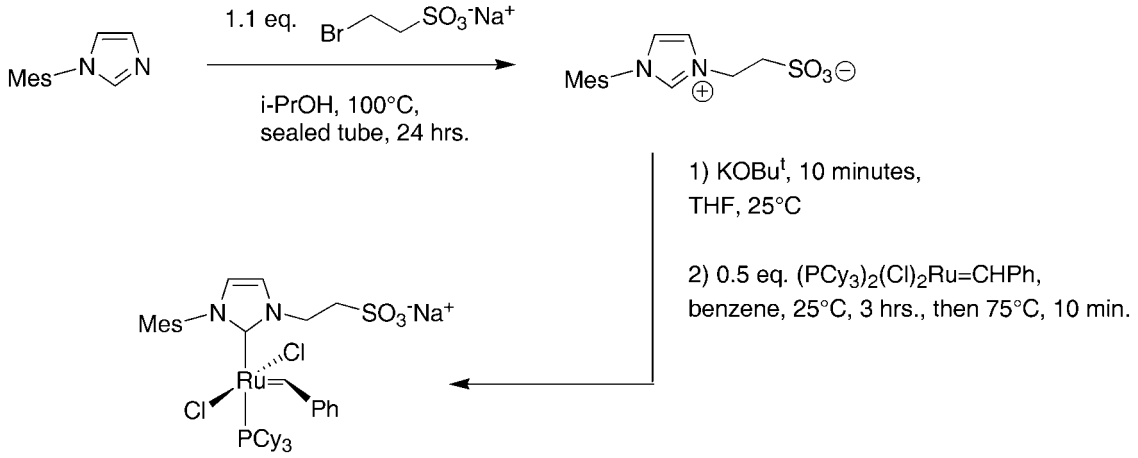
bromoethanesulfonic acid was straightforward. The ligand salt was fully soluble in organic solvents as its zwitterion, allowing the ligand to be easily separated from the sodium bromide byproduct. The ligand salt was then used directly in the synthesis of the ruthenium catalyst. Deprotonation of the salt with potassium *tert*-butoxide and addition of $(PCy_3)_2(Cl)_2Ru{=}CHPh$ produced two alkylidenes upon heating to 80°C. One of these alkylidenes was identified as the *bis*-*tert*-butoxide complex $(NHC)(OBu^t)_2Ru{=}CHPh$ originally observed by Sanford et al.[9] Upon heating at high temperature, this *tert*-butoxide complex decomposed, permitting the isolation of the desired new NHC complex. This new alkylidene remained highly air sensitive, darkening visibly upon exposure to air or attempted purification by column chromatography.

Figure 3. Water-soluble *N*-heterocyclic carbene-coordinated ruthenium alkylidene. Gallivan, J. P.; Jordan, J. P.; Grubbs, R. H. Unpublished results.



The sulfonated catalyst was then subjected to standard RCM conditions (5 mol% catalyst, 0.2 M substrate) with diethyldiallylmalonate in methanol. The reaction went to completion in 1 hour, demonstrating that this catalyst is fully active in protic media. Unfortunately the catalyst was not active for any substrates in water, suggesting that the sulfonated catalyst was not fully amenable to this solvent.

Scheme 2. Synthesis of the *N*-sulfonated imidazolium salt and its use in ruthenium alkylidene synthesis.

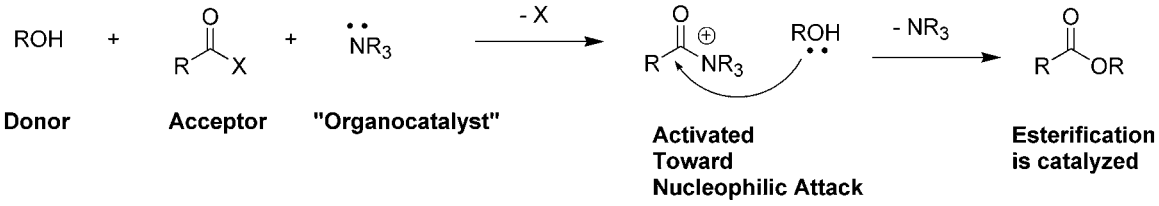


Development of a fully stable water-soluble catalyst that can be readily studied in protic media remains a highly desirable goal. Modification of the sulfonated catalyst described here may provide a new platform for the exploration of ruthenium catalysts in highly polar, protic media. The straightforward synthetic manipulation of *N*-heterocyclic carbenes makes them ideal scaffolds for design of the most optimal water-soluble ligands.

This synthetic flexibility of the NHC's presents an alternative use for these nucleophilic ligands. In particular, the NHC may act as a nucleophile in traditional "organocatalyzed" reactions. Ample evidence exists for the catalysis of nucleophilic reactions by stronger "activating" nucleophiles (Scheme 3).[10] In this example, the nucleophilic amine organocatalyst activates the acyl donor toward attack by the weaker alcohol nucleophile through the generation of a highly reactive acyliminium ion. The stereoselective variant of this reaction remains synthetically important: if the alcohol

contains an α-stereocenter and the organocatalyst is chiral, a single enantiomer of the alcohol may be acylated more rapidly in a potential kinetic resolution.

Scheme 3. An example of organocatalysis: amine-catalyzed esterification.



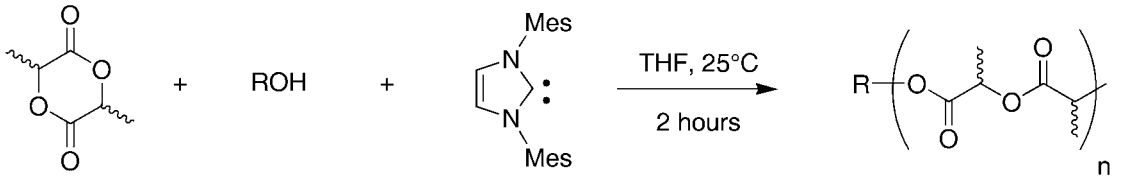
Fu, Miller, and coworkers have developed chiral organocatalysts that carry out this kinetic resolution. Fu's system involves a planar chiral derivative of 4-dimethylaminopyridine that is coordinated with an FeCp* fragment.[11] This planar chiral catalyst can effect the kinetic resolution of secondary alkyl-aryl carbinols with selectivity factors of 32-95 (corresponding to over 92% ee at 50% conversion). Unfortunately the catalyst requires 6 synthetic steps including a nontrivial resolution, reducing the practicality of this route. Alternatively, Miller et al. have pursued a biomimetic combinatorial route to secondary alcohol resolution.[12] By utilizing a split-pool method, octapeptides containing modified histidine residues were found to catalyze the acylation of alkyl-aryl and alkyl-alkyl carbinols with selectivity factors over 50 in select cases. The non-rational design of these catalysts suggests that they may remain inoptimal as "general" acylation catalysts.

Other acylation catalysts have recently emerged, including different chiral DMAP derivatives,[13] other planar chiral heterocycles,[14] and chiral phosphines.[15] In each case the main drawback that prevents widespread generalization of these acylation catalysts remains the relatively non-straightforward catalyst synthesis or resolution. A catalyst

framework that presents more synthetic "handles" for incorporation of chiral moieties is therefore highly desirable.

Once again *N*-heterocyclic carbenes provide a plausible solution to these synthetic issues. The relatively straightforward synthesis of these potential organocatalysts makes them ideal scaffolds for the incorporation of chirality.[16] Prior to the investigation of stereoselectivity, however, the question of functional catalysis by NHC's must be addressed. Recently, Connor et al. have shown that free NHC's can be used to catalyze the ring-opening polymerization of lactone monomers (Scheme 4).[17] These results have demonstrated the ability of NHC's to function as stable nucleophilic catalysts in organic media, meeting the first criterion for small molecule organocatalysis. The next question is one of scope: can NHC's catalyze the standard acylation of carbinols with acetic anhydride?

Scheme 4. Lactide polymerization using *N*-heterocyclic carbene organocatalysis. From Connor, E. F.; Nyce, G. W.; Myers, M.; Möck, A.; Hedrick, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 914-915.



Monomer **Initiator** **Organocatalyst** **high MW poly(lactide)**

Monomer:Initiator = 10:1 to 200:1
Catalyst:Initiator = 0.0083:1 to 1.5:1

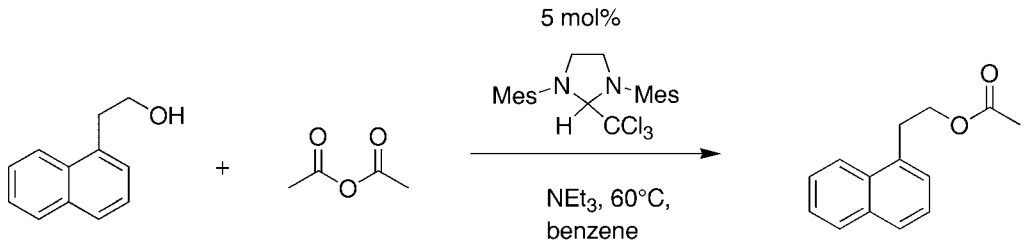
PDI = 1.05-1.33

In order to successfully address this question, free NHC's must be synthesized and manipulated. As discussed in detail in Chapter 2, the free NHC's are impractical benchtop catalysts due to their extreme air- and moisture-sensitivity. The H_2IMes

"chloroform adduct," $H_2IMes(H)(CCl_3)$, should represent the best solution to these problems.[18] If the chloroform adduct could extrude the free NHC under acylation conditions, the reaction may be appropriately catalyzed.

In order to test this proposal, 1-methylnaphthanol was subjected to standard acylation conditions with acetic anhydride as acylating agent and $H_2IMes(H)(CCl_3)$ as catalyst (Scheme 5). As stated in Chapter 2, the temperature of the reaction is critical to efficient production of the NHC: temperatures below 55°C will not result in the extrusion of chloroform from the adduct. At 60°C, the acylation reaction is apparently catalyzed by approximately a factor of four in the presence of the chloroform adduct. There is also a significant change in the reaction color when the substrates and chloroform adduct are heated to the reaction temperature; the NMR tube solution visibly changes to a deep reddish color. In the absence of catalyst the solution remains yellowish thoroughout the reaction. The addition of chloroform or the imidazolium salt $[H_2IMes(H)][Cl]$ to these reactions does not result in either catalysis or color change, prompting us to postulate that the free NHC is in fact the functional catalytic species in these reactions.

Scheme 5. Evidence for organocatalysis by *N*-heterocyclic carbenes in the acylation of primary alcohols.



k (uncatalyzed) X 10^3 = 1.4 ± 0.1 s^{-1}

For the catalyzed reaction, k_{obs} X 10^3 = 5 ± 1 s^{-1}, a factor of four faster than the uncatalyzed reaction.

This leading result demonstrates that NHC's are efficient catalysts in the general acylation reaction of carbinols with acetic anhydride, meeting an important criterion on the path to successful stereoselective catalysis. The next steps will involve the incorporation of chirality into the NHC backbone and subsequent screening for kinetic resolution of racemic secondary alcohols. The chloroform adduct technology described here should result in greatly increased thoroughput in both the synthesis and screening steps of this process.

The "cooperation" between NHC chemistry and ruthenium-catalyzed olefin metathesis continues to bear far-reaching results. The studies described in this chapter are designed to extend and illustrate certain less-studied aspects of this "cooperation." As advances in each field are introduced, the development of more efficient catalysts becomes realizable. The resulting catalysts may then be used for small molecule and materials applications that we can currently only imagine. It is this progression, from fundamental advances in both ligand and catalyst chemistry, that continues to drive the rapidly expanding field of metal-catalyzed olefin metathesis and related chemistries.

Acknowledgements. The author thanks the National Institutes of Health and the National Science Foundation for generous financial support of this research. Dr. Eric Connor (IBM Research Center, Almaden, CA), Dr. Steven Goldberg and Dr. F. Dean Toste (University of California, Berkeley, CA) are thanked for helpful discussions. Dr. Jon Seiders (Merck, San Diego, CA) is thanked for generously providing *N*-mesitylimidazole.

Experimental Section. All manipulations were performed using standard Schlenk technique or in a nitrogen-filled Vacuum Atmospheres glovebox, unless otherwise noted. NMR spectra were recorded on either an Inova 500 MHz or 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. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m). The reported ^{1}H NMR and ^{13}C NMR data refer to the major olefin isomer unless stated otherwise, and no peak assignments were made for the latter. High-resolution mass spectra (EI and CI) were provided by the University of California, Los Angeles Mass Spectrometry Facility. Product ratios were in part determined by gas chromatography/mass spectrometry using a Hewlett-Packard 5890 Gas Chromatograph interfaced with a HP 5970 series mass detector running HP ChemStation Software. Molecular mass calculations were performed with ChemDraw Ultra (Cambridge Scientific) or ChemIntosh Molecular Mass Calculator, version 1.3.

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 either standard *p*-anisaldehyde or potassium permanganate stains. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. The ruthenium catalyst $(PCy_3)_2(Cl)_2Ru{=}CHPh$ was used as obtained from Materia, Inc. Preparation of the chloroform adduct $H_2IMes(H)(CCl_3)$ is described in detail in Chapter 2.

Preparation of *N*-mesityl-*N'*-ethyl-2-sulfonatoimidazolium bromide (2).[19] A thick-walled Schlenk ampoule equipped with large stirbar was charged with *N*-mesitylimidazole (100 mg, 0.5 mmol, 1 eq.), the sodium salt of bromoethanesulfonic acid (106 mg, 0.51 mmol, 1.1 eq.), isopropanol (3 mL), and methanol (10 mL, to solubilize). The headspace was evacuated and the sealed ampoule was heated to 100°C for 24 hours. After this time the reaction mixture was concentrated *in vacuo* to a light brown solid. Extraction with diethyl ether and dry methanol yielded 210 mg of off-white solid that was used in catalyst synthesis without further purification (quantitative yield).

Preparation of (*N*-mesityl-*N'*-ethyl-2'-sulfonatoimidazol-2-ylidene)$(PCy_3)(Cl)_2Ru{=}CHPh$. In the glovebox a large vial equipped with stirbar was charged with imidazolium salt (100 mg, 0.25 mmol, 2.2 eq.) and THF (2.5 mL). A solution of potassium *tert*-butoxide (28 mg, 0.25 mmol, 2.2 eq.) in THF (1 mL) was added in one portion (by pipet) to the vial. The resulting suspension was stirred for 10 minutes at room temperature. The suspension was then transferred by pipet to a Schlenk ampoule previously charged with $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (94 mg, 0.11 mmol, 2.2 eq.) in benzene (3 mL). Upon mixing a rapid color change to dark brown was observed. The ampoule was sealed and removed from the glovebox, and the reaction mixture was

allowed to stir for 3 hours at room temperature. A small aliquot was removed and concentrated *in vacuo* to a greenish solid. ^{1}H NMR showed the presence of desired product and (NHC)(OBu^{t})$_2$Ru=CHPh in a 5:1 ratio. The reaction mixture was subsequently heated to 75°C under nitrogen for 10 minutes, and then concentrated *in vacuo* to a brownish oil that was washed with pentane (2 × 5 mL). The resulting brown solid was then characterized by ^{1}H and ^{31}P NMR. Characteristic resonances: ^{1}H NMR (C_6D_6): δ 20.99 (d, J = 11 Hz, 1H) ppm. ^{31}P NMR (C_6D_6): δ 30.63 ppm.

Acylation of alcohols catalyzed by H_2IMes(H)(CCl_3): General procedure. In the glovebox a screw-cap NMR tube equipped with Teflon septum is charged with the substrate alcohol (0.5 mmol), triethylamine (52 μL, 0.38 mmol), and H_2IMes(H)(CCl_3) (10.6 mg, 0.025 mmol, 5 mol%) in C_6D_6 (1 mL). The tube was sealed, removed from the glovebox, and thermostatted at 60°C for 5 minutes in the NMR probe. Acetic anhydride was then injected into the tube by microsyringe. ^{1}H NMR spectra (8 scans) were recorded every 10 seconds for 83 minutes (500 intervals). Product was monitored by the appearance of a ^{1}H NMR resonance at approximately δ 4.2-4.5 ppm. Kinetics data were fit to a first order exponential using Varian's VNMR software.

Results. For 2-naphthylethanol, rate of product formation in the catalyzed reaction: $k_{obs} \times 10^3 = 5 \pm 1\ s^{-1}$. For the uncatalyzed reaction (without any added H_2IMes(H)(CCl_3)): $k_{obs} \times 10^3 = 1.4 \pm 0.1\ s^{-1}$.

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