UNIVERSITEIT
GENT

Faculty of Science
Department of Inorganic and Physical Chemistry
Centre for Ordered Materials, Organometallics and Catalysis

Ruthenium catalysts for the synthesis of quinolines and enol esters

Hans Vander Mierde

Promoter: Prof. Dr. F. Verpoort

Proefschrift voorgelegd tot het behalen van de graad van
Doctor in de Wetenschappen: Scheikunde

Members of the jury

Prof. Dr. F. Verpoort (Promoter)
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Science only starts to get interesting at the point where it stops.

Wetenschap wordt eigenlijk pas interessant op het punt waar ze ophoudt.

Dankwoord/Acknowledgements

"PLOF!!"

Daar ligt hij dan: mijn doctoraatsproefschrift, de exponent van jaren puffen, zwoegen en zweten. Gelukkig heb ik al die jaren kunnen rekenen op de onvoorwaardelijke steun van een heleboel mensen. Hier komen hun welverdiende 'two pages of fame'.

Mijn eerste 'dankjewel' zou ik willen richten aan mijn promotor, professor Francis Verpoort, om mij de mogelijkheid te geven dit onderzoek te verrichten. Ook in de moeilijke eerste jaren met tegenvallende resultaten, die soms eigen zijn aan wetenschappelijk onderzoek, wist hij mij steeds te verrassen met nieuwe ideeën. Uiteraard mag ik ook de financiële steun van de Universiteit Gent niet vergeten. In mijn job als assistent heb ik niet alleen studenten iets proberen bij te brengen, maar heb ik ook zelf enorm veel geleerd. Verder ben ik dank verschuldigd aan de leden van de jury, voor het kritisch lezen en beoordelen van dit werk.

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Ook bedankt aan 'vaste stoffers' Klaartje, Veerle en Jonas en alle andere mensen die ik hier niet persoonlijk vermeld heb, voor de vele leuke momenten en losse babbels .
Verder verdienen ook alle ATP'ers en praktijkassistenten hun plaatsje op deze pagina. Bedankt Pat voor de constructie van mijn aluminium 'multi-mini-kolom-filtratie-houder' en Danny voor assistentie en onderhoud van het GC toestel. Een speciaal woordje van dank gaat uit naar Claudine, 'moeder van alle doctoraatsstudenten' voor een luisterend oor bij grote en kleine zorgen.
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Mieke, liefste Mieke. Hoeveel van onze conversaties gingen niet als volgt: "Wacht schat, ik zal je helpen met wassen/strijken/poetsen/..." waarop jij evenveel keer antwoordde "Nee hoor, dat is niet nodig. Werk jij maar hard door aan je doctoraat." Duizendmaal dank voor alle steun en begrip tijdens die zware laatste

maanden.
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Eindigen doe ik met een woordje van lof voor mijn ouders. Tijdens mijn universitaire 'carriere' stonden zij steeds op de eerste rij om voor mij te supporteren. Hun tomeloze inzet en grenzeloze liefde waren steeds een stuwende kracht in mijn leven. Hopelijk kan ik hen daarvan met het volbrengen van dit werk een stukje teruggeven.

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Preface: Setting the stage

A major component of practical chemical research deals with the synthesis of organic molecules. In this field, carbon-carbon or carbon-heteroatom bond formation is of fundamental importance. Some of these bond formations are potentially very powerful, but often require a little "help" to be generated efficently at the lowest cost possible. That is where catalysis enter the story. Every chemical reaction has a rate determinant, characteristic activation energy. Sometimes this energy barrier is too high to successfully perform the reaction under normal reaction conditions. A catalyst can lower this activation energy, by providing an alternative reaction pathway. In this way, the reaction rate of slow reaction steps can be substantially enhanced and previously inaccessible reactions can become feasible. Moreover, a well-designed catalyst accelerates only the desired reaction while potential unwanted side reactions remain slow.
Catalysts based on the transition metal ruthenium have been applied in a multitude of reactions, such as atom transfer radical polymerization,[1] Kharasch addition,[2] transfer hydrogenation,[3] hydroamination,[4] enol ester synthesis[5] and a wide variety of metathesis reactions.[6] This non-exhaustive list briefly overviews the wide chemistry panel addressed by ruthenium catalysts. The reactivity and selectivity of a catalyst towards a particular reaction are often determined by the metal coordination sphere of organic and/or inorganic ligands. During their research on metathesis reactions, the group of Grubbs has found that complexation of the ruthenium centre with N,O-bidentate Schiff base ligands results in complexes with improved stability towards air and moisture. The temperature and solvent tolerance was likewise substantially improved.[7] Also the research group of my promotor, Prof. F. Verpoort, has contributed to the development of ruthenium Schiff base catalysts.[8] Several new Schiff base complexes were synthesized and applied in enol ester synthesis, Kharasch addition and metathesis reactions.
At the onset of this work, the primary objective had been formulated as follows: "To further explore the catalytic applicability of ruthenium Schiff base catalysts in a variety of reactions..." Although it is inevitable that the focus of a doctoral research shifts during its course toward the instantaneous needs and the results obtained, this statement still reasonably reflects large part of the PhD work actually achieved. Two specific reactions were selected for the screening of new ruthenium Schiff base catalysts:

- the synthesis of *quinolines* by a modified Friedlander reaction involving a **hydrogen transfer reaction** as the key step, and

- the synthesis of *enol esters* by the nucleophilic addition of carboxylic acids to terminal alkynes, where the **activation of the alkyne triple bond** plays

a central role.

The first reaction was chosen as a consequence of an interesting publication by Cho et al.[9] They reported a modified Friedlander reaction for the synthesis of quinolines, in which a ruthenium catalyzed hydrogen transfer reaction was claimed to play a key role. The best catalyst for this reaction was the so-called first generation Grubbs catalyst. This was quite surprising, as this catalyst is specifically known for its excellent activity in metathesis reactions, but - at that time - not for its capability for hydrogen transfer reactions. Over the past years, the group of Verpoort has specialized in metathesis reactions, amongst others with Grubbs-type catalysts. Hence, the intriguing results of Cho prompted us to get more insight in this modified Friedlander reaction. With the additional knowledge that ruthenium Schiff base complexes are excellent catalysts for transfer hydrogenation reactions,[10] the motivations for addressing this subject are twofold: a) exploring new ruthenium Schiff base catalysts for the synthesis of quinolines, and b) investigating modifications to Grubbs-type catalysts and their effect on the catalytic activity.
The choice for the second reaction is more straightforward. In the research group of Verpoort, Melis has already extensively investigated the synthesis of enol esters with commercial ruthenium catalysts and newly synthesized complexes bearing a triazol ligand.[11] De Clercq has briefly explored some ruthenium Schiff base catalysts,[12] but the field for this kind of complexes was still wide open. The main goal for this subject is to prepare some new, stable and easily accessible ruthenium catalysts with Schiff base ligands and to define their scope and limitations for the coupling reaction between carboxylic acids and alkynes. The stereochemistry of the produced enol esters, as well as the influence of the chosen alkyne and/or acid, is of particular interest.

Outline

This work consists of two major parts. Chapters 1, 2 and 3 report on the synthesis of quinolines, while chapters 4 and 5 deal with the preparation of enol esters.

Chapter 1 provides a general introduction to quinolines. The applications of quinolines are described, along with several methods of synthesis. In particular, the transition metal-catalyzed modification of the Friedlander method, that was used in this work, is highlighted.

Chapter 2 explores the synthesis of quinolines with ruthenium complexes. The influence of several experimental parameters, such as the type of catalyst, base and hydrogen acceptor, are investigated. A critical look at the reaction mechanism provides some new insights. A new method is developed for the problematic synthesis of 3-substituted quinolines.

Chapter 3 reveals that quinolines can also be synthesized in a base-mediated process without the need for an expensive transition metal catalyst. A reaction mechanism similar to that of the Meerwein-Ponndorf-Verley reduction or Oppenauer oxidation is proposed.

Chapter 4 gives an introduction to enol esters. The applications of these compounds are described and a literature overview of synthetic approaches towards enol esters is presented.

Chapter 5 surveys the ruthenium-catalyzed synthesis of enol esters. The focus of this chapter is on the application of ruthenium Schiff base complexes for the coupling of carboxylic acids with alkynes. The addition of N-heterocyclic carbene ligands and bases is discussed.

Chapter 6 summarizes the most important conclusions of this manuscript and evaluates the obtained results.

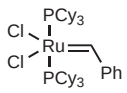
Chapter 7 details the experimental procedures used in this work.

Chapter 8 provides a Dutch summary of this work.

List of abbreviations

BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Boc	tert-Butyloxycarbonyl
BU	3,3-Dimethyl-1-butyne
Bz	Benzyl
cod	1,5-Cyclooctadiene
Cp	Cyclopentadienyl
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[4.5.0]undec-7-ene
DMSO	Dimethylsulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
H_2IMes	1,3-dimesityl-4,5-dihydroimidazol-2-ylidene
IMes	1,3-dimesityl-4,5-imidazol-2-ylidene
KHMDS	Potassium hexamethyldisilazane
L	Ligand
LiHMDS	Lithium hexamethyldisilazane
M	Metal, e.g. in complexes: [M]
Mes	Mesityl = 2,4,6-trimethylphenyl
MPV	Meerwein-Ponndorf-Verley
MPVO	Meerwein-Ponndorf-Verley-Oppenauer
NHC	N-Heterocyclic carbene
NXS	N-halosuccinimide
OC	1-Octyne
OTFA	Trifluoroacetate
OTf	Triflate (trifluoromethanesulfonate, CF_3SO_3–)
o-tol	ortho-Tolyl
PA	Phenylacetylene
PEG	Poly(ethyleneglycol)
RCM	Ring-closing metathesis
RT	Retention time (s)
TEA	Triethylamine
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TOF	Turn-over frequency
TON	Turn-over number
Ts	Tosyl (p-toluenesulfonyl)

List of numbered compounds



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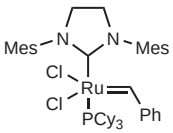

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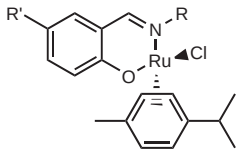
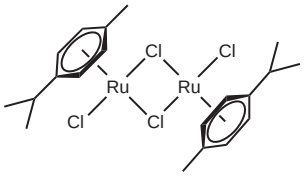


R' = H / NO_2	
4a / 4b	R = Me
5a / 5b	R = cyclohexyl
6a / 6b	R = 2,6-iPrC_6H_3
7a / 7b	R = 4-Br-2,6-MeC_6H_2
8a / 8b	R = 2,4,6-MeC_6H_2
9a / 9b	R = tBu
10a	R = adamantyl



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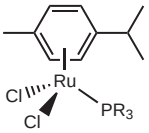
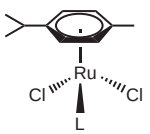
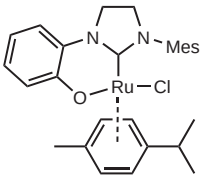


11a R = Ph
11b R = Cy
11c R = nBu
11d R = Me



12 L = IMes
13 L = H_2IMes



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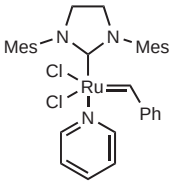

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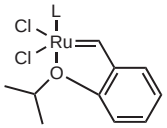
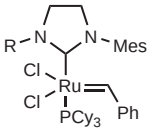
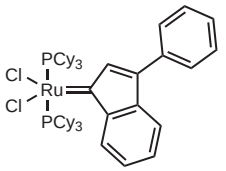


16 L = PCy_3
17 L = H_2IMes



18 R = Me
19 R = cyclohexyl
20 R = n-octyl



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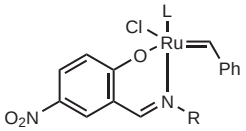
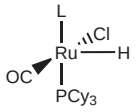
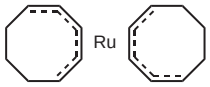


22 L = PCy_3, R = 2,6-iPrC_6H_3
23 L = PCy_3, R = 4-Br-2,6-MeC_6H_2
24 L = H_2IMes, R = 2,6-iPrC_6H_3
25 L = H_2IMes, R = 4-Br-2,6-MeC_6H_2



26 L = PCy_3
27 L = H_2IMes



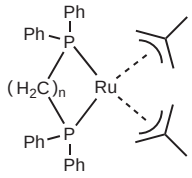
30

$Ru_3(CO)_{12}$

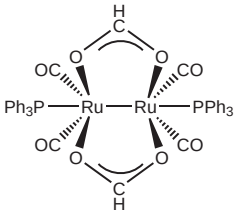
29

$RuCl_3.xH_2O$

31



32a n = 2
32b n = 4



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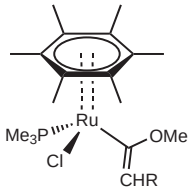

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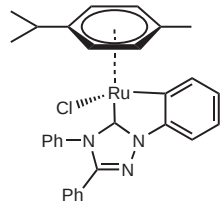

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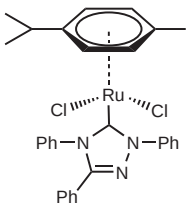

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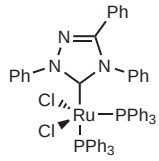

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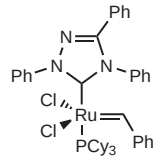

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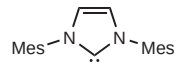
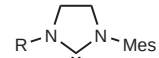
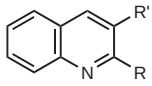


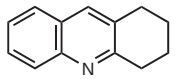
40 *IMes*



39 R = Mes; *H$_2$IMes*
41 R = CH_3



Q1 R = Ph, R' = H
Q2 R = 2-MeC_6H_4, R' = H
Q3 R = 3-MeC_6H_4, R' = H
Q4 R = 4-MeC_6H_4, R' = H
Q5 R = 2-MeOC_6H_4, R' = H
Q6 R = 4-MeOC_6H_4, R' = H
Q7 R = 4-$NO_2C_6H_4$, R' = H
Q8 R = Me, R' = H
Q9 R = nC_5H_{11}, R' = H
Q10 R = Me, R' = nC_4H_9
Q11 R = nC_4H_9, R' = Me
Q12 R = Et, R' = nPr
Q13 R = Ph, R' = Me



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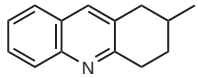

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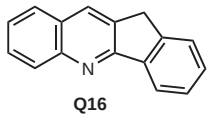

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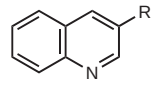
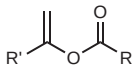


Q17 R = Et
Q18 R = nPr
Q19 R = nC_6H_{13}
Q20 R = iPr
Q21 R = Ph
Q22 R = Bz
Q23 R = CH(Me)Ph



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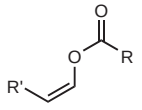

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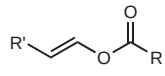

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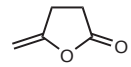

E10a

E1 R = CH_3, R' = Ph
E2 R = CCl_3, R' = Ph
E3 R = Ph, R' = Ph
E4 R = CH_3, R' = nC_6H_{13}
E5 R = CCl_3, R' = nC_6H_{13}
E6 R = Ph, R' = nC_6H_{13}
E7 R = CH_3, R' = $C(Me)_3$
E8 R = CCl_3, R' = $C(Me)_3$
E9 R = Ph, R' = $C(Me)_3$

1

Introduction to quinoline synthesis

1.1 What is quinoline?

Quinoline (sometimes referred to as 1-Benzazine or 2,3-Benzopyridine) is a heterocyclic aromatic compound with the formula C_9H_7N in which a benzene ring and a pyridine ring are fused through a carbon double bond (Figure 1.1). It occurs natu-

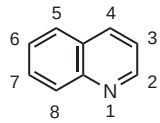

Figure 1.1: The general structure of quinoline.

rally and was originally isolated from coal tar in 1834 by F. Runge.[13,14] The world production of quinoline is over 2000 tons annually, indicating its importance.[15] It is an intermediate in metallurgical processes and in dye, polymer and agrochemical production. In organic synthesis it is sometimes used as a high boiling basic solvent.

The quinoline scaffold is present in many medicinal plant alkaloids. The antipyretic activity of Cinchona bark was already known to the Incas and in the early 17th century the Jesuit missionaries uncovered its antimalarial properties.[16] With the advance of organic chemistry, the alkaloid quinine (Figure 1.2) was isolated and identified as the active compound. This prompted the development of a range of synthetic antimalarials. Difficulty of supply of the natural quinine during the two World Wars intensified those efforts. Loss of efficacy of synthetic drugs due to resistance also meant continuing research into antimalarials. Chloroquine and Pa-

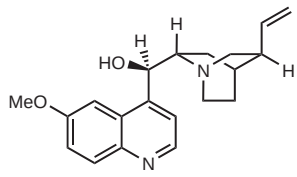

Figure 1.2: Quinine

maquine (Figure 1.3) are two examples of synthetic antimalarial drugs, but many more exist.[17–21] Further applications of quinolines in medicinal chemistry include

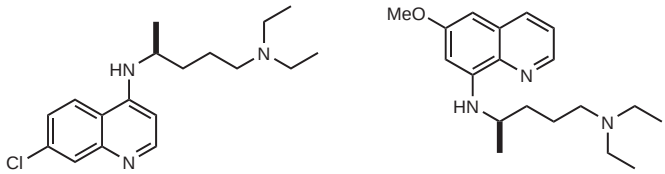

Figure 1.3: Chloroquine (left) and Pamaquine (right).

the use as anti-inflammatory,[22,23] anti-asthmatic,[24,25] antibacterial,[26–29] antihypertensive,[30,31] anticancer[32–35] and tyrosine kinase inhibitory agents.[36]
Quinoline-based polymers are currently under investigation for applications as thermally stable transparent materials in the fields of electronics, optoelectronics and non-linear optics.[37–43] One notable application is the use of polyquinolines in blue LEDs.[44–46]

1.2 Traditional methods of synthesis

At the end of the 19th century several methods for the synthesis of quinolines were developed, named after their inventors. Some of these historically important syntheses will be shortly discussed here.

1.2.1 Skraup/Doebner-von Miller reaction

One of the earliest reports of quinoline synthesis was published in 1880 by Skraup. He discovered that heating aniline with glycerol, sulfuric acid and an oxidizing reagent results in quinolines.[47–49] The details of the reaction sequence are not yet fully understood, but most likely glycerol is dehydrated to acrolein by sulfuric acid and then reacts with aniline by conjugate addition. This intermediate is then cyclized, oxidized and dehydrated to give the quinoline (Figure 1.4). Doebner and von Miller generalized Skraup's method for the synthesis of substituted quinolines by using 1,2-glycols or α,β-unsaturated aldehydes or ketones instead of glycerol.[50]

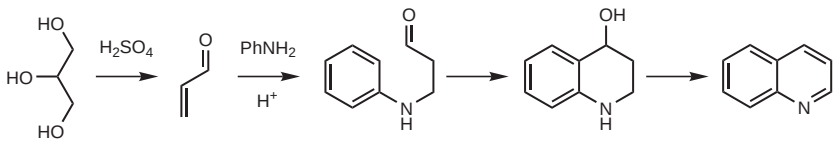

Figure 1.4: Skraup/Doebner-von Miller quinoline synthesis.

This reaction has, however, some major drawbacks. As it can be violently exothermic, a moderator such as iron(II)sulfate is usually added. To improve yields, a variety of oxidizing reagents and additives have been added including iron(III) and tin(IV) salts, nitrobenzenes, iodine and various acids such as boronic and arsenic acid. Recently, solvent-free Skraup/Doebner-von Miller reactions have been developed under microwave irradiation.[51,52]

1.2.2 Combes quinoline synthesis

In the Combes synthesis,[53] aniline is reacted with a 1,3-diketone, ketoaldehyde or dialdehyde providing an enamine. Subsequent cyclodehydration gives the quinoline (Figure 1.5).

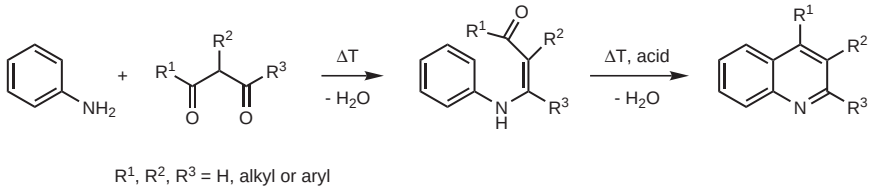

Figure 1.5: Combes quinoline synthesis.

1.2.3 Friedlander quinoline synthesis

Both the Skraup and Combes method suffer from the disadvantage that if the aniline bears a meta-substituent, there are two different ortho positions available for cyclization. This often leads to an isomeric mixture of quinolines. This problem can be avoided by starting with an ortho-substituted aniline. In the Friedlander method, 2-aminobenzaldehyde or 2-aminoketone is combined with an α-methyleneketone (or aldehyde) to furnish a substituted quinoline (Figure 1.6).[54,55] The reaction can be promoted by acid, base or heat. Two possible mechanistic pathways have been suggested for the Friedlander reaction. The first involves initial imine formation, followed by intramolecular Claisen condensation, while the second reverses the order of the steps.[56] Evidence for both proposals exists[13,57–59] and the mechanism may change for the same two partners based upon reaction conditions.

Although the Friedlander method is quite versatile, the primary limitation is the preparation and stability of the 2-aminobenzaldehyde starting products since these

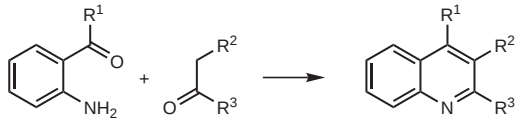

Figure 1.6: Friedlander quinoline synthesis.

compounds are prone to self-condensation. Both electron rich and electron poor 2-aminobenzocarbonyl compounds undergo the Friedlander reaction.[60,61] When the ketone partner has only one reactive methyl or methylene or is symmetrical, only one product is obtained.
In the Niementowski variation, an ortho-aminobenzoic acid is used, resulting in a quinolinol (Figure 1.7).[62] The Pfitzinger extension[63] of the Friedlander protocol

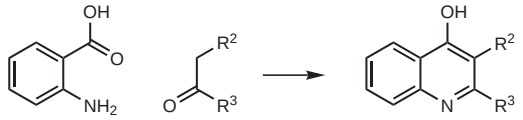

Figure 1.7: Niementowski quinoline synthesis.

relies on the use of isatin which is much more stable than 2-aminobenzaldehydes.[64] Initially quinoline-4-carboxylic acids are formed but subsequent decarboxylation can afford the corresponding quinolines (Figure 1.8). Recent investigations of the

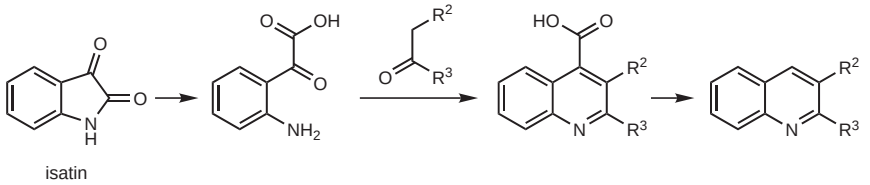

Figure 1.8: Pfitzinger quinoline synthesis.

Friedlander method focus on the replacement of a traditional heating source by microwave irradiation,[65,66] the use of water[67,68] or ionic liquids[69–71] as solvents for environmentally benign processes, solvent free reaction conditions[72,73] and improved acids or bases, e.g. the use of solid acid catalysts.[74–76]

1.2.4 Other named reactions

This is by no means a conclusive list of available methods. Other named reactions for the synthesis of quinolines have been developed by Camps,[77,78] Knorr,[79,80] Conrad-Limpach[81,82] and others but their description falls outside the scope of this work. For more information, the reader can find some excellent reviews and books on this subject.[17,83]

1.2.5 Classic organic synthesis

Undoubtedly, hetero Diels-Alder reactions are one of the most powerful tools in organic chemistry to prepare heterocycles. It should therefore be no surprise that it has been widely employed in the synthesis of the quinoline ring system. The aza Diels-Alder or imino Diels-Alder reaction as it is mostly called, is a [4+2] cycloaddition reaction between N-arylimines (the conjugated diene) and alkenes (the dienophile). Generally, tetrahydroquinolines are obtained. Sometimes, the multi-component Povarov approach[84] is used in which the imine is in situ generated in a condensation reaction between an aromatic amine and an aromatic aldehyde. A representative example of both methods is shown in Figure 1.9. Lewis acids like

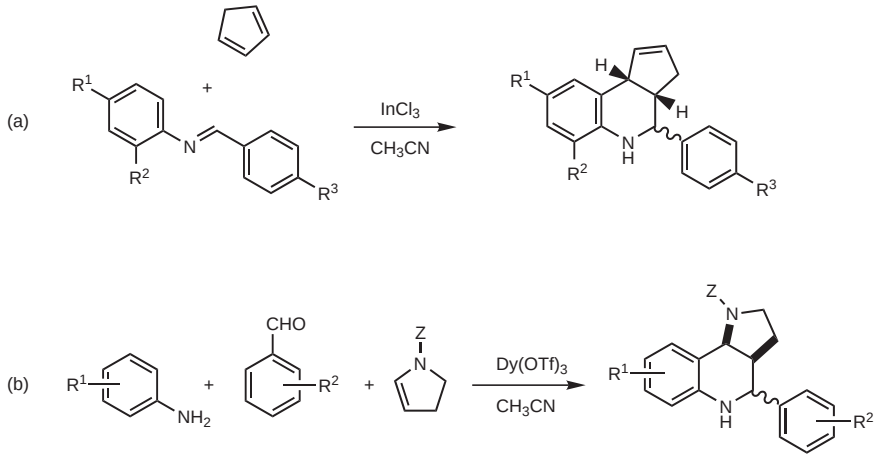

Figure 1.9: (a) Quinolines via [4+2] cycloaddition reaction.[85]
(b) Quinolines via the Povarov reaction.[86]

$InCl_3$,[85,87–94] $Yb(OTf)_3$,[95–97], $Dy(OTf)_3$,[86,98] and $BF_3.Et_2O$[96,99] are often added as catalyst (10 - 20 mol%) to increase the reaction rate and selectivities. Ishitani used $Yb(OTf)_3$ in combination with the chiral ligand (*R*)-(+)-BINOL to further increase the enantioselectivity.[100]
Other catalysts that have also been used are CF_3COOH,[68,97,101] $SmI_2(THF)_2$,[102] $BiCl_3$,[103] $SbCl_3$,[104], VCl_3,[105] and $Ce(NH_4)_2(NO_3)_6$.[106]

1.3 Transition metal-catalyzed approaches

The synthesis of nitrogen-containing heterocycles, such as quinoline, is the subject of extensive research in organic chemistry, because the quinoline scaffold is present in many biologically active compounds. However, many traditional methods that have been addressed in the previous paragraphs suffer from harsh reaction conditions, low stereoselectivity or consist of multiple steps, resulting in low overall yields, limiting their applicability.

1.3.1 The modified Friedlander quinoline synthesis

The Friedlander method is generally considered to be the most versatile method of synthesis although its full potential is inhibited due to the use of unstable aminobenzaldehydes. This problem of self condensation of the 2-aminobenzaldehydes can be circumvented by starting from the cheaper and more stable 2-aminobenzylalcohol. This method was first proposed by Cho and Shim.[9] They reacted 2-aminobenzylalcohol with a series of ketones in the presence of a ruthenium catalyst and a base in dioxane for 1 h at 80 °C. A 2-aminobenzylalcohol/ketone/base ratio of 1:2:1 gave the best results. The general reaction scheme is presented in Figure 1.10.

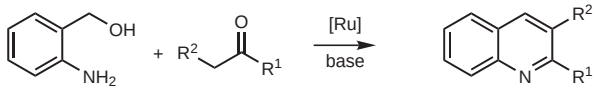

Figure 1.10: General reaction scheme for the modified Friedlander method.

The suggested reaction mechanism is shown in Figure 1.11. In the first step, 2-

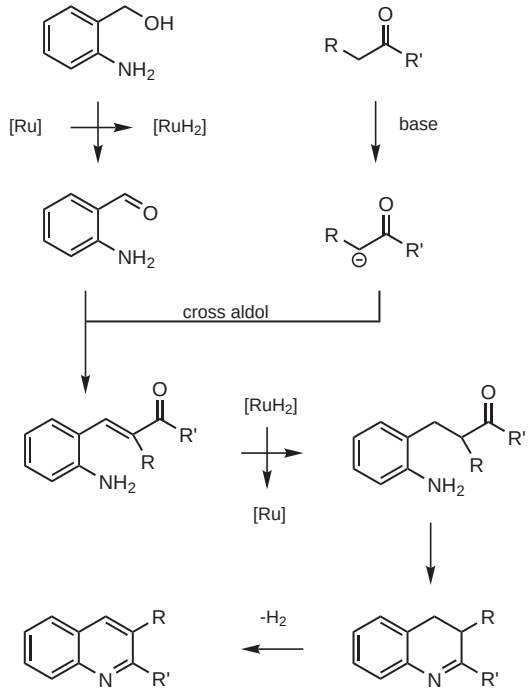

Figure 1.11: Suggested mechanism of the modified Friedlander method.

aminobenzaldehyde is generated in situ by a catalytic oxidation of 2-aminobenzylalcohol. In the presence of a base, a cross-aldol reaction occurs between the aldehyde and a ketone to form an α,β-unsaturated ketone which is subsequently hydrogenated by the dihydridoruthenium complex $[RuH_2]$ generated by the initial oxida-

tion reaction. This way, the catalyst is regenerated and a new oxidation/reduction cycle can start. The combination of both catalytic steps is in fact a hydrogen transfer reaction. The final step is a condensation reaction between the amine and the ketone followed by a H_2-elimination to form the quinoline.
Among the few ruthenium catalysts that were tested by Cho, the first generation Grubbs' catalyst $RuCl_2(=CHPh)(PCy_3)_2$ (**1**, Figure 1.12) gives the highest quinoline yield (>99% after 1 h). Also $RuCl_2(PPh_3)_3$ and $RuH_2(PPh_3)_4$ showed good results (yields >90%) but other catalysts such as $Ru_3(CO)_{12}$ and cyclopentadienyl complexes were less efficient.

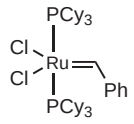

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Figure 1.12: Grubbs' first generation catalyst (**1**).

More recently, this research group has published results using the copper(II) catalyst $CuCl_2$ along with KOH under O_2-atmosphere.[107] Although this catalytic system is cheaper than ruthenium complexes, higher temperatures (100°C), longer reaction times (5 h) and higher amounts of base (3 equivalents) are required to achieve only moderate yields, ranging from 40 to 80%, depending on the nature of the ketone.
The same researchers also reported the use of Pd/C as a catalyst for this reaction,[108] but again, after 20 hours at 100°C only moderate conversions were obtained. To compensate for these drawbacks, a heterogeneous approach was applied by adding poly(ethyleneglycol) (PEG) to the reaction mixture.[109] This allowed easy separation of the catalyst by solidifying it along with PEG by cooling down the reaction mixture, followed by filtration. Good yields were obtained (generally 70-90%) and the recovered catalyst could be reused five times without any loss of catalytic activity. The best results were achieved with $Pd(OAc)_2$ as a Pd-source, rather than $PdCl_2$ or Pd/C.
In another heterogeneous approach, Kaneda et al. prepared a ruthenium-grafted hydrotalcite.[110] Quinolines were obtained through aerobic oxidation (O_2, 1 atm) by the Ru species, followed by an aldol reaction on the base sites of the hydrotalcite. This method has the added advantage that an inorganic base is no longer required. High quinoline yields were obtained after 20 h at 100°C in toluene.
Two iridium catalysts, $[IrCl(cod)]_2$ and $IrCl_3$ in combination with phosphine ligands, were described by Ishii under solvent-free conditions to give quinolines in good yields.[111] Based upon their results, they suggested an inversed pathway, i.e. first imine formation, followed by an intramolecular aldol condensation.
In an alternate approach[112] 2-aminobenzylalcohol was reacted with alcohols instead of ketones (Figure 1.13). In this setup, also the alcohol has to be oxidized to a ketone, effectively doubling the required number of transfer hydrogenation reactions. To facilitate the reaction, 1-dodecene was added as hydrogen acceptor.

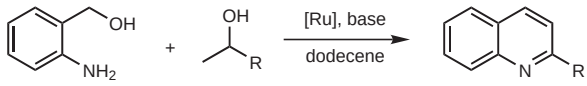


Figure 1.13: Modified Friedlander reaction from alcohol substrates.

Naturally, this reaction proceeded much slower and also resulted in somewhat lower quinoline yields. Here, $RuCl_2(PPh_3)_3$ proved to be the catalyst of choice.
The use of $RuCl_2(DMSO)_4$ for the modified Friedlander reaction was recently reported by Martinez and Yus.[113–115] They achieved excellent quinoline yields with this system after a reaction time of 24 to 72 hours. In a slightly modified adaptation, 2-aminoketones were reacted with alcohols to afford quinolines (Figure 1.14).[116]

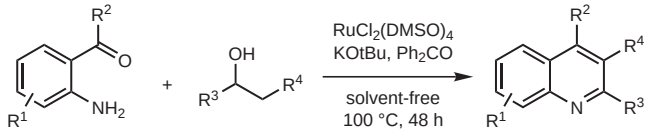


Figure 1.14: Friedlander reaction from 2-aminoketones and alcohols.

Another method, developed by Li and Mulvihill, involves the use of nitrobenzaldehydes (Figure 1.15). 2-Nitrobenzaldehyde is converted into 2-aminobenzaldehyde via reduction of the nitro group to an amino group by iron under acidic conditions. In a second step, the addition of ketones and KOH affords the quinoline in excellent yields.

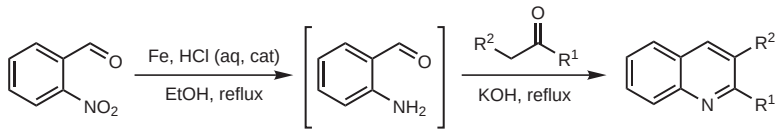


Figure 1.15: Modified Friedlander reaction using nitrobenzaldehydes.

1.3.2 Other transition metal catalyzed methods

Ruthenium

One of the earliest reports on ruthenium catalyzed quinoline synthesis was published by Watanabe, Tsuji and Ohsugi.[117] They found that the reaction of aniline with 2,3-unsaturated alcohols such as allyl alcohol and crotyl alcohol in the presence of $RuCl_2(PPh_3)_3$ gave 2,3-alkylquinolines in good yields (Figure 1.16). Tsuji and Watanabe were also the first to report a ruthenium catalyzed Skraup reaction.[118] Aminoarenes were reacted with 1,3-propanediol under non-acidic conditions with $RuCl_3.nH_2O$, two equivalents of $P(nBu)_3$ ligand and a nitroarene as hydrogen acceptor (Figure 1.17 (a)). Further investigations[119] revealed that diglyme was a

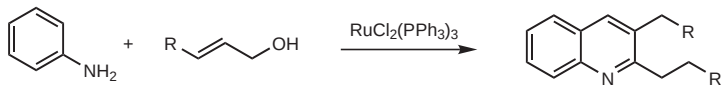


Figure 1.16: $RuCl_2(PPh_3)_3$-catalyzed reaction of aniline with allyl alcohol.

superior solvent and that the hydrogen acceptor could be omitted (Figure 1.17 (b)).

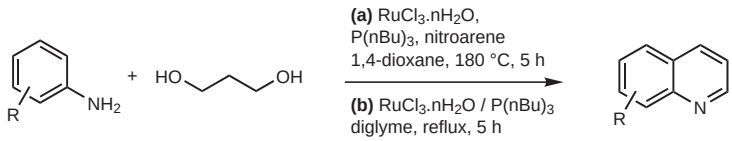


Figure 1.17: Ruthenium-catalyzed Skraup reaction.

The research group of Cho and Shim extensively explored the ruthenium catalyzed reaction of anilines with a variety of amines (Figure 1.18). The reaction of ani-

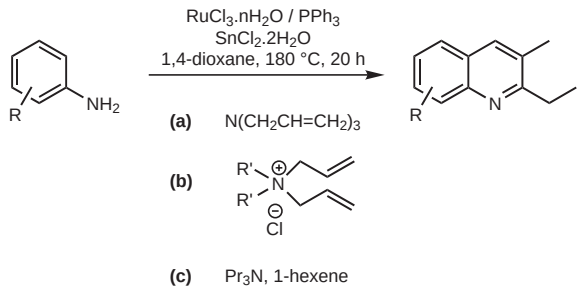


Figure 1.18: Ru-catalyzed reaction of aniline with (a) allylamines, (b) allylammonium chlorides and (c) trialkylamines.

line with triallylamines was catalyzed by $RuCl_3.nH_2O$ together with PPh_3 and $SnCl_2.2H_2O$ in dioxane at 180 °C for 20 hours to give quinolines in good yields.[120] Also tris(3-hydroxypropyl)amine,[121] allylammonium chlorides,[122] and even trialkylamines in the presence of a hydrogen acceptor[123] react with anilines to give quinolines.

This reaction is not restricted to aniline. When nitroarenes are used, the nitrogroup functions as hydrogen scavenger and it is consequently reduced to an amine which can then undergo a similar reaction as described above (Figure 1.19). In this case, $RuCl_2(PPh_3)_3$ is the best catalyst, and both trialkylamines[124] and tetraalkylammonium bromides[125] were shown to produce quinolines in good yields.

A distinctively different approach was used by Arisawa, Theeraladanon, et al.[126–129] Figure 1.20 shows how substituted quinolines were synthesized by ring-closing metathesis (RCM) of α,ω-dienes derived from 2-isopropenylaniline by the Grubbs' first and second generation catalysts (complexes **1** and **2** respectively).

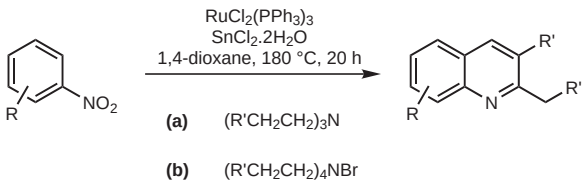


Figure 1.19: Ru-catalyzed reaction of nitroarenes with (a) trialkylamines and (b) tetraalkylammonium bromides.

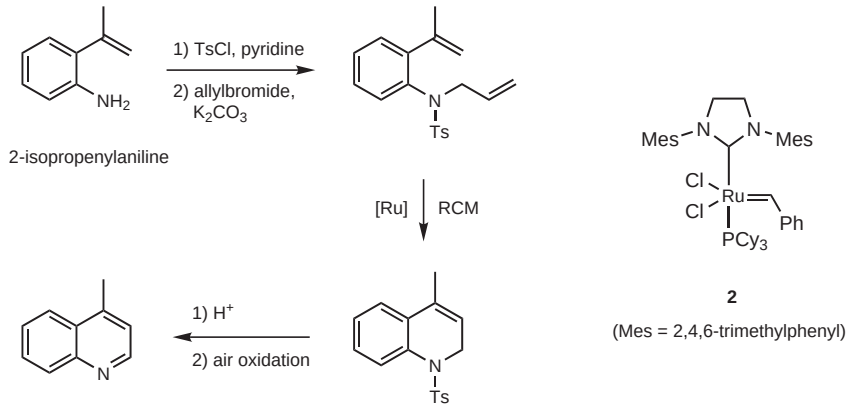


Figure 1.20: Synthesis of quinolines using ring-closing metathesis.

The total synthesis of the natural product (+)-(S)-angustureine was achieved using the ring-closing metathesis reaction as one of the key steps (Figure 1.21).[130]

Palladium

Also palladium complexes have been explored for the synthesis of nitrogen heterocycles.[131,132] Larock and Kuo described the palladium catalyzed coupling of o-iodoanilines with allylic alcohols to yield quinolines (Figure 1.22).[133] The same strategy was applied by Mahanty et al.[134] They used $PdCl_2(PPh_3)_2$ to react N-acylated o-iodoanilines with terminal acetylenic carbinols in a Sonogashira coupling. In a subsequent cyclization step NaOEt facilitated the formation of quinolines (Figure 1.23 (a)). To avoid the use of costly trifluoroacetic anhydride for the generation of o-iodotrifluoroacetanilide, a $Pd(OAc)_2$ catalyzed cyclization has been proposed (Figure 1.23 (b)). Similarly, Cho applied $PdCl_2(PPh_3)_2$ with CuI in a one pot reaction of o-iodoanilines with propargylic alcohols.[135] When 1,2-disubstituted olefins, such as dimethyl maleate, are used in combination with o-iodoanilines, quinolones are obtained (Figure 1.24).[136]

An ene-type cyclization of 1,7-enynes catalyzed by a cationic (*S*)-BINAP-Pd(II) complex, leading to quinoline derivatives bearing a quaternary carbon center, was described by Hatano and Mikami (Figure 1.25).[137] The reaction was highly enantioselective (>99 %ee).

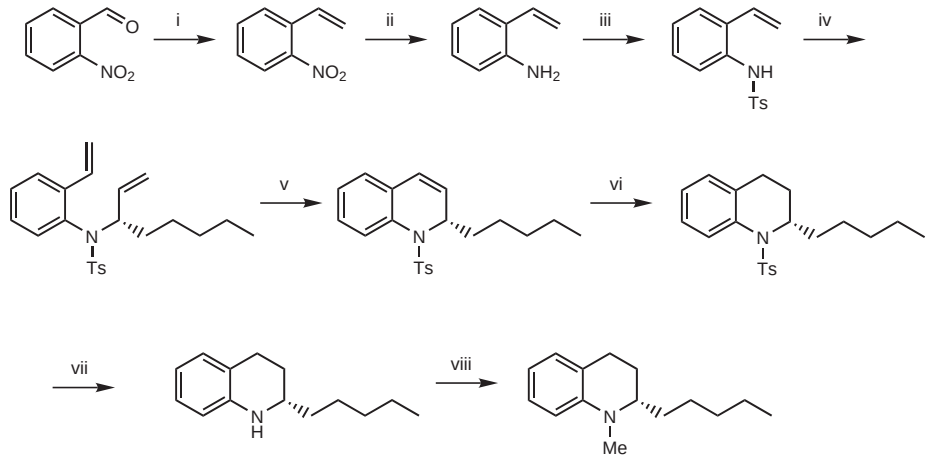


Figure 1.21: Total synthesis of Angustureine using RCM. Reagents and conditions: (i) Ph_3PMeBr, $KN(TMS)_2$, THF, rt, 1 h, 90%; (ii) Zn powder, AcOH, rt, overnight, 72%; (iii) TsCl, pyridine, CH_2Cl_2, rt, 1 h, 86%; (iv) (S)-1-Octen-3-ol, diethyl azodicarboxylate, PPh_3, THF, rt, 2 h, 78%; (v) $(H_2IMes)(PCy_3)(Cl)_2Ru{=}CHPh$, CH_2Cl_2 0.01 M, 50 °C, 1 h, 92%; (vi) PtO_2, H_2, MeOH, rt, 12 h, 94%; (vii) anthracene sodium, Et_2O, -65 °C, 10 min, 99%; (viii) MeI, K_2CO_3, THF, reflux, 10 h, 80%.

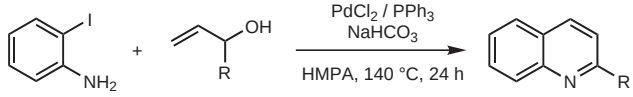


Figure 1.22: Pd-catalyzed coupling of o-iodoaniline with allylic alcohols.

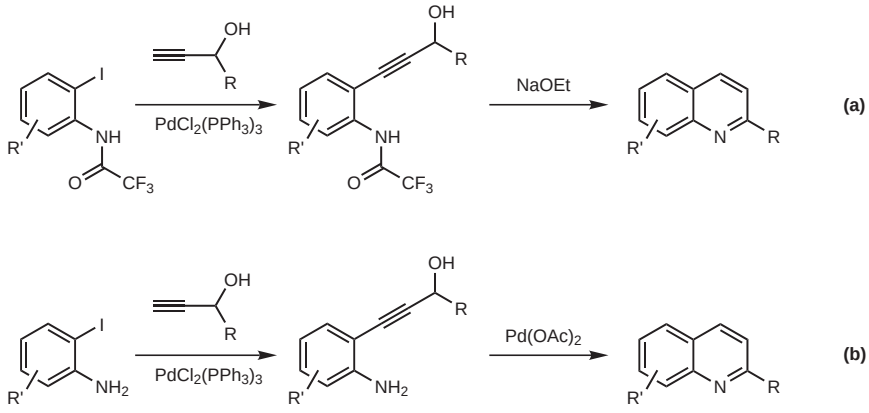


Figure 1.23: Pd-catalyzed coupling of (a) o-iodotrifluoroacetanilide or (b) o-iodoanilines with terminal acetylenic carbinols.

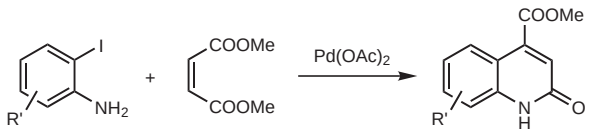


Figure 1.24: Palladium-catalyzed synthesis of quinolones.

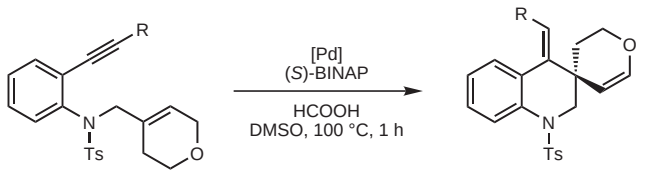


Figure 1.25: Quinolines via [Pd]/(*S*)-BINAP-catalyzed ene-type cyclization.

Rossi et al. prepared 2-aryl-4-amino-quinolines through a palladium-mediated multicomponent domino reaction, starting from 2-ethynyl-arylamines, aryl iodides, carbon monoxide and primary amines (Figure 1.26).[138] The process involves carbonylative coupling between 2-ethynyl-arylamines and aryl iodides, followed by inter- and intramolecular nucleophilic addition to a carbon-carbon triple bond and carbon-oxygen bond, respectively.

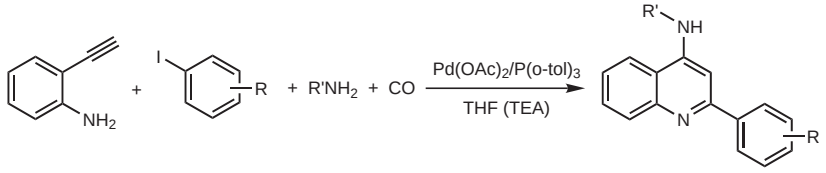


Figure 1.26: Pd-mediated multicomponent domino reaction leading to quinolines.

Very recently, Gabriele reported the synthesis of substituted quinolines through copper or palladium-catalyzed heteroannulation-dehydration of 1-(2-aminoaryl)-2-yn-1-ols.[139] The first step consists of the Grignard reaction between the appropriate alkynylmagnesium bromide and 2-aminoaryl ketones. In the second step, $CuCl_2$ or PdX_2 + KX (X = Cl or I) catalyzed the cyclodehydration reaction (Figure 1.27).

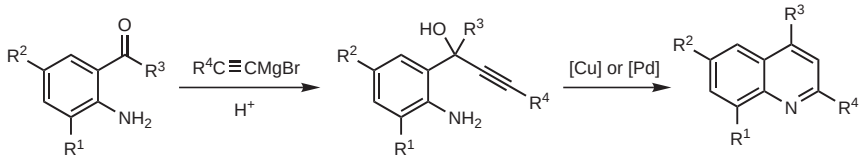


Figure 1.27: Quinolines through Pd or Cu-catalyzed cyclodehydration.

Rhodium

A few rhodium-catalyzed reactions are known, but their applications are rather limited. $RhCl_3.3H_2O$ combined with PPh_3 was found to catalyze the reaction between aniline and ethylene to yield 2-methylquinoline and N-ethylaniline (Figure 1.28 (a)).[140] $[Rh(cod)_2]BF_4$ with PPh_3 catalyzes the reaction of aniline with styrene (Figure 1.28 (b)).[141] A side reaction of the latter example is the anti-Markovnikov hydroamination of styrene to N-(2-phenylethyl)aniline, and also the formation of ethylbenzene. An interesting intramolecular hydroaminomethylation reaction of 2-isopropenylanilines by an ionic diamino rhodium catalyst was presented by Vieira and Alper (Figure 1.28 (c)). This reaction is atom economical and occurs with high chemo- and regioselectivity.[142]

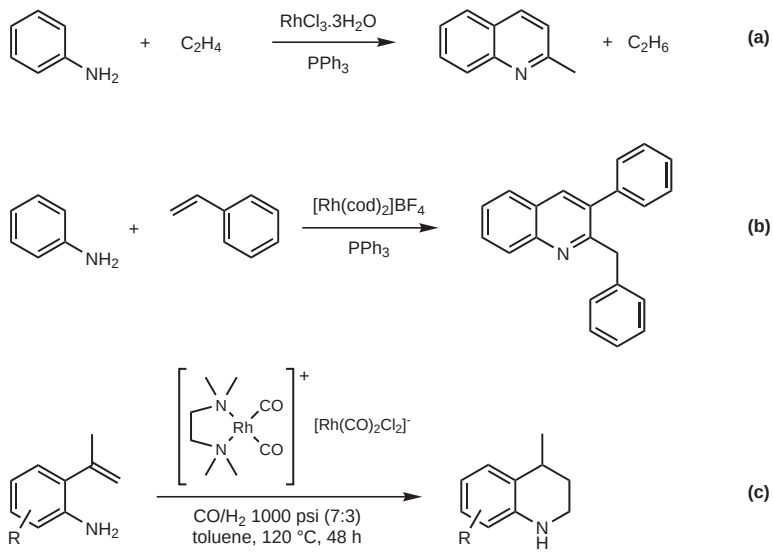


Figure 1.28: Rhodium catalyzed quinoline and hydroquinoline synthesis.

Cobalt

Jacob and Jones reported the selective conversion of diallylanilines and arylimines to quinolines catalyzed by the $Co_2(CO)_8$ complex (Figure 1.29).[143,144]

Other transition metals

In a reaction that bears resemblance with the Pd-assisted coupling reactions involving a Sonogashira coupling, Korivi and Cheng recently prepared 2,4-substituted quinolines through a nickel-catalyzed cyclization of arynyl aryl ketones with 2-iodoanilines (Figure 1.30).[145]

The iridium complex $[Ir(cod)Cl]_2$ catalyzes the three component coupling reaction between an arylamine and two aldehydes, to yield quinolines in moderate to good yields (Figure 1.31).[146] Although both aldehydes were not added simultaneously,

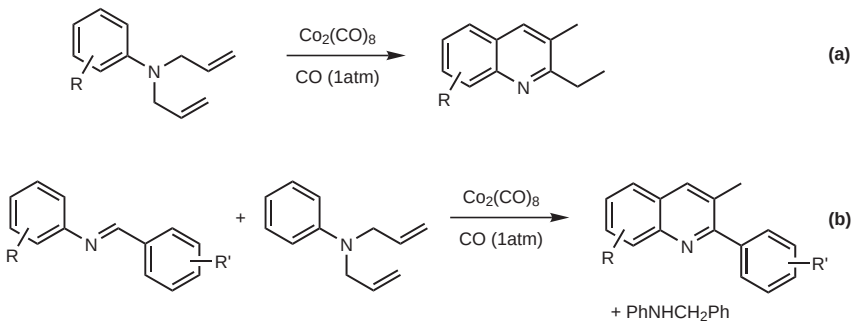


Figure 1.29: Conversion of (a) diallylanilines and (b) arylimines to quinolines by $Co_2(CO)_8$.

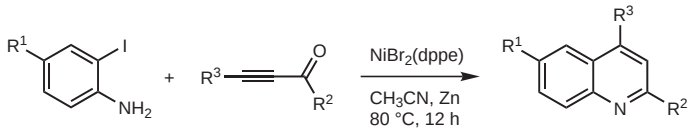


Figure 1.30: Nickel catalyzed quinoline synthesis.

but one after another with some time in between to allow consumption of the first aldehyde, the resulting products were usually a mixture of different quinolines.

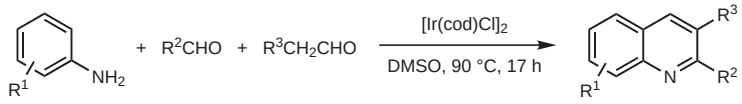


Figure 1.31: Iridium catalyzed quinoline synthesis.

A gold-catalyzed Friedlander reaction was applied to the condensation of 2-amino-arylketones with β-keto-esters, β-diketones, β-keto-amides and β-keto-sulfides to afford a variety of 2,3,4-trisubstituted quinolines (Figure 1.32).[147]

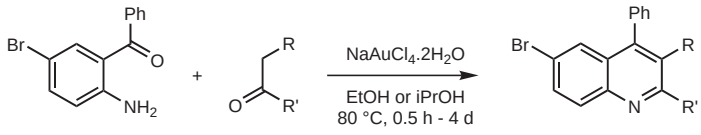


Figure 1.32: Gold catalyzed Friedlander reaction.

1.4 The development of the modified Friedlander method

1.4.1 Introduction

The group of Cho and Shim was the first to report a ruthenium catalyzed protocol for the Friedlander method. This protocol was deduced from their remarkable findings in a ruthenium catalyzed transfer hydrogenation. As shown in the reaction mechanism of the modified Friedlander protocol (Figure 1.11 on page 6), the ruthenium catalyst is used to oxidize the alcohol of 2-aminobenzylalcohol to an aldehyde. In this process the original catalyst [Ru] is converted into the hydride complex [RuH_2]. For this process to be truly catalytic, the [RuH_2] complex should be able to transfer both hydrogens to a hydrogen acceptor. This regenerates the original [Ru] complex so it can start a new catalytic cycle. Cho and Shim proposed that the α,β-unsaturated ketone that is formed in the cross aldol condensation performs as a hydrogen acceptor.[112] Although we will show later that this assumption is not entirely correct, it illustrates nicely that the entire process is in fact a catalytic hydrogen transfer reaction.

1.4.2 Catalytic transfer hydrogenation

Transition metal-mediated hydrogen transfer reactions find their roots in the Oppenauer oxidation[148] or its reverse reaction, the Meerwein-Ponndorf-Verley (MPV) reduction.[149–151] In the Oppenauer oxidation, a secondary alcohol is oxidized to the corresponding ketone by aluminum isopropoxide. The reaction is carried out with excess acetone to shift the equilibrium to the desired products. The MPV reduction is exactly the opposite. A ketone is reduced to the corresponding alcohol using isopropanol as solvent. A six-membered cyclic transition state is proposed as intermediate (Figure 1.33).[152]

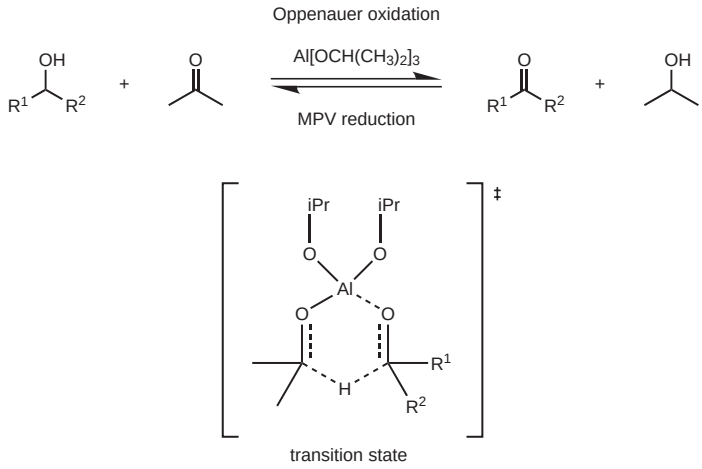


Figure 1.33: Oppenauer oxidation / MPV reduction.

Although this is a gentle method for converting ketones into alcohols and vice versa, one disadvantage is that the aluminum salt is often required in stoichiometric amounts. This represents a major drawback for upscaling and industrial applications.[153] When it was found that certain transition metal complexes, and ruthenium in particular, acted as efficient catalysts for these reactions, research efforts in this domain increased exponentially.[154–171] The reason for the popularity of transfer hydrogenation is found in its operational simplicity. Contrary to traditional hydrogenation, the use of hazardous H_2 gas is avoided and no pressure vessels are needed. Also the use of stoichiometric amounts of metal-hydrides such as $LiAlH_4$ with the accompanying waste products is avoided. In a typical transfer hydrogenation reaction, isopropanol is applied both as solvent and as hydrogen donor. It is oxidized to acetone that can be removed from the reaction mixture by distillation. To promote the reaction, inorganic bases such as KOH are added as co-catalyst.[153,155,157,172] A general reaction mechanism for the transition metal-catalyzed hydrogen transfer is presented in Figure 1.34. It is mechanistically different from the MPV reaction in the way the hydrogens are transferred. With transition metals it is believed that the reaction involves the formation of a metal hydride. For non-transition metals, a cyclic intermediate is proposed.[153,173]

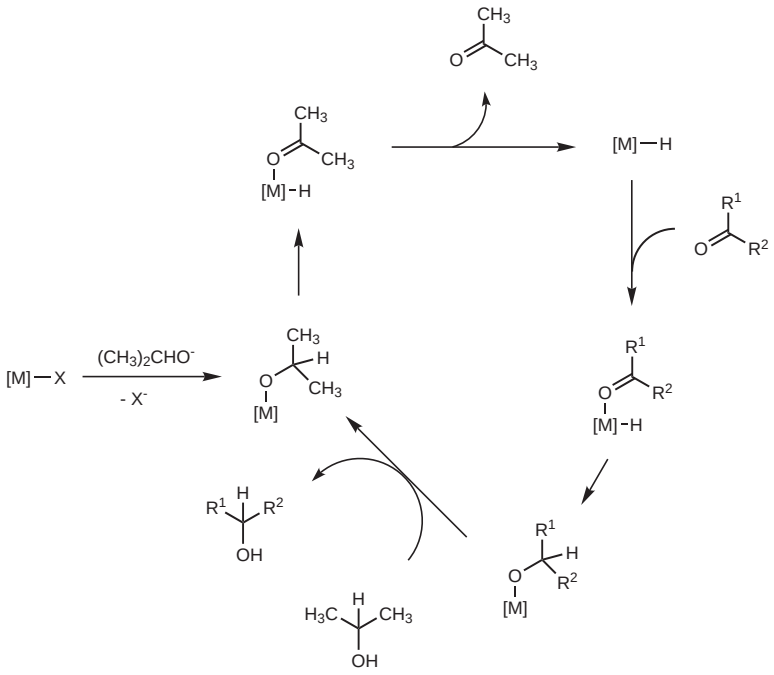


Figure 1.34: General mechanism of transfer hydrogenation.

Nowadays, research on H_2-transfer reactions and hydrogenation in general, focuses almost exclusively on the asymmetric hydrogenation of ketones to chiral alcohols. This is not surprising as chiral alcohols are omnipresent in nature. The last decades, tremendous progress has been made in this area and high enantioselectivities are

obtained with the use of appropriate ligands.[3,173–179] Figure 1.35 shows a representative example of ruthenium catalysts that have been developed. Some of the most important are Ru(II) complexes containing monotosylated 1,2-diamines, discovered in 1995 by Hashiguchi, Ikariya, Noyori and co-workers.[180] In 2001 Noyori and Knowles (together with Sharpless) were awarded the Nobel prize for their successful efforts in this field. All examples of catalysts given thus far are based on ruthenium because it is by far the most popular transition metal in hydrogen transfer reactions. Besides ruthenium, also complexes based on Ir[175,181–185] and Rh[186–192] are frequently used and a few reports describe Ni,[193,194] Pd,[195,196] and Sm[197] complexes.

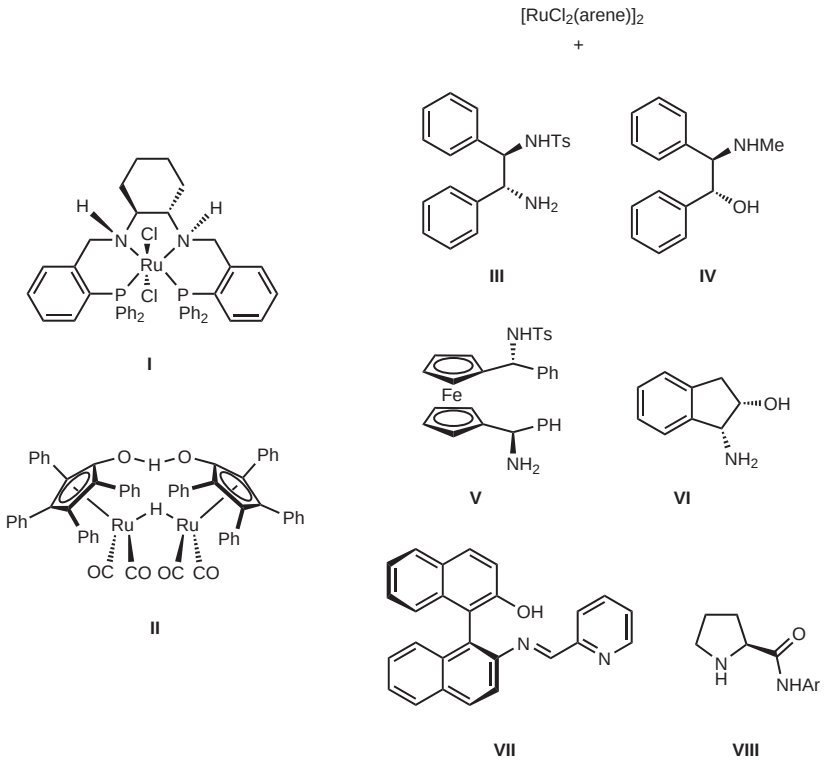


Figure 1.35: Examples of catalysts and ligands for asymmetric transfer hydrogenation. References: I,[198] II,[199,200] III,[201] IV,[202] V,[203] VI,[204] VII,[205] VIII[206].

1.4.3 Extension to the Friedlander reaction

In their research on the transfer hydrogenation of ketones by alcohols with ruthenium catalysts, Cho and Shim have found the formation of unusual transfer hydrogenation products (Figure 1.36).[207] Under all circumstances, the test reaction of acetophenone with 1-butanol gave rise to the unconventional alkylated products 1-phenylhexan-1-ol and 1-phenylhexan-1-one instead of the expected direct transfer hydrogenation product 1-phenylethanol. The best results in terms of total yield

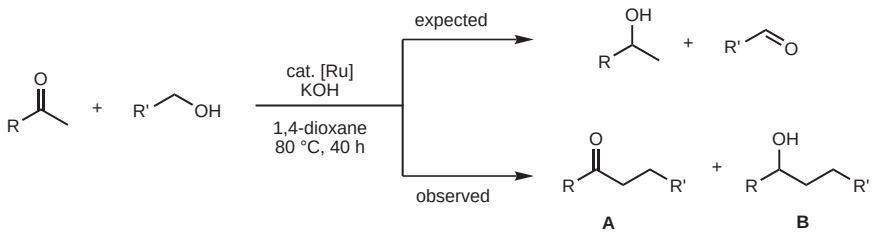


Figure 1.36: Unusual transfer hydrogenation reaction.

and selectivity were obtained with $RuCl_2(PPh_3)_3$ and a ketone/alcohol ratio of 1:3. The reaction could be extended to a wide range of combinations of ketones and primary alcohols with good to excellent yields of the corresponding coupled secondary alcohols. Figure 1.37 shows the proposed reaction mechanism.[207] The

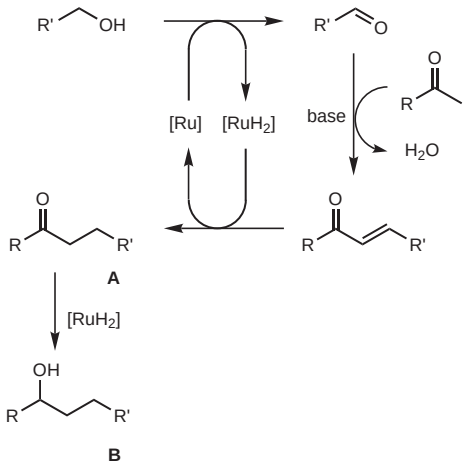


Figure 1.37: Proposed reaction mechanism for the oxidative coupling of alcohols with ketones.

primary alcohol is oxidized to an aldehyde that undergoes a cross aldol reaction with a ketone in the presence of a base. The double bond of the α,β-unsaturated ketone that is formed, is subsequently hydrogenated by the $[RuH_2]$ species formed in the initial oxidation step, to give **A**. A second hydrogenation gives the final alcohol **B**. Although it was not mentioned in their manuscript, the $[RuH_2]$ species responsible for this second hydrogenation is most likely formed from the oxidation of excess alcohol, or even dioxane which is known to act as a hydrogen donor in Ru or Rh catalyzed hydrogenation reactions.[156,208,209] Since no asymmetric or chiral ligands are used, this reaction is not enantioselective.

The formation of **A** can be favoured when equimolar amounts of alcohol and ketone are used in combination with 1-dodecene as hydrogen acceptor.[210] When compound **A** contains a nitrogen atom that can react intramolecularly with the

ketone function, a nitrogen heterocycle can be formed. For instance, when 2-aminobenzylalcohol is used, as shown in Figure 1.11, quinolines are generated.
This is not a 'classical' transfer hydrogenation as described in the previous paragraph. Generally, in transfer hydrogenation, the reduction of ketones to chiral alcohols is studied. Isopropanol is used as hydrogen source and it is oxidized to acetone. For the modified Friedlander method, it is the oxidation reaction of the alcohol that is of primordial importance.

2

Ruthenium catalyzed synthesis of quinolines

2.1 Introduction

In the modified Friedlander method, 2-aminobenzylalcohol is oxidatively cyclized with ketones to yield substituted quinolines. A ruthenium catalyst facilitates the involved transfer hydrogenation. Figure 2.1 shows the general reaction scheme of this method. In literature, the first generation Grubbs catalyst (**1**) has been reported

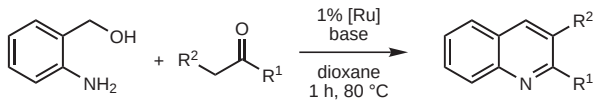


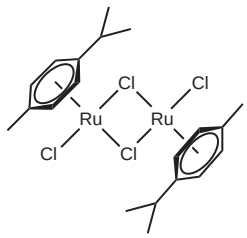
Figure 2.1: Ruthenium catalyzed quinoline synthesis.

to be the best catalyst for this reaction. However, only a few ruthenium complexes are described for this method[9,113] and there has not been an extensive survey of the systematic modification of different catalytic systems. This is quite surprising, knowing that the aforementioned catalyst is especially known for its activity towards olefin metathesis reactions[6,211] and, up till now, not for hydrogen transfer reactions. Given our experience in the synthesis of ruthenium complexes,[212–219] this prompted us to investigate some potentially interesting complexes for the modified Friedlander synthesis by systematically modifying the ligand environment of the ruthenium center. The catalyst, however, is not the only parameter that is important for this method. As the reaction mechanism suggests (see Figure 1.11 on page 6), also the base plays a key role that requires further investigation. As the

modified Friedlander method involves a hydrogen transfer, an additional hydrogen acceptor may be useful to increase the reaction rate and/or quinoline yields.

2.2 Ruthenium catalysts

The vast amount of publications on transfer hydrogenation show that an incredible number of ruthenium catalysts have been developed for this reaction. Many of them are based on $[RuCl_2(\eta^6\text{-arene})]_2$ complexes with asymmetric or chiral ligands. Since chirality is obviously not an issue in the oxidation of an alcohol to a ketone, there is no need for these rather expensive and often difficult to synthesize ligands. Complexes of the type $[RuCl_2(\eta^6\text{-arene})]_2$ are easily accessible, although these precursors are not very active themselves. The incorporation of suitable ligands, such as N,O-bidentate Schiff bases or phosphines, greatly improves their activity for hydrogen transfer[10,220–225] and other oxidation reactions[226–228] With these considerations in mind, complexes with readily available N,O-bidentate Schiff base ligands or phosphine ligands were synthesized from the precursor $[RuCl_2(p\text{-cymene})]_2$ (**3**, Figure 2.2).



3

Figure 2.2: The ruthenium dimer $[RuCl_2(p\text{-cymene})]_2$.

2.2.1 Synthesis of Ruthenium-arene complexes

The ruthenium dimer **3** was prepared from $RuCl_3.nH_2O$ and α-terpinene, according to literature procedures.[229] The synthesis of complexes of the type RuCl(p-cymene)(Schiff base) has previously been described by De Clercq,[230] but by following this method, the obtained complexes still contained impurities, such as unreacted **3** and Schiff bases. Therefore, an optimized procedure is presented here. The synthesis consists of three straightforward steps and is shown in Figure 2.3. First (a) the Schiff base is prepared by a condensation reaction between an amine and salicylaldehyde or 5-nitrosalicylaldehyde, in refluxing ethanol or THF for aromatic and aliphatic amines respectively. The Schiff bases of the aromatic amines precipitated upon cooling to 0 °C and were collected as a yellow powder by filtration. The Schiff bases of aliphatic amines were obtained as a viscous yellow oil by

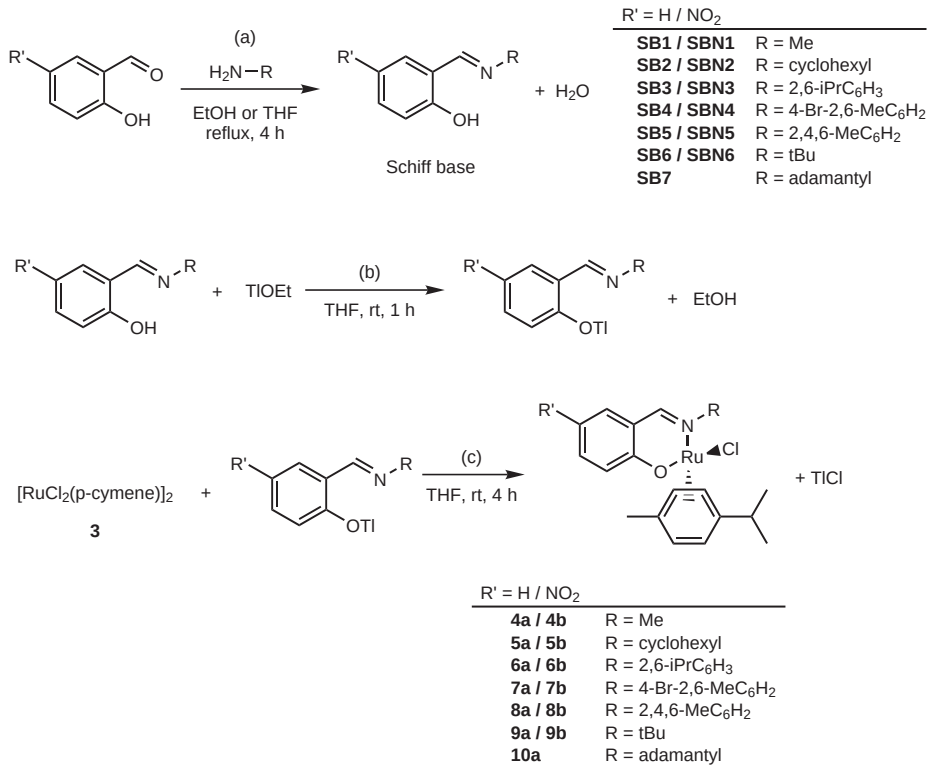


Figure 2.3: Synthesis of RuCl(p-cymene)(Schiff base) complexes.

evaporating the solvent. In a second step, (b) thallium ethylate is added to a solution of the Schiff base in THF, and a pale yellow precipitate started to form after a few minutes. This Tl-salt of the Schiff base was used in the next step without further purification or characterization. Finally, (c) to a solution of the Tl-salt in THF is added 0.5 equivalents of $[RuCl_2(p\text{-cymene})]_2$. A grey precipitate of TlCl formed almost immediately. After 4 hours, the solvent volume was reduced to 1 mL, and the mixture was purified by column chromatography to afford the pure desired complexes **4a,b-8a,b**. The synthesis of complexes **9a,b** and **10a**, with a very steric aliphatic group on the Schiff base nitrogen, was unsuccessful. These compounds were very unstable and decomposed completely during column chromatography.

Comparing our spectroscopic data with those of De Clercq, some inconsistencies surfaced. The most remarkable difference is the position of the imine proton in ^{1}H-NMR spectroscopy. Where De Clercq reported a resonance at 9.95 ppm for component **4a**, which is actually very close to that of the original Schiff base **SB1**, we found 7.68 ppm, a value that is shifted upfield due to complexation with ruthenium. The same is true for other Schiff base complexes, which leads us to believe that De Clercq did not achieve complexation of the Schiff base with the ruthe-

nium metal. Further evidence for this hypothesis is found in the chemical shifts of the p-cymene ligand. In the ruthenium dimer **3**, the four aromatic protons of the p-cymene ligand are pairwise chemically but not magnetically equivalent, and therefore give rise to the usual AA'XX' spin system. This is illustrated in Figure 2.4. In the complexes discussed here, they should appear as four separate signals,

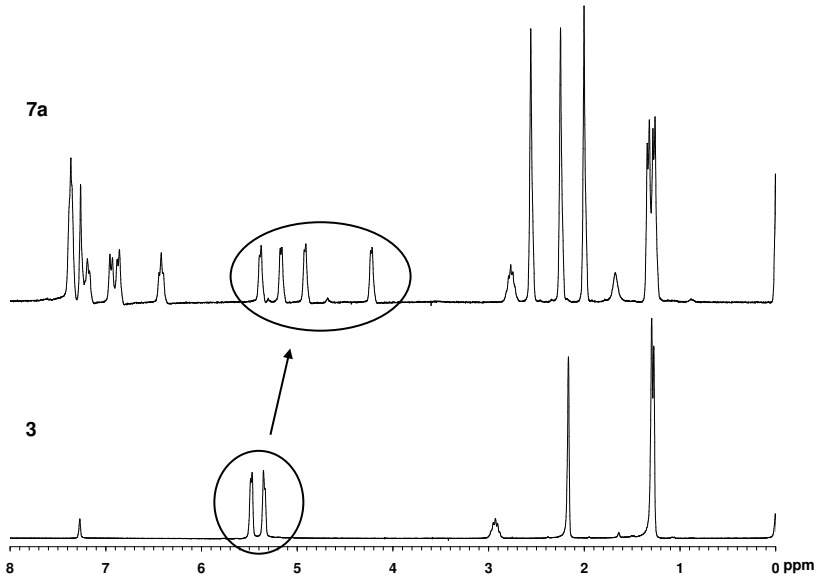


Figure 2.4: ^{1}H-NMR spectra for $[RuCl_2(p\text{-cymene})]_2$ **(3)** and **7a**.

because they are no longer equivalent. This is not only evidenced by our own spectra, which indeed show four separate peaks, but also by other researchers.[231] The synthesis of **11a,b** from the precursor **3** and the appropriate phosphine ligand (Figure 2.5) has been reported previously.[232,233]

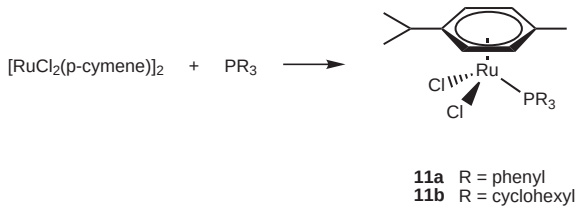


Figure 2.5: Synthesis of $RuCl(p\text{-cymene})(PR_3)$.

During the last two decades, tremendous progress has been made in many ho-

mogeneous catalytic reactions using N-heterocyclic carbene ligands.[234,235] They were originally introduced as phosphine mimics, but have proven to be superior in many cases.[236] The incorporation of NHC ligands increases the thermal stability of organometallic complexes and reduces their sensitivity towards oxidation. Two types of NHC's that were used in this work are displayed in Figure 2.6.

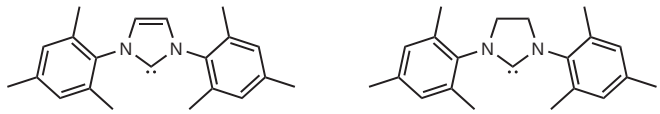


Figure 2.6: The NHC ligands IMes and H_2IMes.

The synthesis of NHC-arene complex **13** with H_2IMes as the NHC ligand has proven to be a real challenge. Thus far, no-one has succeeded in its isolation and/or characterization. A few reports exist with catalytic tests performed with the *in situ* generated complex, but no evidence is provided that the actual active catalysts is truly compound **13**.[237,238] The unsaturated analogue **12** was readily prepared using the standard method of Nolan[239] as shown in Figure 2.7 (A). The addition of the free carbene, generated and isolated by Arduengo's method,[240] to **3** affords **12**. Method (B) is a slight modification. By using potassium hexamethyl disilazane (KHMDS), the free carbene is generated in situ, and no further workup of the air and moisture sensitive free carbene is needed. Addition of 0.5 equivalents of **3** gives **12** as a brown solid.
Various attempts to synthesize **13** have failed. Figure 2.7 (C)-(E) shows three strategies that have been employed. Method (C) is the classical synthesis that Nolan et al. have applied for **12**. Method (D) again uses KHMDS, avoiding the handling of the sensitive free carbene by generating it in situ. In method (E), first the CO_2-adduct of H_2IMes is prepared by bubbling CO_2 gas through a flask charged with the free carbene, generated in the reaction of H_2IMes with a KHMDS solution, according to a method by Delaude.[241] This adduct is then reacted with **3**. In all cases, the originally orange-red solution of **3** turned from brown to dark green in a matter of minutes upon addition of the NHC carbene, leading us to believe that rapid decomposition occurs. None of these methods afforded the desired compound, instead a complex mixture of unidentifiable compounds was obtained.
Ledoux was able to coordinate a bidentate analogue of H_2IMes via the strategy shown in Figure 2.8.[217] The NHC salt (1-mesityl-3-(2-hydroxyphenyl)-4,5-dihydroimidazolium chloride) was synthesized according to a procedure describe by Grubbs et al.[242] Treatment of ethylchlorooxoacetate with 2,4,6-trimethylaniline affords an N-(mesityl)-oxanilic acid ethyl ester. Subsequent reaction with 2-aminophenol gives a bis-amide that is reduced with borane to the diamine, which is then reacted with triethyl orthoformate to give the NHC salt. Treatment of this salt with 2 equivalents of KHMDS results in the free carbene with the deprotonated alcohol function. Addition of 0.5 equivalents **3** then affords complex **14**. It should be noted that for reasons yet unknown, the last step of this procedure, i.e. the

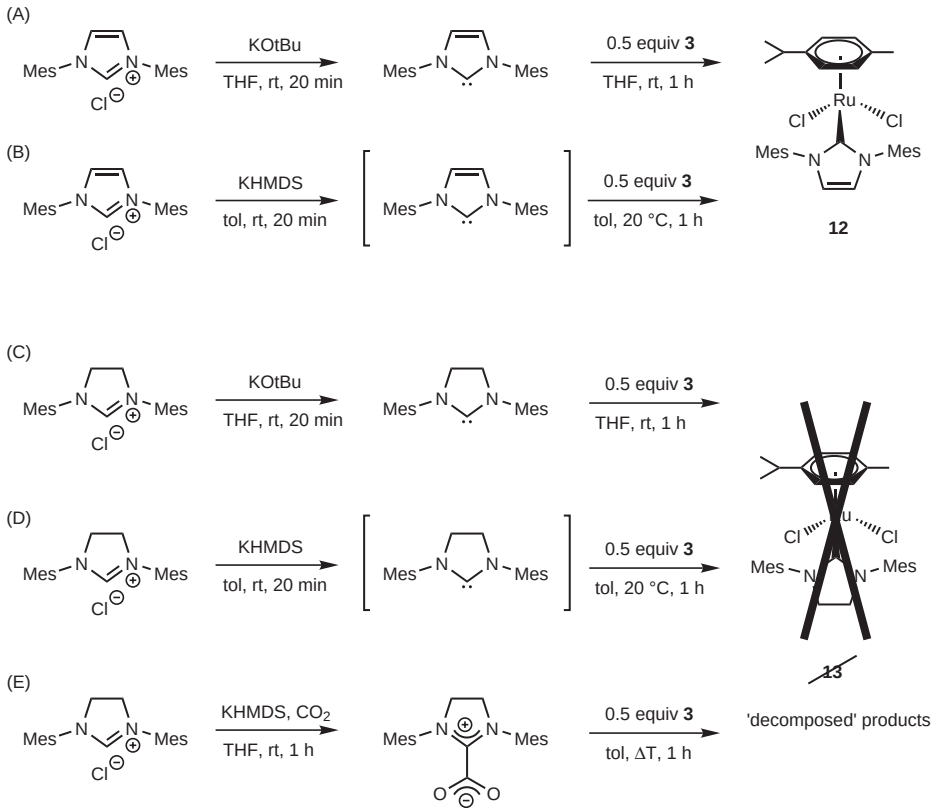


Figure 2.7: Synthesis of $RuCl_2$(p-cymene)(NHC) complexes **12** and **13**. Mes = mesityl = 2,4,6-trimethylphenyl.

complexation reaction, is sometimes difficult to reproduce.

2.2.2 Quinoline synthesis with Ru-arene complexes

The results of the catalytic tests with the catalysts described above are summarized in Table 2.1 and compared with the result of **1** which was reported as the best catalyst to date. The reaction between 2-aminobenzylalcohol (1.0 mmol) and acetophenone (2.0 mmol) in the presence of 0.01 mmol catalyst in 3 mL 1,4-dioxane is chosen as the model reaction for these tests (Figure 2.9). The base KOH is added as a 4 M solution in MeOH (vide infra, 1 mmol, 250 μL). After 1 hour of reaction at 80 °C, a small sample of typically 30 μL of the reaction mixture was purified on a small column (silica gel, ethyl acetate) to eliminate inorganic salts and the catalyst. All yields were determined by gas chromatography, based on 2-aminobenzylalcohol.

After one hour, the Grubbs first generation catalyst **1** gives a quinoline yield of 74%. Interestingly, the control experiment without catalyst shows 9% conversion. None

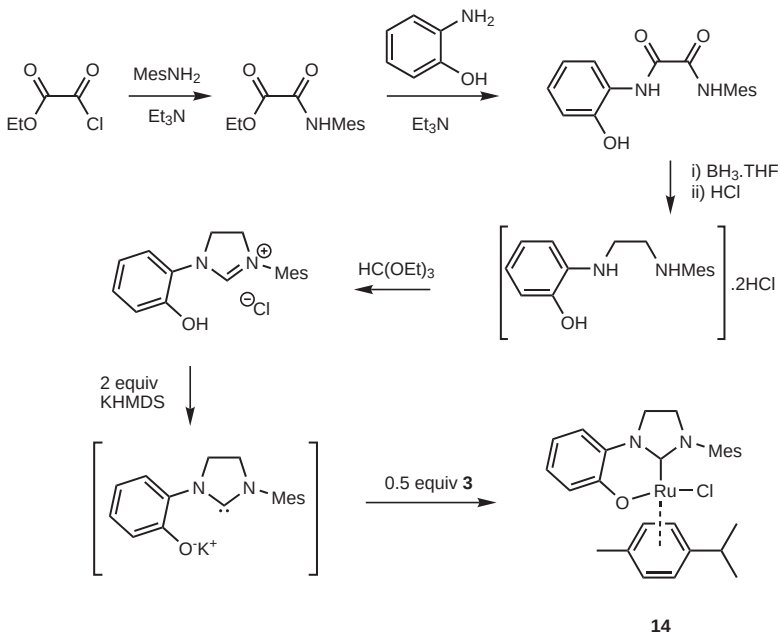


Figure 2.8: Synthesis of **14** with a bidentate NHC ligand.

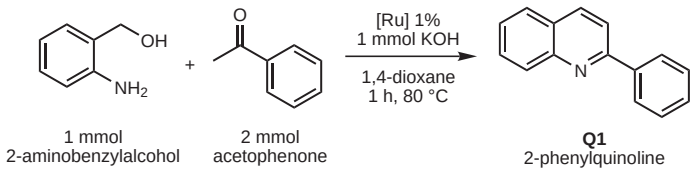


Figure 2.9: Model reaction for quinoline synthesis.

of the synthesized Schiff base complexes **4a,b-8a,b** show significant catalytic activity, even though similar ruthenium complexes with Schiff base ligands have been used in transfer hydrogenation reactions. The implementation of N,O-bidentate ligands does not improve the quinoline yield, on the contrary, most yields are even lower than that of the precursor **3**. In situ addition of ethanolamine to **3** results in a slightly increased yield (25% compared to 15% after 1 hour) but the overall yield remains poor. Because of these low yields it is hard to distinguish between the different catalysts. A general trend seems to be a lower activity for catalysts with a nitro group on the Schiff base.
The in situ-addition of 5 equivalents PPh_3 (versus catalyst **3**) also results in a small increase in yield. Upon the use of a large excess of 100 equivalents of PPh_3 the yield diminishes again. This is probably due to a saturation effect of the catalyst: the vacant site for accepting hydrogen becomes blocked by excess phosphine. With

Table 2.1: Quinoline synthesis from $[RuCl_2(\eta^6\text{-arene})]_2$ based catalysts[a]

Entry	Catalyst	Yield (%)
1	**1**	74
2	no catalyst	9
3	**3**	15
4	**4a**	13
5	**4b**	13
6	**5a**	14
7	**5b**	13
8	**6a**	15
9	**6b**	10
10	**7a**	14
11	**7b**	12
12	**8a**	13
13	**8b**	12
14	**11a**	40
15	**11b**	53
16	**14**	26
17	**3** + ethanolamine (0.20 mmol)	24
18	**3** + PPh_3 (0.05 mmol)	25
19	**3** + PPh_3 (1.0 mmol)	19

[a] Reaction conditions: 2-aminobenzylalcohol (1.0 mmol), acetophenone (2.0 mmol), catalyst (0.01 mmol) and KOH (1.0 mmol) in dioxane (3 mL) at 80 °C for 1 h. Yields based on 2-aminobenzylalcohol and determined by GC analysis.

isolated complexes **11a** and **11b**, moderate conversions of respectively 40% and 53% were achieved. Thus, phosphine ligands clearly have a positive influence on the conversion. This can also be seen when the phosphine ligand in **11a** is replaced by an NHC ligand in complex **14**: the conversion drops to 26%. Compared to the first generation Grubbs catalyst, ruthenium-arene complexes perform poorly, with the exception of complexes containing phosphine ligands. These results indicate that the choice of ligands is crucial for this reaction.

2.2.3 Quinoline synthesis with Ru-carbene complexes

As shown in the previous paragraph, the activity of Ru-arene complexes for transfer hydrogenation was limited, compared to **1**. Both type of complexes have some major differences in their set of ligands: η^6-arene ligands and N,O bidentate Schiff base for the first, and phosphine ligands and a carbene for the latter. To further investigate the influence of changes in the ligand environment, variations on the Grubbs first generation catalyst (Figure 2.10) will be examined in the next set of experiments.
Many catalysts of this type are already known and each one has its own benefits for specific applications, usually situated in the field of olefin metathesis. Exchange of

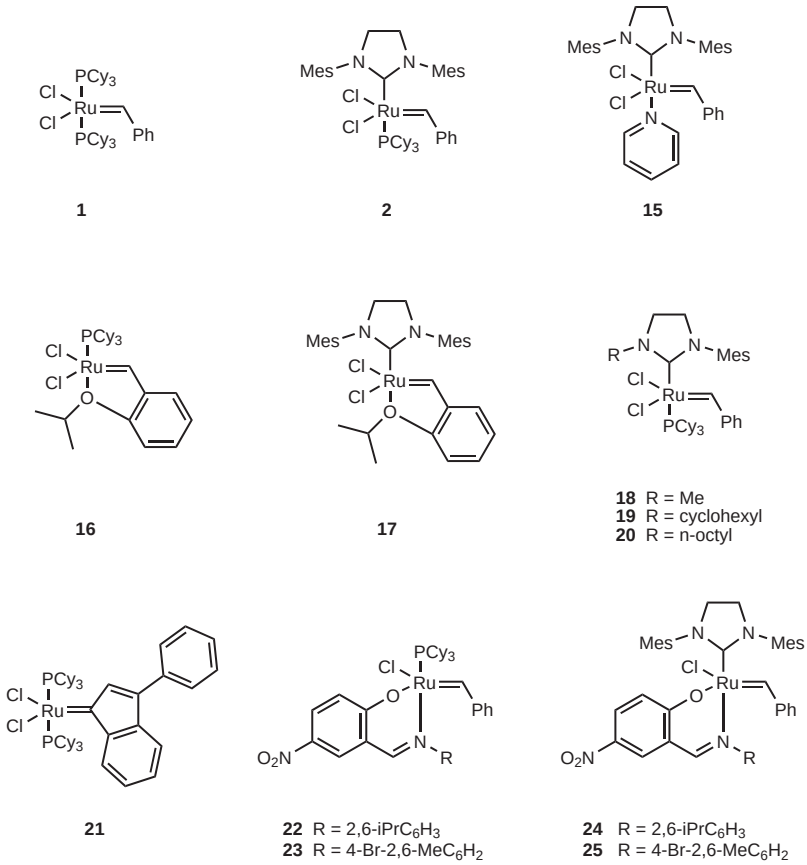


Figure 2.10: Ruthenium catalysts based on the first and second generation Grubbs catalyst.

one phosphine ligand in **1** leads to the so-called Grubbs second generation catalyst **2**.[243] This catalyst has shown a higher activity and selectivity in several metathesis reactions. The second phosphine can be replaced by a weakly coordinating heterocyclic ligand such as pyridine to give **15**, often referred to as the third generation Grubbs catalyst.[244] Fürstner developed complex **21** with an indenylidene ligand instead of the benzylidene.[245] The Hoveyda catalyst **16** and its second generation analogue **17** are very robust aryl-ether chelate complexes.[246,247] Other variations, such as modifying the NHC-ligand or the inclusion of Schiff base ligands have been developed in our research group and by others (complexes **18**-**20**,[213] **22**-**23**[7] and **24**-**25**[212]). The results of the catalytic tests are summarized in Table 2.2.
The replacement of a phosphine ligand by the NHC ligand H_2IMes clearly improved catalytic activity, resulting in 100% conversion for **2** after 1 hour compared to 74% for **1**. This might be attributed to the higher σ-donating ability of the NHC ligand, making it more suitable to stabilize the [RuH_2] species with a presumably higher

Table 2.2: Quinoline synthesis from Grubbs type catalysts[a]

Catalyst	Yield (%)
1	74
2	100
15	53
16	74
17	84
18	52
19	72
20	75
21	33
22	38
23	14
24	53
25	26

[a] Reaction conditions: 2-aminobenzylalcohol (1.0 mmol), acetophenone (2.0 mmol), catalyst (0.01 mmol) and KOH (1.0 mmol) in dioxane (3 mL) at 80 °C for 1 h. Yields based on 2-aminobenzylalcohol and determined by GC analysis.

oxidation state compared to the original catalyst. Variation of the NHC ligand through replacement of one mesityl group by aliphatic groups, such as methyl or cyclohexyl, as in compounds **18**, **19** and **20** decreased the quinoline yield. The bulkiness of the amino side group seems to play a role here, which is evidenced in the series methyl < cyclohexyl ≈ n-octyl < mesityl, where the complex with the bulkier group shows the highest quinoline yield.
It is remarkable that the NHC ligand in **14** has a detrimental effect, whereas with the Grubbs catalysts, the activity is increased. Even more remarkable is the relatively low conversion achieved with **15** while it is similar to **2** in structure. We are currently unable to explain this peculiar behaviour but apparently, the presence of at least one phosphine ligand is required to achieve good yields. Replacing the benzylidene ligand of **1** with a bulkier indenylidene ligand in complex **21** decreases the conversion.
The Hoveyda catalysts show a similar behaviour as the Grubbs catalysts. The first generation Hoveyda catalyst (**16**) has an equal activity as **1**. Changing the phosphine ligand by H_2IMes increases the yield, albeit not so spectacular as with the Grubbs catalysts.
When N,O-bidentate Schiff base ligands are introduced on Grubbs type catalysts (compounds **22**, **23**, **24** and **25**) the conversion drops notably. This confirms the poor results achieved with the Ru-arene Schiff base complexes described earlier. The nature of the Schiff base also seems to play some role here. Compound **22** with R = 2,6-*i*PrC_6H_3 has a significantly higher yield (38%) than **23** with R = 4-Br-2,6-MeC_6H_2 (only 14%). Complementary to previous results, their second generation analogues **24** and **25** have a slightly improved performance (53% versus

38% and 26% versus 14% respectively), but in general, the use of Schiff base ligands is not very attractive for the preparation of quinolines by this method.
When the reaction is monitored over time, it is revealed that the yields after one hour are not necessarily final yields. The catalysts are still active after one hour of reaction. Complex **2** reaches full conversion after 60 minutes, **1** after 90 minutes and also **11a** and **11b** eventually reach full conversion after 6 and 5 hours respectively, as shown in Figure 2.11.

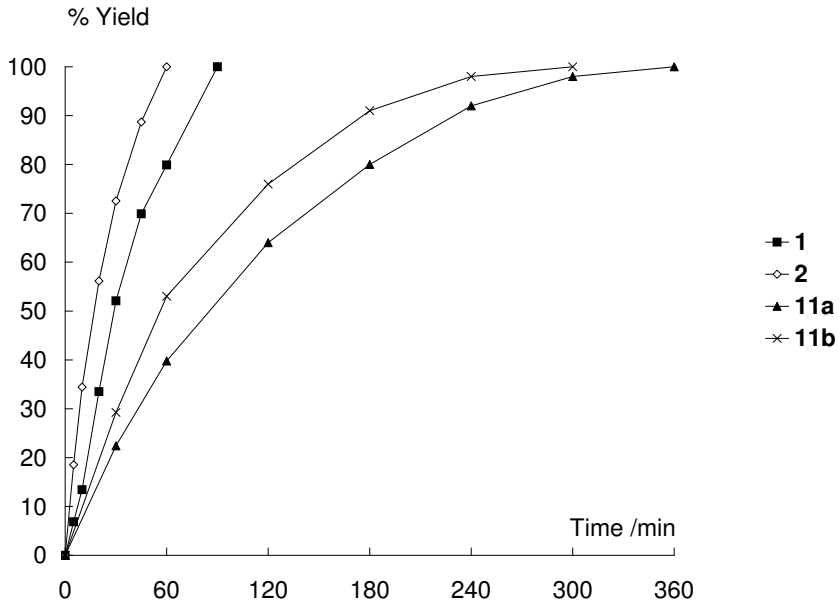
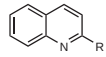
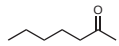
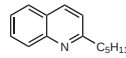
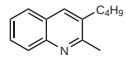
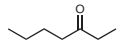
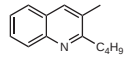
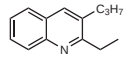
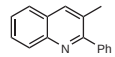
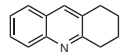
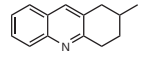
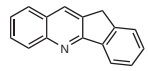


Figure 2.11: Monitoring of the reaction over time. Reaction conditions: 2-aminobenzylalcohol (1.0 mmol), acetophenone (2.0 mmol), catalyst (0.01 mmol) and KOH (1.0 mmol) in dioxane (3 mL) at 80 °C.

2.2.4 Quinoline synthesis from other ketones

To assess the scope of the modified Friedlander method, 2-aminobenzylalcohol was reacted with a variety of ketones in the presence of **1** and **2**. The results are shown in Table 2.3. From these results, it is obvious that the second generation outperforms the first generation Grubbs catalyst. For all ketone substrates, a higher quinoline yield was obtained for **2** compared to **1**. Entry 1 is the model reaction with acetophenone. As shown in the tests of the catalysts in the previous paragraph, after one hour full conversion is achieved with **2** versus 75% with **1**. The ketones in entres 2, 3 and 4 are derivatives of acetophenone with a methyl substituent on the aromatic ring in the ortho, meta and para position respectively. All quinoline yields with these sustituted acetophenones are lower, but apparently an ortho substituent

Table 2.3: Ruthenium catalyzed quinoline synthesis from a variety of ketone substrates[a]

Entry	Ketone	Quinoline		Yield (%) **1**	Yield (%) **2**
					
	R =	R =			
1	Ph	Ph	**Q1**	75[b]	100[c]
2	2-MeC_6H_4	2-MeC_6H_4	**Q2**	31	66
3	3-MeC_6H_4	3-MeC_6H_4	**Q3**	63	91
4	4-MeC_6H_4	4-MeC_6H_4	**Q4**	64	86
5	2-$MeOC_6H_4$	2-$MeOC_6H_4$	**Q5**	38	87
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**Q6**	47	74
7	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	**Q7**	0	0
8	Me[d]	Me	**Q8**	65	100
9			**Q9**	34	76
			**Q10**	8	18
10			**Q11**	21	51
			**Q12**	7	15
11			**Q13**	72	87
12			**Q14**	72	100
13			**Q15**	78	100
14			**Q16**	17	30

[a] Reaction conditions: 2-aminobenzylalcohol (1.0 mmol), ketone (2.0 mmol), catalyst (0.01 mmol) and KOH (1.0 mmol) in dioxane (3 mL) at 80 °C for 1 h. Yields based on 2-aminobenzylalcohol and determined by GC analysis.
[b] Isolated yield: 65%
[c] Isolated yield: 94%
[d] 5.0 mmol

has the largest influence as the yield of **Q2** is much lower than that of **Q1** (no substituent) or **Q3** and **Q4** with a meta or para methyl group on acetophenone.

Also a methoxy group on acetophenone results in lower quinoline yields (entries 5 and 6). The difference between the ortho and para position however is not so pronounced as with the methyl substituents and it is even reversed between **1** and **2**. The reaction is inhibited when the strong electron withdrawing substituent NO_2 is present on the aromatic ring of acetophenone (entry 7). This result contradicts preliminary results published by Cho et al. who reported a yield of 40% for **Q7**.[9] They have, however, never used this ketone again in later publications.
When acetone is used as ketone, relatively low yields (maximum 38% with **1** and 62% with **2**) are obtained. This is most probably a result from the high volatility of acetone. Therefore, a larger excess of 5.0 mmol is used with this substrate, which results in good to excellent yields of 65% and 100% respectively, as shown in entry 8.
Entries 9 and 10 illustrate that a mixture of two quinolines is formed when two α-protons are available in an asymmetric ketone. Figure 2.12 shows an example with 2-heptanone. Two deprotonated forms of 2-heptanone can be formed, one with the negative charge on the methyl group, and the other with the negative charge on the pentyl group. The first one is more stable than the second, as in the second, the inductive effect (+I) of the pentyl group destabilizes the negative charge. This is also reflected in the distribution of the quinolines: **Q9** is more abundant then **Q10**, the ratio of **Q9**/**Q10** being 4.2. The same effect applies to 3-heptanone,

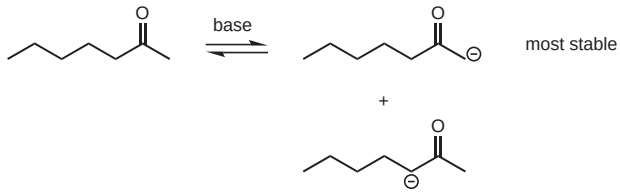


Figure 2.12: Abstraction of an α-proton by the base.

but the difference between the side-chains of the ketone is smaller: an ethyl group versus a butyl group. Therefore, the ratio between **Q11** and **Q12** is also a little lower, with a value of 3.4. For the same reasons, it can be understood that the yields with 3-heptanone as substrate are a little lower than with 2-heptanone. The ratio of **Q9**/**Q10** and **Q11**/**Q12** is the same for **1** and **2** as can be expected since the only action of the catalyst is to facilitate the transfer hydrogenation.
This is evidently not observed with symmetric ketones such as cyclohexanone and 4-methylcyclohexanone (entries 12 and 13). The yields with the ketone substrate 1-indanone are fairly low and the reaction mixture turns deep purple. It is suspected that some side-reactions compete with quinoline synthesis, but due to difficulty of purification, no evidence has been found for this assumption.

2.2.5 Isolation and characterization of the quinolines

All quinolines were isolated and fully characterized by ^{1}H and ^{13}C-NMR spectroscopy. The retention time of the pure quinolines was compared with the original

chromatogram for verification, and also the sensitivity of the FID (flame ionization detector) of the GC for each component was determined. The isolation method proposed by Cho and Shim[9] was found to be unsatisfactory. They filtered the reaction mixture through a short silica gel column (ethyl acetate), washed the resulting solution with brine and dried it over Na_2SO_4. Removal of the solvent left a crude mixture, which was separated by column chromatography (silica gel, ethyl acetate-hexane mixture) to give quinolines. However, by using this method, we were unable to separate the quinoline from unreacted ketone. Therefore, we have developed a more efficient isolation procedure. First, the catalyst and inorganic salts are removed from the reaction mixture by column chromatography (short column, ethyl acetate). The volume of the resulting solution was reduced and by passing the mixture through a second column with ethyl acetate/hexane as eluent in a 1:4 ratio, also unreacted 2-aminobenzylalcohol is removed. The solvent volume was reduced and HCl was added as a 4 N solution in dioxane. For most quinolines, a precipitation formed, that was filtered and suspended again in an aqueous solution of KOH. The aqueous phase was extracted with dichloromethane and after evaporation of the solvent, the quinoline was obtained as a pure compound. The yields of isolated quinolines are typically 5-10% lower than the yields determined by GC. When the quinoline did not precipitate upon addition of HCl, as was the case with **Q8** - **Q12**, an aqueous extraction of the ethyl acetate phase was performed. Then, KOH was added to the combined water phases and they were extracted with CH_2Cl_2 as usual.
The mixture of quinolines **Q9** and **Q10** could be separated by a tedious column chromatography (ethyl acetate/hexane, 1:4). The reaction mixture was evaporated, to minimize the volume to be applied to the column and a long column was used. Every 1.5 mL was collected in a small vial and analyzed by GC. The major compound **Q9** eluated first, closely followed by **Q10** with only a minor overlap of the compounds. Both compounds could thus be isolated and characterized separately. The same technique was unsuitable for the mixture of **Q11** and **Q12**. Although **Q11** started to eluate slightly before **Q12** and could be collected as a pure compound, it was impossible to obtain pure **Q12** as it was always accompanied by the other isomer **Q11**. Hence, **Q11** was characterized as a pure compound, and by comparison of the NMR-spectra of pure **Q11** with the mixture, **Q12** was characterized.

2.3 Influence of the base

The role of the base in the modified Friedlander method is to abstract the α-proton of the ketone, so it can undergo a cross-aldol reaction with the oxidized 2-aminobenzylalcohol (Figure 2.13). The pK_a value of the α-proton is approximately 16 for acetophenone. Typically, KOH is used by most other researchers and although KOH is insoluble in dioxane, it is seldomly specified under which conditions it is added. Therefore, a thorough survey of the influence of the base was performed. The results are shown in Table 2.4.
When large pellets of KOH are used, the conversion after one hour is only 8% but this can be increased to 67% with KOH powder. An even higher conversion of 74% is achieved when KOH is added as a 4 M solution in methanol. This is probably

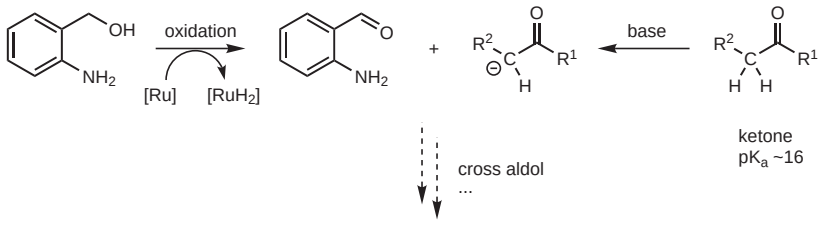


Figure 2.13: The role of the base in the modified Friedlander method.

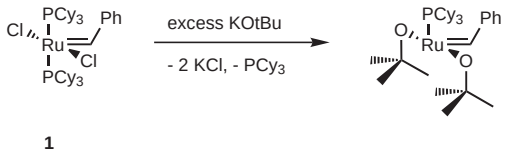
Table 2.4: Influence of the base[a]

Entry	Base (1 mmol)	pK_a[b]	Yield (%)
1	KOH (pellets)	15.7	8
2	KOH (powder)	15.7	64
3	KOH (4 M in MeOH)	15.7	74
4	NaOH (powder)	15.7	38
5	NaOH (4 M in MeOH)	15.7	48
6	NaOEt (powder)	15.9	74
7	KOtBu (powder)	17.0	98
8	LiHMDS (0.5 M in toluene)	≈ 26[c]	27
9	Triethylamine	10.6	0
10	DBU	12.8	0
11	0.4 mmol KOH (4 M in MeOH)	15.7	67
12	2.0 mmol KOH (4 M in MeOH)	15.7	73

[a] Reaction conditions: 2-aminobenzylalcohol (1.0 mmol), acetophenone (2.0 mmol), **1** (0.01 mmol) and base (1.0 mmol, except for entries 11 and 12) in dioxane (3 mL) at 80 °C for 1 h. Yields based on 2-aminobenzylalcohol and determined by GC analysis.
[b] pK_a values of the protonated form of the base.
[c] pK_a value in THF

caused by the increased solubility. As an added advantage, this not only results in a higher yield, it is also much more practical. When KOH was used as a base in this manuscript, unless otherwise noted, it was added as a 4 M solution in methanol. The yield is substantially lower when NaOH is used, either as powder (entry 4) or as a 4 M solution in MeOH (entry 5). This may be explained by the smaller size of the sodium cation, resulting in a lower solubility. It is, however, surprising that a cation change from potassium to sodium leads to such a big difference. Sodium ethoxide (entry 6) has approximately the same base strength as NaOH, yet a higher yield, comparable to KOH, is achieved. Again, the higher solubility of NaOEt because of the aliphatic ethyl group can explain these results. An other common base, KOtBu, has a higher basic strength, which is reflected in the higher quinoline

yield (entry 7). Not only the basic strength is important, as is evidenced by entry 8. Lithium bis(trimethylsilyl)amide (LiHMDS) has a pK_a of approximately 26, but only 27% quinoline yield is obtained. Both bases have a non-nucleophilic character, but maybe LiHMDS is too aggressive and deactivates the catalyst.
Grubbs et al. have also shown the exchange of the chloride ligands with the tertiary butoxy group, which implies that, when KOtBu is used, a different catalytic center may be formed.[244,248] For **1**, this is illustrated in Figure 2.14.



1

Figure 2.14: Reaction of **1** with excess KOtBu.

Organic bases such as triethylamine (entry 9) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, entry 10) have the advantage of being readily soluble in dioxane, but their low basicity prevents them from being effective bases for this reaction. Although the proton abstraction is base-catalyzed, an equimolar ratio of base and ketone gives the best results, as can be deduced from entries 3, 11 and 12. A higher concentration of base does not further improve the yield. Figure 2.15 illustrates the effect of the base even better. With KOtBu and **2**, full conversion is reached after only 20 minutes, compared to 60 minutes with KOH.
A similar trend is observed with other ketone substrates, as shown in Table 2.5. The stronger base KOtBu gives higher quinoline yields than KOH for almost all ketones. The only two exceptions are acetone (entry 8) and 1-indanone (entry 14) were KOH is the preferred base in combination with **2**. Even with a stronger base, combining 2-aminobenzylalcohol with 4-nitro-acetophenone, does not lead to any formation of quinolines.
There is, however, a small but notable difference between KOH and KOtBu. With 2-heptanone, the ratio of **Q9**/**Q10** is 4.2 for KOH and 2.9 for KOtBu, meaning there is a higher selectivity with KOH. With 3-heptanone the difference is less pronounced (3 versus 2.6). This is likely caused by the stronger basic strength of KOtBu, which results in less distinction between the two α-protons.

2.4 Solvent preparation: flushing with argon

All reactions with the corresponding yields that have been described thus far, have been performed without any manipulation of the used products. All compounds were used as received from commercial sources, including the solvent, 1,4-dioxane. Although the solvent was of >99,8% purity and delivered in a container with a septum and molecular sieves inside to ensure dryness, comparison of our results for **1** and KOH with those of Cho revealed lower yields for our reactions. The model reaction of 2-aminobenzylalcohol with acetophenone gave 74% quinolines in our case, compared to 100% reported by Cho.[9] One possible reason is the presence of

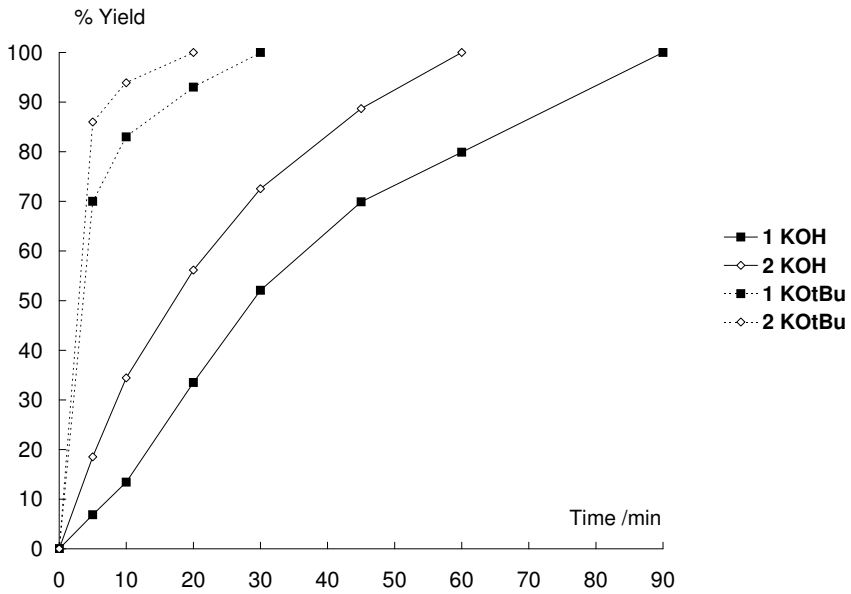


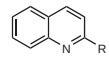
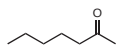
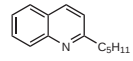
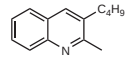
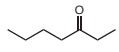
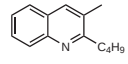
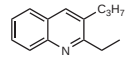
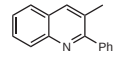
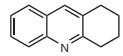
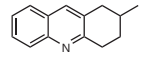
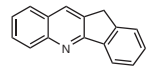
Figure 2.15: KOH versus KOtBu for **1** and **2**. Reaction conditions: 2-aminobenzylalcohol (1.0 mmol), acetophenone (2.0 mmol), catalyst (0.01 mmol) and base (1.0 mmol) in dioxane (3 mL) at 80 °C for 1 h.

dissolved gases in dioxane, in particular oxygen, resulting in lower yields. Flushing the solvent with argon gas, prior to use, to remove these dissolved gases could solve this problem. To assess this expectation, the same set of experiments with **1** and KOH was performed again and the solution of 2-aminobenzylalcohol in dioxane was flushed with argon for 30 minutes, before adding the ketone, catalysts and base. The first column in Table 2.6 repeats the earlier results for easy comparison. The second column presents the results when flushed dioxane is used. It is obvious that flushing the solvent prior to use has a huge influence on the quinoline yield. The results that are obtained now, are comparable to the results published by Cho. As a consequence, all further reactions concerning quinoline synthesis that are described in this work have been performed with flushed dioxane.

2.5 Turn-over number and turn-over frequency

The determination of the turn-over number (TON) for the model reaction of 2-aminobenzylalcohol with acetophenone in the presence of KOtBu and **2** was carried out by lowering the catalyst concentration and measuring the maximum yield. A catalyst loading of 0.1% still results in full conversion within 1 h. With a catalyst loading of 0.01%, a maximum yield of 85% is observed after 5 h, meaning a TON as high as 8500 was achieved, showing the potential of this catalytic system. The

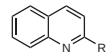
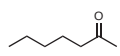
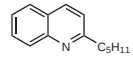
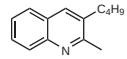
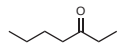
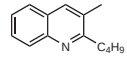
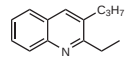
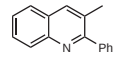
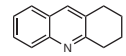
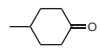
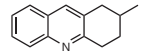
Table 2.5: Ruthenium catalyzed quinoline synthesis from a variety of ketone substrates with KOtBu as base[a]

Entry	Ketone	Quinoline		Yield (%) **1**	**2**
					
	R =	R =			
1	Ph	Ph	**Q1**	98	100
2	2-MeC_6H_4	2-MeC_6H_4	**Q2**	98	100
3	3-MeC_6H_4	3-MeC_6H_4	**Q3**	97	100
4	4-MeC_6H_4	4-MeC_6H_4	**Q4**	100	100
5	2-$MeOC_6H_4$	2-$MeOC_6H_4$	**Q5**	100	100
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**Q6**	96	95
7	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	**Q7**	0	0
8	Me[b]	Me	**Q8**	76	68
9			**Q9**	61	65
			**Q10**	21	22
10			**Q11**	65	62
			**Q12**	25	23
11			**Q13**	100	100
12			**Q14**	97	100
13			**Q15**	100	100
14			**Q16**	21	22

[a] Reaction conditions: 2-aminobenzylalcohol (1.0 mmol), ketone (2.0 mmol), catalyst (0.01 mmol) and KOtBu (1.0 mmol) in dioxane (3 mL) at 80 °C for 1 h. Yields based on 2-aminobenzylalcohol and determined by GC analysis.
[b] 5.0 mmol

calculation of the turn-over frequency (TOF) at the beginning of the reaction (after the first 5 minutes), fully quantifies the difference between the catalytical systems. With KOH, complex **1** has a TOF of 1.7 min^{-1} (measured after 20 min because of the observed induction period), while that of **2** is twice as large (3.8 min^{-1}). Using

Table 2.6: Quinoline synthesis in flushed dioxane, using **1** and KOH[a]

Entry	Ketone	Quinoline		Yield (%) /	flushed
					
	R =	R =			
1	Ph	Ph	**Q1**	75[b]	100[c]
2	2-MeC_6H_4	2-MeC_6H_4	**Q2**	31	59
3	3-MeC_6H_4	3-MeC_6H_4	**Q3**	63	88
4	4-MeC_6H_4	4-MeC_6H_4	**Q4**	64	98
5	2-$MeOC_6H_4$	2-$MeOC_6H_4$	**Q5**	38	66
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**Q6**	47	74
7	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	**Q7**	0	0
8	Me[b]	Me	**Q8**	65	100
9			**Q9**	34	68
			**Q10**	8	17
10			**Q11**	21	52
			**Q12**	7	19
11			**Q13**	72	100
12			**Q14**	72	75
13			**Q15**	78	100

[a] Reaction conditions: 2-aminobenzylalcohol (1.0 mmol), ketone (2.0 mmol), **1** (0.01 mmol) and KOH (1.0 mmol) in dioxane (3 mL) at 80 °C for 1 h. Yields based on 2-aminobenzylalcohol and determined by GC analysis.
[b] 5.0 mmol

KOtBu the TOF increases spectacularly to 14.0 and 17.0 min^{-1} respectively for **1** and **2**.

2.6 The influence of a hydrogen acceptor

As part of the hydrogen transfer reaction, the oxidation of 2-aminobenzylalcohol to 2-aminobenzaldehyde is catalyzed by a ruthenium catalyst (Figure 2.16). In this

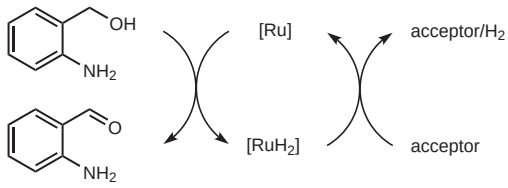


Figure 2.16: Oxidation reaction of 2-aminobenzylalcohol to 2-aminobenzaldehyde.

process, the catalyst is converted into a $[RuH_2]$ species that can no longer perform a new oxidation reaction. Therefore, a hydrogen acceptor needs to be present in the reaction mixture to regenerate the catalyst. The researchers Cho and Shim proposed that the α,β-unsaturated ketone that is formed in the cross-aldol reaction between 2-aminobenzaldehyde and the ketone, fulfills this role. This proposal is based on their results from the α-alkylation of ketones with primary alcohols as shown in Figure 1.37 on page 18. Although we do not dispute that this may also be the case for the modified Friedlander reaction, our findings suggest that also a second mechanism may be at work here.

The analysis of the reaction samples by gas chromatography revealed that the chromatograms did not only show unreacted starting products 2-aminobenzylalcohol and ketone in addition to the produced quinoline, but also an unexpected new peak. In many cases this peak partially or completely overlapped with the ketone peak. An example of a chromatogram with separated peaks, is shown in Figure 2.17. The new peak was identified as the corresponding alcohol of the ketone which is the result of hydrogenation of the ketone by the $[RuH_2]$ complex, resulting in the regeneration of the catalyst. We believe that it is exactly for this reason, that two equivalents of ketone give the best results to perform the reaction. One equivalent is consumed in the reaction and the other equivalent act as a hydrogen acceptor for the regeneration of the catalyst. Reports from other researchers did not mention this peak, nor did they mention the presence of the alcohol. The function of the ketone as hydrogen acceptor is described by us for the first time.[249]

The use of other hydrogen acceptors was examined by using only one equivalent of the ketone 2-methylacetophenone versus 2-aminobenzylalcohol, instead of two equivalents. Table 2.7 presents the quinoline yields. With 1 equivalent of benzophenone, a quinoline yield of 91% is achieved after one hour. Compared to the reaction with two equivalents of ketone, this yield is somewhat lower. This can be explained by the fact that the reaction proceeds faster with two equivalents of the ketone reagent. Also a difference in hydrogen acceptor capability may play a role, since this hydrogen transfer is an equilibrium reaction. Increasing the amount of benzophenone to 2 equivalents, is slightly counterproductive. Another common hydrogen acceptor, 1-dodecene, was less effective, even at two equivalents. The use of nitrobenzene as hydrogen scavenger has been described by some authors,[250] but this resulted in unwanted side-products and no quinoline.

When the reaction is carried out without hydrogen acceptor, a maximum yield of 71% is achieved. The ketone peak has completely disappeared on the GC chro-

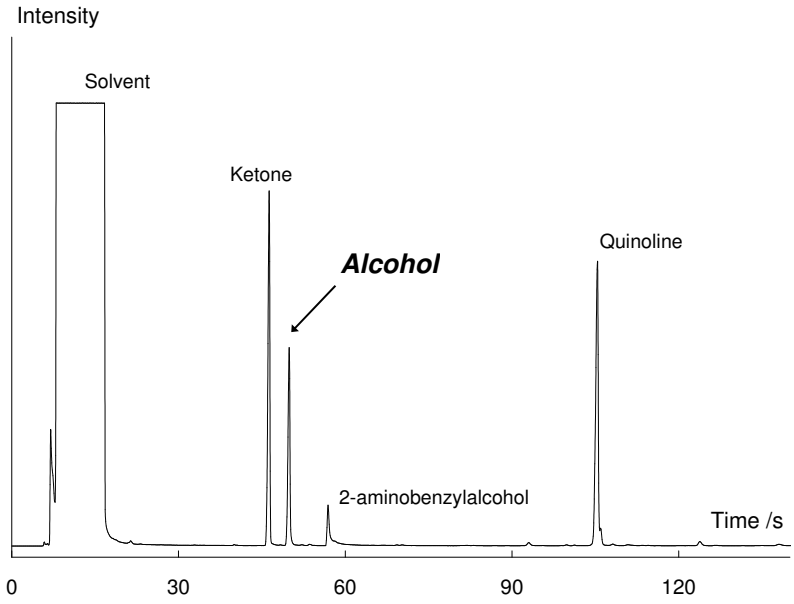


Figure 2.17: Chromatogram of a typical reaction mixture.

Table 2.7: Effect of a hydrogen acceptor on quinoline synthesis[a]

Entry	Additive	Quantity	Yield[b] (%)
1	Benzophenone	1 mmol	91 (100)
2	Benzophenone	2 mmol	83 (100)
3	1-Dodecene	1 mmol	52
4	1-Dodecene	2 mmol	72
5	Nitrobenzene	1 mmol	0[c]
6	Nitrobenzene	2 mmol	0[c]
7	none		51 (71)

[a] Reaction conditions: 2-aminobenzylalcohol (1.0 mmol), 2-methylacetophenone (1.0 mmol), **1** (0.01 mmol) and KOH (1.0 mmol) in dioxane (3 mL) at 80 °C for 1 h. Yields based on 2-aminobenzylalcohol and determined by GC.
[b] The value of the maximum yield, achieved after 90 minutes, is indicated in parentheses.
[c] No quinoline was formed, but the GC chromatogram showed many other unidentified compounds

matogram and a new peak of the alcohol has appeared, accounting for approximately 0.30 mmol. This is, however, in contradiction with the previous statement of catalyst regeneration by the ketone, as with a 1:1 ratio, 0.50 mmol of the alcohol and a maximum quinoline yield of only 50% is to be expected. This means that there must be an alternative pathway that allows for catalyst regeneration. Probably two mechanisms allow the catalyst to be regenerated: one mechanism involves the ketone, the other may involve the hydrogenation of the unsaturated ketone as proposed by Cho.

2.7 Reaction mechanism

2.7.1 General reaction scheme

A plausible reaction mechanism for the modified Friedlander synthesis is presented in Figure 2.18. First, in step (a), 2-aminobenzylalcohol **A** is oxidized

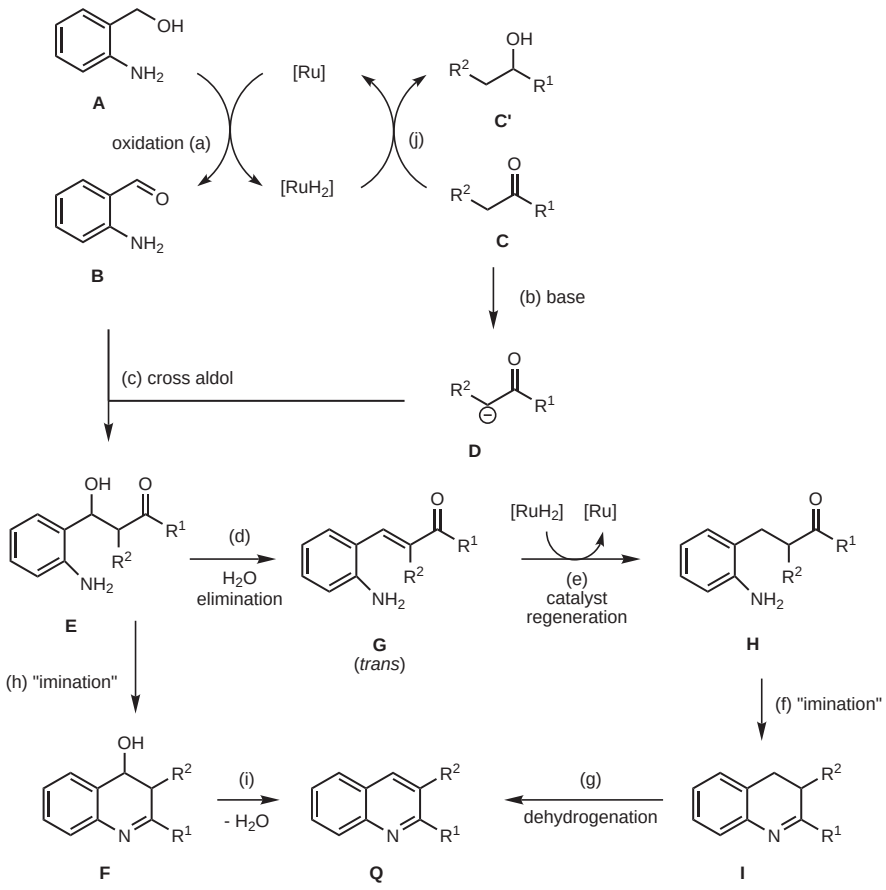


Figure 2.18: Proposed reaction mechanism.

to 2-aminobenzaldehyde **B** by the ruthenium catalyst that is hydrogenated to a hydrido-ruthenium complex. Step (j) shows how the catalyst is regenerated by a hydrogen transfer reaction in which the ketone **C** is reduced to the corresponding alcohol **C'**. This role can also be fulfilled by another hydrogen acceptor, e.g. benzophenone. Under basic conditions, the aldehyde **B** and the ketone **D** undergo a cross aldol reaction. Cho proposed that the α,β-unsaturated ketone **G** is formed immediately,[112] but this transition actually proceeds through the intermediate **E** which undergoes H_2O elimination in the formation of **G**. We believe that this intermediate **E** actually plays a very important role in the reaction mechanism. As shown in step (h), the aldol product **E** can cyclize via imine condensation ("imination") and a subsequent H_2O elimination in step (i) leads to the quinoline. This represents an alternative pathway in the formation of quinolines.
In the original pathway proposed by Cho, shown in steps (d) - (g), a base catalyzed H_2O elimination of **E** results in the *trans* enone **G**. The *cis* product is not likely to be formed due to steric hindrance. Compound **G** is then hydrogenated by a $[RuH_2]$ species. Imine condensation and subsequent dehydrogenation lead to the desired quinoline **Q**. Thus, the reaction most likely consists of two distinctively different pathways. The first can explain why the ketone is partially reduced to the corresponding alcohol, and the second explains why not *all* of the ketone is reduced.
Proof that the conversion of **G** to **H** occurs, is found when benzylalcohol is reacted with acetophenone in dioxane in the presence of **1** and KOH (Figure 2.19). Instead

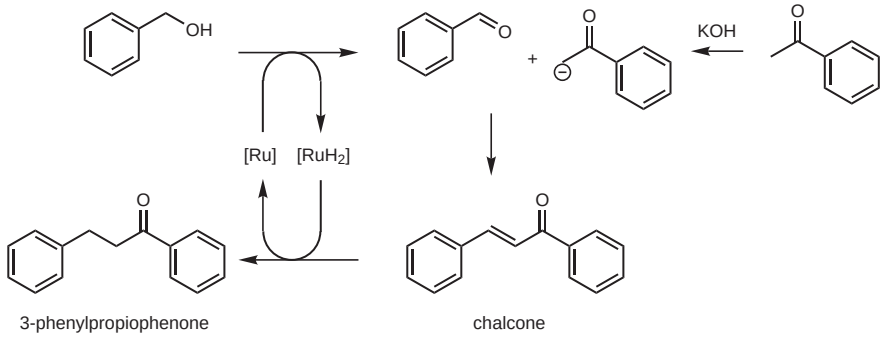


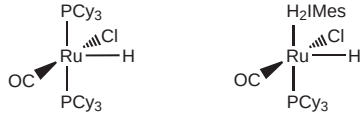
Figure 2.19: Ru-catalyzed coupling between benzylalcohol and acetophenone.

of the expected chalcone, 3-phenylpropiophenone is formed, which means that the double bond of chalcone is hydrogenated by the $[RuH_2]$ complex, regenerating the catalyst in the process. Similar coupling reactions have been performed by Cho et al. and it were in fact these findings that led them to the modified Friedlander method (see paragraph 1.4). Also, the results of these coupling reactions can explain their proposed reaction mechanism for the Friedlander method and why they never investigated other possibilities. With our results, we have now proposed a more complete reaction mechanism describing two possible pathways towards quinolines.
As a note aside, one could argue that also the oxidation of methanol to formalde-

hyde could be the reason of the reduction of the ketone. When the reaction is carried out with KOH powder in the absence of methanol, the alcohol **C'** is still formed, albeit in slightly smaller quantities. This means that methanol oxidation certainly contributes to the formation of **C'**, but not exclusively and not to a major extent.
Theoretically, the order of steps (a) and (f) could be reversed, i.e. first a condensation reaction between the amine and the ketone to form an imine, followed by the catalytic oxidation and cross aldol reaction. This is, however, not observed. The reaction of 2-aminobenzylalcohol with acetophenone in basic media did not lead to imines. To exclude the possibility of ruthenium-catalyzed imine formation, aniline was reacted with acetophenone in the presence of **1** under standard reaction conditions used for the experiments, but again, no imines were formed. The interested reader can find an excellent article by Muchowski and Maddox, dealing with the mechanism of the Friedlander synthesis.[56]

2.7.2 Reaction mechanism concerning the catalyst

The examination of the catalytic ruthenium species was extremely difficult, and, at this point, only suggestions and "educated guesses" can be made. We attempted an NMR study to elucidate the mechanism concerning the catalyst but due to the very complex nature of the reaction mixture, only little information could be obtained.
It is observed that, when KOH is added to the reaction mixture of 2-aminobenzylalcohol, ketone and **1** or **2** in dioxane, the color of the solution turns from pink to brown/black. This color change does not occur in the absence of a catalyst, so it can be assigned to chemical changes involving the catalyst. The effect of the base was tested by adding KOH (in MeOH) to a solution of **1** in deuterated dioxane. The reaction mixture immediately turned from pink to green/yellow and continued to darken to brown over time. The original signal of **1** in ^{31}P-NMR at 36.9 ppm disappeared and new peaks showed up at 9.6 (free PCy_3) and 46.9 ppm (oxidized PCy_3), amongst others. In the ^{1}H-NMR spectrum, the carbene proton at 19.80 ppm slowly disappeared and hydride peaks at -16.4 and -23.1 ppm showed up. The ^{13}C-NMR spectrum reveals a new peak at 204 ppm. All these results are in agreement with a report by Mol who studied the degradation of **1** with primary alcohols,[251–253] and they point in the direction of the formation of a new ruthenium species **26** shown in Figure 2.20. However, this is certainly not the only complex



26 **27**

Figure 2.20: Ruthenium hydride complexes obtained from **1** and **2**.

that is formed, as can be deduced from the presence of several other peaks in the

^{31}P-NMR spectrum. The same kind of observations were made for **2** and complex **27**.
Via an alternative procedure, both **26** and **27** were synthesized by Mol[251–253] and comparison of their spectroscopic data confirmed that these complexes are formed from **1** and **2** respectively in reaction with primary alcohols in the presence of a base.
We have also synthesized these complexes and they were isolated as a yellow powder. They were highly sensitive to air and moisture. Even in a sealed vial under argon atmosphere, they turned from yellow to brown and eventually black in a matter of hours. When these complexes were used for quinoline synthesis, their color immediately changed from yellow to dark brown upon addition of dioxane. The results in Table 2.8 show that nearly identical yields are obtained for **1** and **2** and their corresponding hydride complexes **26** and **27**.

Table 2.8: Synthesis of quinolines with hydride complexes[a]

Complex	Yield (%)
1	45.5
26	48.9
2	95.4
27	94.4

[a] Reaction conditions: 2-aminobenzylalcohol (1.0 mmol), acetophenone (2.0 mmol), KOH (1.0 mmol) and catalyst (0.01 mmol) in 3 mL dioxane, 80 °C for 30 min. Yields based on 2-aminobenzylalcohol and determined by GC analysis.

Thus, it can be concluded that **1** and **2** are merely the pre-catalysts that are converted to the real active species during the reaction. The nature of the active catalyst is still unclear, although it is likely that a hydride complex such as **26** or **27** is an intermediate in the hydrogen transfer reaction, as it was shown that they are both able to catalyze the synthesis of quinolines and nearly identical yields were obtained in comparison with their parent complexes.
The reactions with KOtBu show a different behaviour. When KOtBu is added to the reaction mixture containing **1** or **2**, the color changes from pink to deep red. This is in accordance with the formation of tert-butoxy complexes reported by Grubbs (see Figure 2.14) as these complexes were described to be red.[244,248] Exactly how these complexes mediate the hydrogen transfer is still uncertain.

2.8 Synthesis of 3-substituted quinolines

2.8.1 Introduction

Thus far, only ketones have been reacted with 2-aminobenzylalcohol, affording 2-substituted or 2,3-disubstituted quinolines. When an aldehyde is used instead of a ketone, the formation of 3-substituted quinolines can be expected, as shown in Figure 2.21. It was found however, that under the standard reaction conditions used

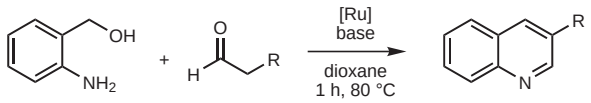


Figure 2.21: Theoretical formation of 3-substituted quinolines.

for ketones, little or no quinolines were formed from the reaction with aldehydes. The chromatograms (for an example see Figure 2.22) showed many unidentified peaks and no quinolines could be isolated by the acidic/basic extraction as described in paragraph 2.2.5. It is believed that the aldehyde is rapidly consumed in a self-aldol reaction, before it is able to react with 2-aminobenzylalcohol. This assumption is supported by the fact that the same peaks appear when only the aldehyde is reacted in the presence of a base. This would also explain why the peak of 2-aminobenzylalcohol is still quite large as there is no more free aldehyde available to react with. Longer reaction times did not affect the size of the observed peaks in the chromatogram very much.

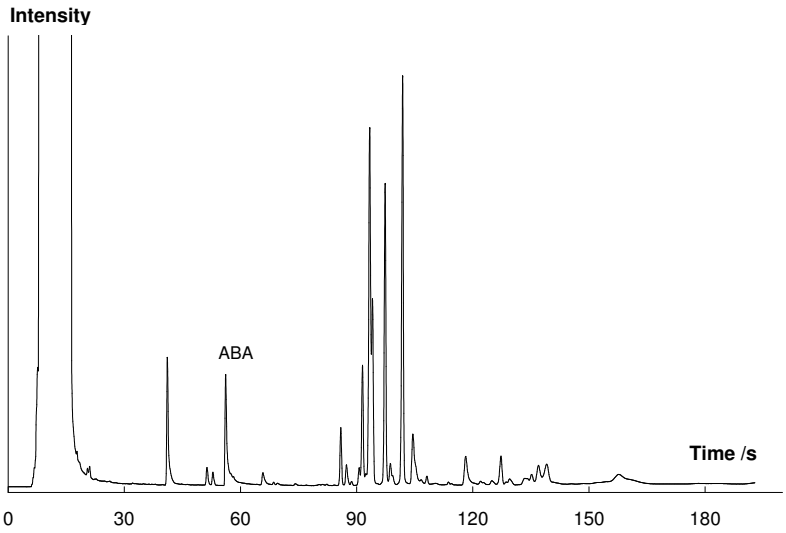


Figure 2.22: Chromatogram of the reaction with the aldehyde octanal. ABA = 2-aminobenzylalcohol.

Almost immediately after our initial attempts, Cho and Shim published a procedure for the synthesis of 3-substituted quinolines. They also found that a one-pot reaction resulted in very low quinoline yields ($\approx 20\%$), even after a prolonged reaction time of 20 hours.[254] However, a step-by-step procedure with an initial treatment of 2-aminobenzylalcohol in the presence of $RuCl_2(PPh_3)_3$ and KOH in dioxane at

80 °C for 15 hours, followed by the addition of the aldehyde and stirring for 5 hours at 80 °C, resulted in higher yields (≈ 50-60%). The addition of a hydrogen acceptor did not affect the yield. In later reports, they have also used a Cu(II) and a Pd(0) catalyzed protocol for the synthesis of 3-substituted quinolines.[107,109] This procedure of Cho was probably based on the work of Kaneda et al. who first reacted 2-aminobenzylalcohol with a ruthenium-grafted hydrotalcite in toluene in an oxygen atmosphere (1 atm) at 100 °C for 10 h. Then the aldehyde was added and allowed to react for 12 h at 100 °C.[110]
This method has some disadvantages as long reaction times are required in both steps and only moderate quinoline yields are obtained. A frequently formed side-product 2-alkyl-2,4-dihydro-1*H*-benzo[*d*][1,3]oxazine (Figure 2.23) complicates the isolation of the desired quinoline.

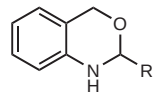


Figure 2.23: 2-alkyl-2,4-dihydro-1*H*-benzo[*d*][1,3]oxazine

2.8.2 Development of a new method for the synthesis of 3-substituted quinolines

When we attempted to prepare 3-substituted quinolines by the method of Cho, i.e. reacting 2-aminobenzylalcohol in the presence of a a ruthenium catalyst for 15 hours, followed by addition of the aldehyde, with **1** or **2** in combination with KOH or KOtBu, again, very complex chromatograms comparable to that of Figure 2.22 were obtained and no pure quinoline could be isolated, neither by acidic/basic extraction, nor by column chromatography. The same self-aldol products were seen by GC analysis.
To suppress the self-aldol reaction of the aldehyde, it was added slowly - every 15 minutes - in ten small portions of 0.20 mmol to a solution of 2-aminobenzylalcohol, **2** and KOtBu in dioxane. Before each addition, a sample was taken from the reaction mixture and analyzed by GC. After the last addition, the solution was allowed to react for an additional hour. It is observed that the peak of 2-aminobenzylalcohol slowly disappears and that a new peak appears which could be assigned to the 3-substituted quinoline. Isolation of this quinoline by acidic/basic extraction and characterization by ^{1}H and ^{13}C-NMR confirmed its structure. Also peaks of self-aldol reactions are seen, but they are much smaller then in the one-pot reactions. In addition to the quinoline peak, another peak appeared at a slightly higher retention time. The compound corresponding to this peak was later identified as the 2-alkyl-2,4-dihydro-1*H*-benzo[d][1,3]oxazine (see Figure 2.23) from the reaction between 2-aminobenzylalcohol and the aldehyde. During the additions of the aldehyde, this peak increases in size. After the last addition it slowly disappears again while the quinoline peak continues to increase. This strongly suggests that first the oxazine is formed and then converted to the quinoline. Exactly how this oxazine is formed

and transformed to the quinoline will be detailed in the discussion on the reaction mechanism in paragraph 2.8.4.
To verify this hypothesis, first 2-aminobenzylalcohol was reacted with two equivalents of octanal. Analysis by GC confirms that 2-aminobenzylalcohol quantitatively reacts with the aldehyde to give the oxazine. The extra equivalent of the aldehyde will act as hydrogen acceptor in the oxidative cyclocondensation reaction of the oxazine. Subsequently, **2** and KOtBu were added. Analysis of the reaction mixture by GC indeed confirmed that the initial oxazine is converted into the quinoline. The reaction is shown in Figure 2.24.

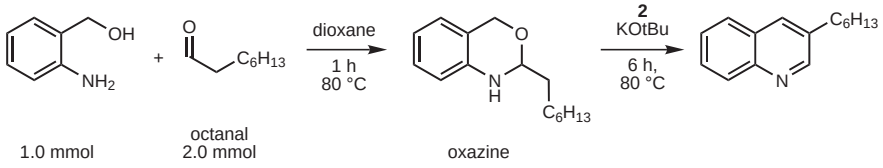


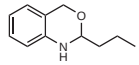
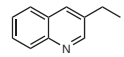
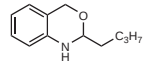
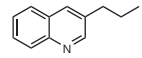
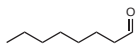
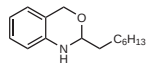
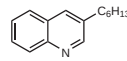
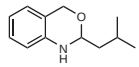
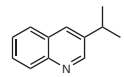
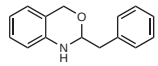
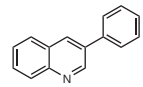
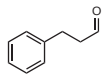
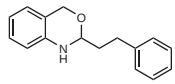
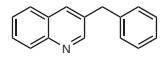
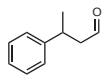
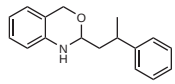
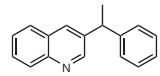
Figure 2.24: Two-step synthesis of 3-substituted quinoline from octanal

The reaction was performed with a variety of aldehydes and the results are presented in Table 2.9. All yields were determined with dodecane as internal standard after one hour of reaction (after preliminary oxazine formation). From these results, it is clear that only relatively low quinoline yields are obtained. Several samples show the presence of 2-aminobenzylalcohol, even though it was originally completely consumed in the oxazine formation. This is an indication that the oxazine decomposes again which may be caused by water in the reaction mixture. Besides this oxazine decomposition, self-aldol peaks of the aldehydes are present. This self-aldol reaction lowers the amount of aldehyde that functions as necessary hydrogen acceptor, limiting the maximum yield in consequence.

2.8.3 Optimization of the reaction parameters

An optimization process was carried out and the most important results are presented in Table 2.10. 3-Phenylpropionaldehyde was used as the aldehyde and the reported yields were determined after 1 hour of reaction.
To eliminate the presence of water, several reactions were performed with molecular sieves in the reaction mixture (entries 1-3). Entry 1 again illustrates the importance of a sacrificial hydrogen acceptor. With a 1:1 ratio of 2-aminobenzylalcohol and the aldehyde, only 15% quinolines are formed because of the absence of a hydrogen acceptor. An additional equivalent of aldehyde can fullfill this function (entry 2), but the aldehyde is prone to self-condesation reactions which limits its applicability. The best option is to add an “inert” hydrogen acceptor that does not undergo self-aldol reactions nor cross-aldol reactions with the aldehyde. Benzophenone is a good candidate for this role as the chromatogram of entry 3 does not show significant amounts of side-products. This is also reflected in the higher yield (44% versus 31%).
Further experiments (entries 4-7) show variations in the amount of KOtBu and

Table 2.9: Synthesis of 3-substituted quinolines[a]

Aldehyde	Oxazine		Quinoline		Yield (%)
		**O1**		**Q17**	47
		**O2**		**Q18**	42
		**O3**		**Q19**	26
		**O4**		**Q20**	50
		**O5**		**Q21**	43
		**O6**		**Q22**	42
		**O7**		**Q23**	31

[a] Reaction conditions: i) 2-aminobenzylalcohol (1.0 mmol) and aldehyde (2.0 mmol) in 3 mL dioxane, 80 °C for 1 h; ii) **2** (0.01 mmol) and KOtBu (1.5 mmol), 80 °C for 1 h. Yields determined by GC analysis with dodecane as internal standard.

benzophenone. It is clear from entry 5 with the same conditions as used in entry 3, that the use of molecular sieves to absorb water does not increase the yield. Apparently, the presence of water is not a major issue, but rather the self-aldol reaction of the aldehyde poses the biggest problem. Higher amounts of base and benzophenone hinder the reaction, as seen in entries 6 and 7. The best results are obtained with an equimolar ratio of all reactants, but longer reaction times than 1 hour will be required to obtain higher yields. The reaction proceeds much slower when KOH is used instead of KOtBu.

Figure 2.25 nicely shows the progress of the reaction with butanal as the aldehyde. First 2-aminobenzylalcohol reacts with the aldehyde to form the oxazine. The graph shows that this reaction is already complete within 30 minutes. Other aldehydes, especially those with aromatic rings react a little slower and require approximately 60 minutes to fully react with the amine. After the addition of the catalyst, base and hydrogen acceptor, the oxazine is converted to the quinoline. This second reaction proceeds very fast in the first 30-45 minutes and then continues at a slower rate. It is assumed that KOtBu is partially decomposed to KOH and tert-butanol by the water that is formed during the cyclocondensation of the oxazine. With the weaker base KOH the reaction still continues, but at a slower

Table 2.10: Optimization process for the synthesis of 3-substituted quinolines[a]

		Molar ratio (mmol)				
Entry	Sieves	ABA[b]	Aldehyde[c]	KOtBu	BP[d]	Yield (%)
1	+	1	1	2	0	15
2	+	1	2	2	0	31
3	+	1	1	2	1	44
4	-	1	1	1	1	66
5	-	1	1	2	1	46
6	-	1	1	2	1.5	44
7	-	1	1	3	1.5	40
8	-	1	1	KOH, 2	1	6

[a] Reaction conditions: i) 2-aminobenzylalcohol and 3-phenylpropionaldehyde in 3 mL dioxane, 80 °C for 1 h; ii) **2** (0.01 mmol), KOtBu or KOH and benzophenone, 80 °C for 1 h. Yields determined by GC analysis with dodecane as internal standard.
[b] ABA = 2-aminobenzylalcohol
[c] 3-phenylpropionaldehyde
[d] BP = benzophenone

rate as was previously shown in Table 2.10, entry 8. This is confirmed when slightly higher amounts of KOtBu (1.2 equivalents) and benzophenone (1.1 equivalents) are used. The reaction is now complete within 2 hours as is illustrated by curves 2' and 3'. The general reaction scheme with optimized conditions is shown in Figure 2.26.
With these optimized reaction conditions, the same reactions with the various aldehydes were carried out again. Table 2.11 presents the results. Good to excellent yields are obtained for all 3-substituted quinolines after 3 hours of reaction. The chromatograms of the aromatic aldehydes (entries 5-7) still show some unreacted oxazine, but longer reaction times did not increase the yields.

2.8.4 Reaction mechanism

The proposed reaction mechanism is shown in Figure 2.27. The reaction between 2-aminobenzylalcohol and the aldehyde does not give imines, as one might expect at first sight. Instead a 1,3-oxazine is formed. This oxazine can not cyclize to a quinoline by itself, however, it is at equilibrium with the imine. This ring-chain tautomerism has been well studied and described by others.[255–262] From the NMR spectra, it can be concluded that the equilibrium for the described compounds is shifted to the side of the oxazine since no peaks of imine hydrogens or imine carbons could be seen. Raman spectroscopy shows a very small band at 1610 which might be attributed to a C=N stretch vibration. This means that only very small amounts of imine are present in the reaction mixture, but naturally, when the

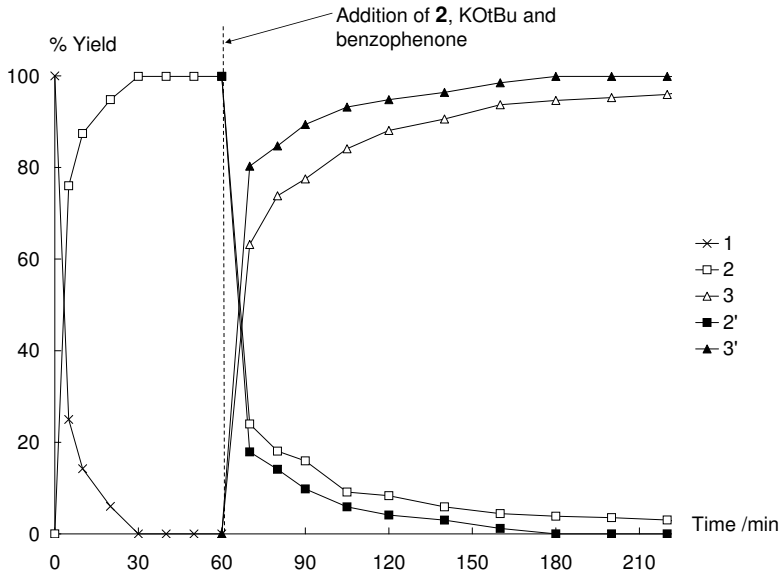


Figure 2.25: Progress of the reaction steps in the synthesis of 3-substituted quinolines. 1 = 2-aminobenzylalcohol, 2/2' = oxazine, 3/3' = 3-substituted quinoline. Curves 2 and 3 represent the reaction with equimolar amounts of reactants, while in 2' and 3' a slight excess of KOtBu and benzophenone is used.

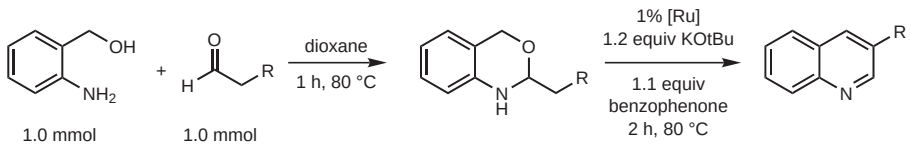
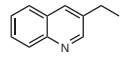
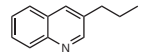
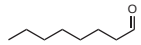
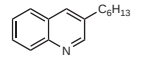
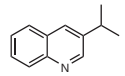
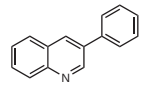
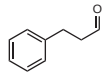
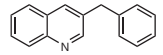
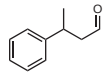
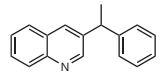


Figure 2.26: Optimized reaction scheme for the synthesis of 3-substituted quinolines

imine is consumed in the cyclization reaction, the equilibrium is reinstated, effectively driving the reaction to completion.
The benzylic alcohol function of the imine is then catalytically oxidized to a benzaldehyde function. The ruthenium hydride species that is generated in this oxidation process, is regenerated by benzophenone as hydrogen scavenger. A strong base abstracts an α-proton of the imine and in the final cyclization step, the quinoline is formed. It should be noted that the sequence of the oxidation and the proton abstraction steps might be interchangeable.

Table 2.11: Synthesis of 3-substituted quinolines[a]

Entry	Aldehyde	Quinoline		Yield (%)
1			**Q17**	94
2			**Q18**	95
3			**Q19**	>99
4			**Q20**	>99
5			**Q21**	84
6			**Q22**	85
7			**Q23**	71

[a] Reaction conditions: i) 2-aminobenzylalcohol (1.0 mmol) and aldehyde (1.0 mmol) in 3 mL dioxane, 80 °C for 1 h; ii) **2** (0.01 mmol), KOtBu (1.2 mmol) and benzophenone (1.1 mmol), 80 °C for 2 h. Yields determined by GC analysis with dodecane as internal standard.

2.9 Conclusions on Ru-catalyzed quinoline synthesis

Substituted quinolines are important compounds in medicinal chemistry. The ruthenium-catalyzed modification presents an attractive alternative for the classical Friedlander method. The handling of unstable aminobenzaldehydes is avoided as they are generated in situ in a catalytic hydrogen transfer reaction from the oxidation of 2-aminobenzylalcohol. Several ruthenium catalysts were tested for this reaction and it was found that the occupation of the ligand sphere around the ruthenium center plays a very important role. The incorporation of N,O-bidentate ligands was ineffective, while strong σ-donating phosphine or NHC ligands had a beneficial effect on the rate of conversion. The second generation Grubbs catalyst **2** gives the highest quinoline yields in the shortest amount of time.
Besides the catalyst, also the base plays an important role. Traditionally KOH is used, but we have shown that the stronger base KOtBu greatly increases the reaction rate. The presence of a hydrogen acceptor is required to obtain good quinoline yields and to allow for the regeneration of the hydrogenated catalyst. A second equivalent of the ketone reactant conveniently fulfills this role, although

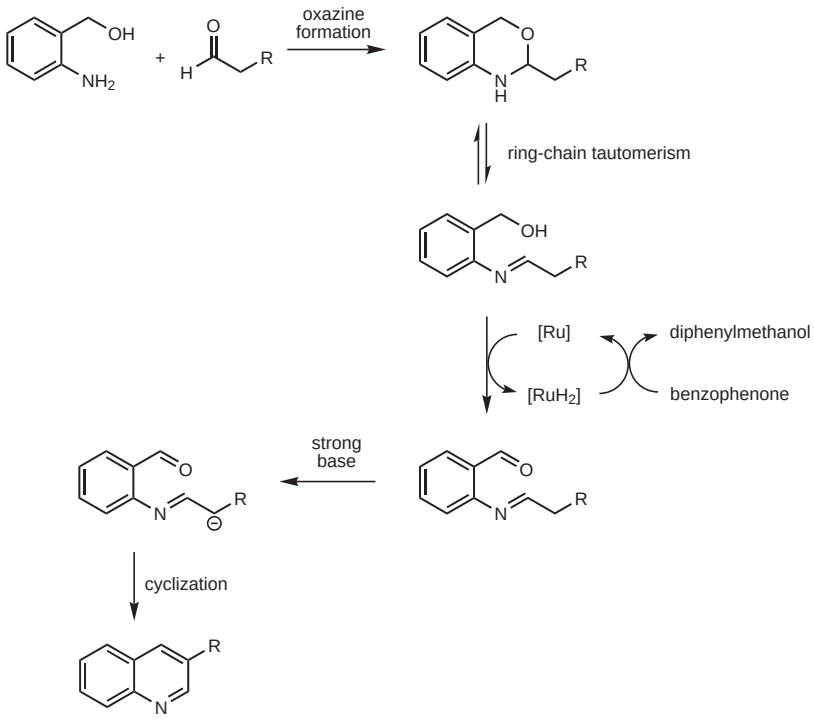


Figure 2.27: Proposed reaction mechanism for the synthesis of 3-substituted quinolines

other hydrogen acceptors such as benzophenone can also be used. Removing gases from the solvent by flushing it with argon gas enhances the reaction rate.
Based on the experimental results, a reaction mechanism that consists of two distinctively different pathways is proposed. The exact nature of the catalytic species could not be determined, but the results in combination with literature data point in the direction of a ruthenium-carbonyl-hydride complex.
A new and convenient two-step alternative to the cumbersome synthesis of 3-substituted quinolines from aldehydes was developed. First a 1,3-oxazine is formed from the reaction between 2-aminobenzylalcohol and the aldehyde. The subsequent addition of a ruthenium catalyst, a strong base and a hydrogen acceptor affords the 3-substituted quinolines in good to excellent yields.

3

Base-mediated synthesis of quinolines

3.1 Introduction

Of all the ruthenium catalysts that were examined for the modified Friedlander method, the second generation Grubbs catalyst **2** gave the highest quinoline yields in the shortest amount of time. Some major drawbacks of this catalyst are its high price and the time consuming synthesis of the NHC ligand H_2IMes. The use of KOtBu instead of KOH improved the reaction rate with a factor 3 (60 minutes for KOH versus 20 minutes for KOtBu, Figure 2.15). Catalysts of the type $RuCl_2(PR_3)$(p-cymene) such as **11a** and **11b** are cheaper and more easily accessible. If the use of KOtBu with these catalysts would reduce the reaction time, in a similar fashion as with **2**, from 5 or 6 hours to 2 hours or less, perhaps an economically more viable catalytic system would be created. When this was tested, surprisingly, conversions and reaction rates comparable to those of **2** were achieved (Figure 3.1). At first, this was attributed to the formation of a similar active catalyst from complexation of **11a,b** with KOtBu as was suggested for **2** (Figure 2.14). It was believed that two chlorine ligands were exchanged for tert-butoxy ligands as shown in Figure 3.2. However, when we tried to synthesize **28** from the reaction of **11a,b** or **3** with KOtBu, only decomposed products were obtained. Furthermore, a blank experiment (Table 2.1, entry 2) showed that a quinoline yield of 9% was achieved with KOH in the absence of a catalyst. This implies that the synthesis of quinolines can be mediated solely by a base. This is confirmed when the reaction is executed with only KOtBu and no catalyst (Figure 3.1, dotted line). Without catalyst, a conversion of only 60% is achieved after 30 minutes, while the ruthenium catalyzed reactions reach full conversion. This means that the presence of ruthenium certainly enhances the reaction rate, but it is not a mandatory requirement to perform the reaction. As the next set of results will show, a higher amount of base results in higher conversions. Likely, some amount

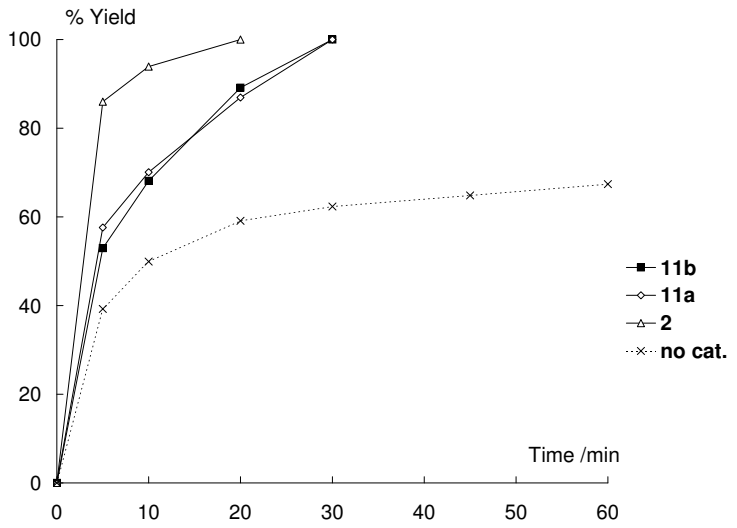


Figure 3.1: Quinoline synthesis with **11a,b** and KOtBu. Reaction conditions: 2-aminobenzylalcohol (1.0 mmol), acetophenone (2.0 mmol), catalyst (0.01 mmol) and KOtBu (1.0 mmol) in dioxane (3 mL) at 80 °C for 1 h. Yields determined by GC with dodecane as internal standard.

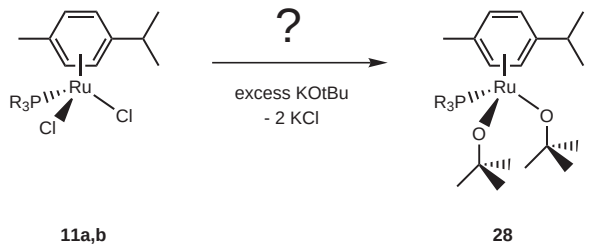


Figure 3.2: Initially suggested active catalyst for **11a,b** with KOtBu.

of base is consumed in another step of the reaction, e.g. the base catalyzed H_2O elimination. In this step, the hydroxy ion OH^- is released, which is a weaker base than KOtBu. This would also explain why the reaction still continues after 30 minutes, but at a much slower rate. These hypotheses will be explored in more depth in the discussion on the reaction mechanism in paragraph 3.3.

3.2 Synthesis of quinolines from ketones

The performance of several bases was examined for the reaction between 2-aminobenzylalcohol and acetophenone. The results are shown in Figure 3.3. The highest

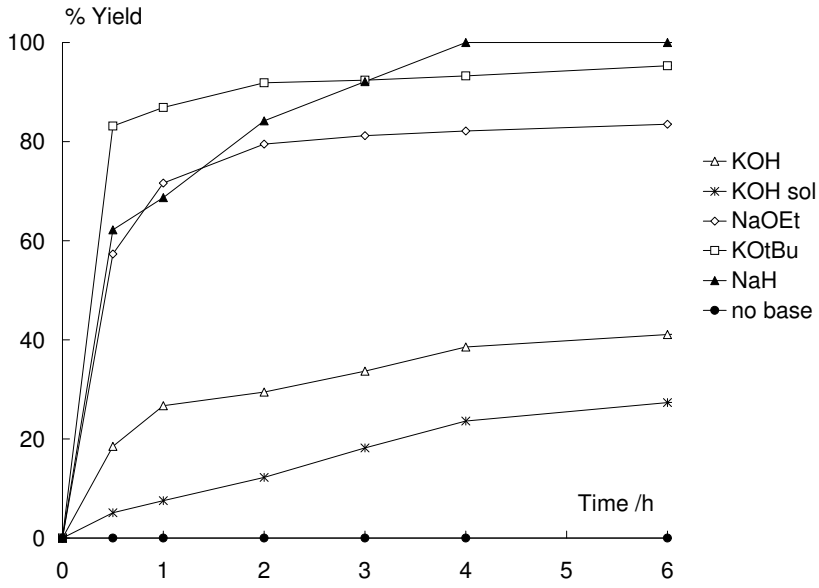
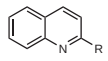
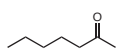
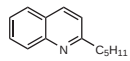
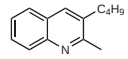
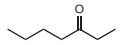
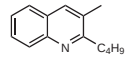
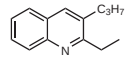
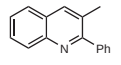
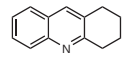


Figure 3.3: Base-mediated quinoline synthesis. Reaction conditions: 2-aminobenzylalcohol (1.0 mmol), acetophenone (2.0 mmol) and base (1.5 mmol) in dioxane (3 mL) at 80 °C. Yields determined by GC with dodecane as internal standard.
KOH sol = KOH as a 4 M solution in MeOH.

quinoline yields are obtained with the stronger bases KOtBu, NaH and NaOEt. The reaction does not proceed in the absence of a base. It is remarkable that, contrary to the ruthenium catalyzed process, the reaction proceeds faster with KOH powder than with KOH as a solution in methanol. When NaH was used, the solution started bubbling immediately as a result of evolving hydrogen gas and the reaction vials were only placed at 80 °C when all bubbling had ceased.
The reaction was carried out with a variety of ketone substrates in the presence of the bases KOtBu, NaOEt or NaH. The results after one hour of reaction are presented in Table 3.1. It is clear that the highest quinoline yields are obtained with KOtBu. Although Figure 3.3 suggests that NaH gives higher yields after 4 hours, the use of NaH is severely hindered by the evolution of hydrogen gas, making this base very impractical.
The presence of a substituent on the aromatic ring of acetophenone results in lower yields (entries 2-6), but whereas the 2', 3', and 4' methyl-substituted compounds

Table 3.1: Base-mediated quinoline synthesis from a variety of ketone substrates[a]

Entry	Ketone	Quinoline		Yield (%) KOtBu	NaOEt	NaH
						
	R =	R =				
1	Ph	Ph	**Q1**	94	63	64
2	2-MeC_6H_4	2-MeC_6H_4	**Q2**	65	40	58
3	3-MeC_6H_4	3-MeC_6H_4	**Q3**	59	50	53
4	4-MeC_6H_4	4-MeC_6H_4	**Q4**	62	42	34
5	2-$MeOC_6H_4$	2-$MeOC_6H_4$	**Q5**	99	53	60
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**Q6**	47	27	38
7	Me[b]	Me	**Q8**	17	19	22
8			**Q9**	30	23	25
			**Q10**	17	7	6
9			**Q11**	61	19	43
			**Q12**	15	3	7
10			**Q13**	83	39	49
11			**Q14**	51	29	39

[a] Reaction conditions: 2-aminobenzylalcohol (1.0 mmol), ketone (2.0 mmol), catalyst (0.01 mmol) and KOH (1.0 mmol) in dioxane (3 mL) at 80 °C for 1 h. Yields based on 2-aminobenzylalcohol and determined by GC analysis.
[b] 5 mmol.

have comparable yields, the difference between 2' and 4' methoxy-substituted acetophenone is remarkable. With an ortho-substituted ketone the yield is twice as high compared to a para-substituted ketone.
When two different α-protons are available in a ketone, a mixture of two quinolines is obtained (see entries 8 and 9). While the use of KOtBu gives higher yields, the selectivity is lower. For 2-heptanone the ratios are 1.8:1 for KOtBu versus 3.3:1 and 4.2:1 for NaOEt and NaH respectively. A similar effect is observed for 3-heptanone. In comparison to the ruthenium catalyzed reactions, the yields obtained with acetone (entry 7) and 2-heptanone (entry 8) are markedly lower. This is the result of self-condensation of the ketones in a base-catalyzed aldol condensation whereby α,β-unsaturated ketones are formed. The GC chromatogram of 2-heptanone shows

the formation of heptanone dimers and trimers (Figure 3.4 A).

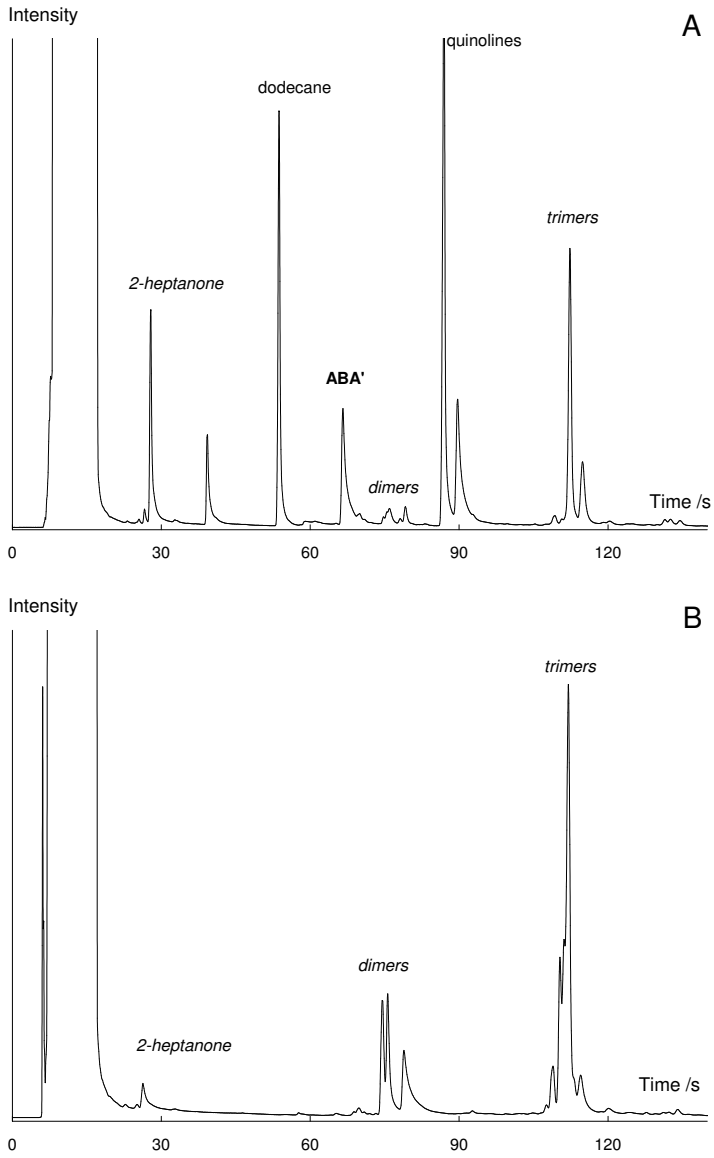


Figure 3.4: A. Quinoline synthesis with 2-heptanone.
B. Reaction of 2-heptanone in the presence of KOtBu.

This is confirmed in a verification experiment where 2-heptanone is reacted in the presence of KOtBu. The same peaks appear in the chromatogram, shown in Figure 3.4 B. Analysis of this mixture with GC-MS shows a molecular weight of 210 and 306 corresponding with respectively the dimers and trimers of 2-heptanone. Each

of those compounds has several isomers, which is also reflected by multiple peaks in the chromatogram.
This self-condensation is much less pronounced with the other ketones, and it is not observed in the ruthenium catalyzed process. Thus, the formation of quinolines is in competition with the aldol reaction. When 2-heptanone is gradually added to a reaction mixture containing 2-aminobenzylalcohol and KOtBu in dioxane, the aldol reaction is suppressed and quinoline yields of 56 and 28% are obtained for 2-pentylquinoline **Q9** and 3-butyl-2-methyl-quinoline **Q10** respectively.
The examination of the chromatograms of this base-mediated process also revealed two other new peaks at approximately 66 and 89 seconds, that were not observed in the ruthenium catalyzed reactions. Both peaks appear in almost all reactions with different ketones and different bases, thus it was supposed that they were intermediate products formed from 2-aminobenzylalcohol. Again, GC-MS analysis offered the solution. The molecular weight of 2-aminobenzylalcohol is 123.15 g mol^{-1}. The compound that eluates after 66 seconds, further referred to as **ABA'** has a molecular weight of 165 (= 123 + 42), and the compound eluating at 89 seconds, further called **ABA"**, has a molecular weight of 207 (= 123 + 42 + 42). The fragmentation patterns of both compounds show an initial mass loss of 43, which is typical for acetyl fragments. Compound **ABA"** subsequently loses another fragment of the same molecular weight. Hence it was deduced that compound **ABA'** was the mono-acylated and **ABA"** the di-acylated product, as shown in Figure 3.5.

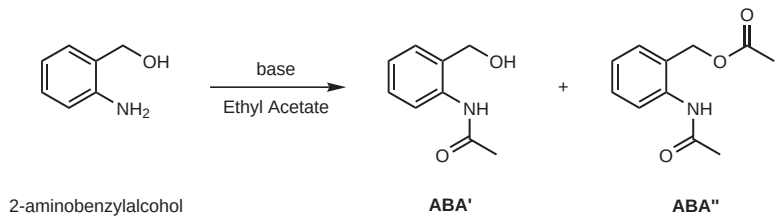


Figure 3.5: Reaction of 2-aminobenzylalcohol with ethyl acetate in the presence of a base.

The initial mystery of the presence of both compounds can actually be explained very easily. In the presence of a base, unreacted 2-aminobenzylalcohol reacts with ethyl acetate that is used as eluent in the purification procedure on a small column. A series of experiments confirms this proposal. When 2-aminobenzylalcohol is stirred for 1 h with KOtBu in dioxane at 80 °C and eluated with ethyl acetate on a small column, both **ABA'** and **ABA"** appear on the chromatogram. When acetone is used as eluent, only the original peak of 2-aminobenzylalcohol is present. Furthermore, when 2-aminobenzylalcohol is reacted with 1 equivalent of ethyl acetate and KOtBu in dioxane, and eluated with acetone, both **ABA'** and **ABA"** show up in the chromatogram. Additionally, compound **ABA"** was synthesized independently by reacting 2-aminobenzylalcohol with 2.2 equivalents of acetyl chloride. The structure was confirmed by ^{1}H and ^{13}C-NMR characterization and the retention time on GC was identical to that of previous measurements. Synthe-

sis and isolation of pure compound **ABA'** was problematic as di-acylation could not be avoided. A procedure to distinguish between O-acylation and N-acylation for ethanolamine has been described,[263] but this procedure did not work for 2-aminobenzylalcohol. Confirmation that **ABA'** is the N-acylated product is given by the fragmentation pattern of the GC-MS spectra. First a mass loss of 43 is observed, then a mass loss of 17, which can only be attributed to the loss of OH. This eliminates the possibility of O-acylation.

3.3 Reaction mechanism

The exact reaction mechanism of this base-mediated process is not yet fully understood, but it certainly involves a hydrogen transfer. The GC chromatograms clearly show conversion of the ketones into the corresponding alcohols during the reaction. It is believed that a mechanism similar to that of Meerwein-Ponndorf-Verley reduction / Oppenauer oxidation (MPVO) may be responsible for this. Purely base-catalyzed MPVO reductions with KOtBu and H_2 have been reported under very demanding reaction conditions with temperatures of 150-200 °C, high H_2 pressures and reaction times of several hours.[264–266]
The amine function of 2-aminobenzylalcohol seems to play an important role, since the reaction of benzylalcohol with ketones did not produce any coupling products. This leads us to propose a reaction mechanism as shown in Figure 3.6. For reasons of clarity, unnecessary atoms have been omitted. One equivalent of ketone **C** acts as hydrogen acceptor and is converted to the corresponding alcohol in the oxidation process of 2-aminobenzylalcohol. A cross aldol reaction between the aldehyde and deprotonated ketone, followed by a cyclization step and H_2O elimination, leads to the quinoline. The proposed intermediate is nearly identical to that of the MPVO reaction, but an additional interaction between the amine and the alkali kation might provide favourable conditions for the hydrogen transfer. This mechanism differs from the one for the ruthenium catalyzed reactions in the way the hydrogens are transferred. With transition metals it is believed that the reaction involves the formation of a metal hydride. For non-transition metal metals, the MPVO-mechanism with a cyclic intermediate is proposed.[153,173]
The reported yields in in Table 3.1 are yields after one hour of reaction. When the yields are measured after two hours, it is seen that they have increased with 5 to 10% for all quinolines and they continue to increase over time. This can be rationalized as follows. Once the initial stronger base is consumed, the reaction continues at a slower rate with OH^-. This hydroxyl anion can be generated in the base catalyzed H_2O-elimination of **E** or by the reaction between the strong base and a H_2O molecule that is liberated in the imine formation. This suggests that this reaction is in fact base-catalyzed.
Further support for this base-catalyzed mechanism is found when 2-aminobenzylalcohol (1.0 mmol) is reacted with acetophenone (2.0 mmol) with only 0.50 mmol KOtBu. After one hour, the yield is 45%, but after 6 hours the yield has increased to 59% which can only mean a base is still present in the reaction mixture. Unfortunately, the basic strength of KOH is too low to make this process truly base-catalyzed, thus equimolar (and preferably higher) amounts of a stronger base are required to obtain good quinoline yields.

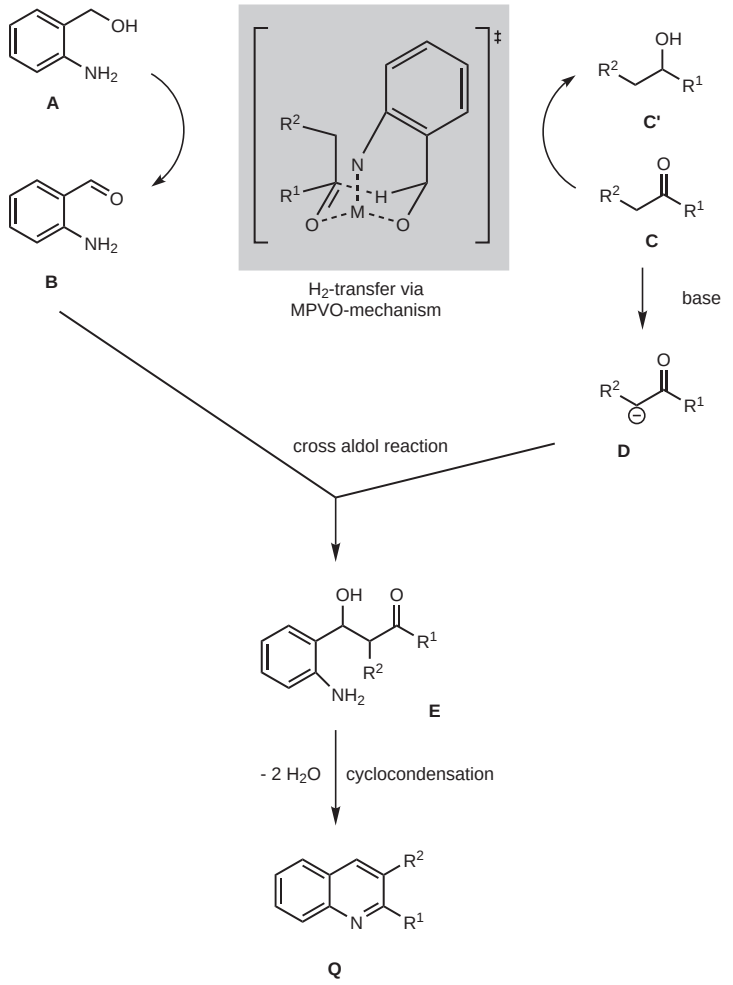
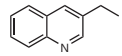
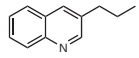
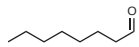
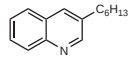
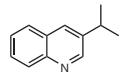
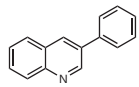
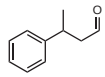
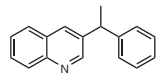
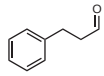
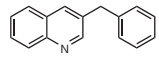


Figure 3.6: Proposed reaction mechanism, based on the MPVO mechanism.

3.4 Synthesis of 3-substituted quinolines

Also the synthesis of 3-substituted quinolines was attempted. After oxazine formation (1 hour at 80 °C), both KOtBu and benzophenone were added to the reaction mixtures and the solution was stirred for 2 hours at 80 °C. The results are presented in Table 3.2 With the exception of **Q21**, higher yields are obtained in the base-mediated process compared to the ruthenium-catalyzed process. Almost all quinolines are formed in nearly quantitative yield.
As to the reaction mechanism, a sequence comparable to that of the ruthenium catalyzed process for 3-substituted quinolines is proposed as shown in Figure 3.7. First 2-aminobenzylalcohol reacts with the aldehyde to afford the oxazine. Via ring-chain

Table 3.2: Base-mediated synthesis of 3-substituted quinolines[a]

Entry	Aldehyde	Quinoline		Yield (%)
1			**Q17**	97
2			**Q18**	>99
3			**Q19**	>99
4			**Q20**	>99
5			**Q21**	78
6			**Q22**	95
7			**Q23**	98

[a] Reaction conditions: i) 2-aminobenzylalcohol (1.0 mmol) and aldehyde (1.0 mmol) in 3 mL dioxane, 80 °C for 1 h; ii) KOtBu (1.2 mmol) and benzophenone (1.1 mmol), 80 °C for 2 h. Yields determined by GC analysis with dodecane as internal standard.

tautomerism, the oxazine is at equilibrium with the corresponding imine. Then the benzylic alcohol of the imine is oxidized and this oxidation reaction most probably follows the MPVO-mechanism with a cyclic intermediate (unnecessary atoms and atomic charges are omitted for reasons of clarity). Abstraction of a proton by a strong base results in an intramolecular aldol condensation and cyclization to the 3-substituted quinoline.

3.5 Conclusions on the base-mediated synthesis of quinolines

A new base-mediated process for the preparation of quinolines was developed in which an expensive transition metal catalyst is no longer required. The best results in terms of quinoline yield were obtained with KOtBu. Other strong bases such as NaOEt also afford quinolines, but they give lower yields. The use of NaH is rather cumbersome because of the evolution of hazardous hydrogen gas.
Also 3-substituted quinolines could be synthesized by this base-mediated process. In a two step reaction, first the 1,3-oxazine is prepared by reaction of 2-aminobenzylalcohol with the aldehyde. In the second step, the addition of a strong

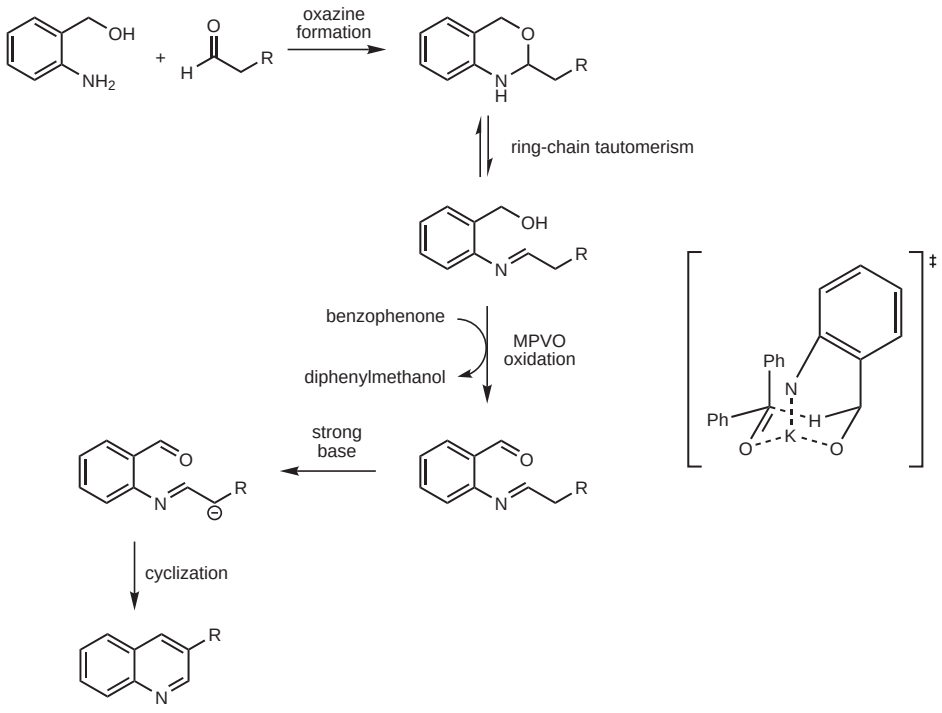


Figure 3.7: Proposed reaction sequence, based on the MPVO mechanism.

base such as KOtBu yields 3-substituted quinolines in nearly quantitative yields. The reaction mechanism probably proceeds via the MPVO-mechanism with a cyclic intermediate in which also the nitrogen of 2-aminobenzylalcohol (or the oxazine/imine) plays an important role.

4

Introduction to enol esters

4.1 Definition

The name *enol esters* is directly derived from the molecular structure of these compounds: they combine an enol function and an ester group, sharing the oxygen atom that both functionalities have in common (Figure 4.1). Enol esters are also commonly referred to as *vinyl esters*.

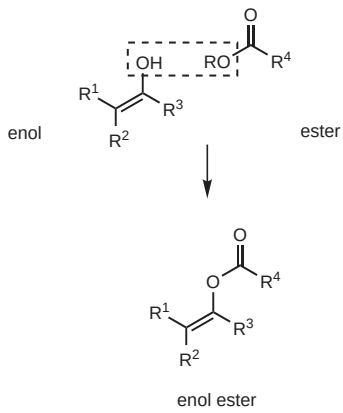


Figure 4.1: The general structure of enol esters.

4.2 Applications of enol esters

Enol esters are very useful reagents for carbon-carbon or carbon-heteroatom bond formations via generation of their enolates. They can be used as acylating agents in reactions that require very mild reaction conditions. Some specific examples of acylation reactions are outlined in Figure 4.2.

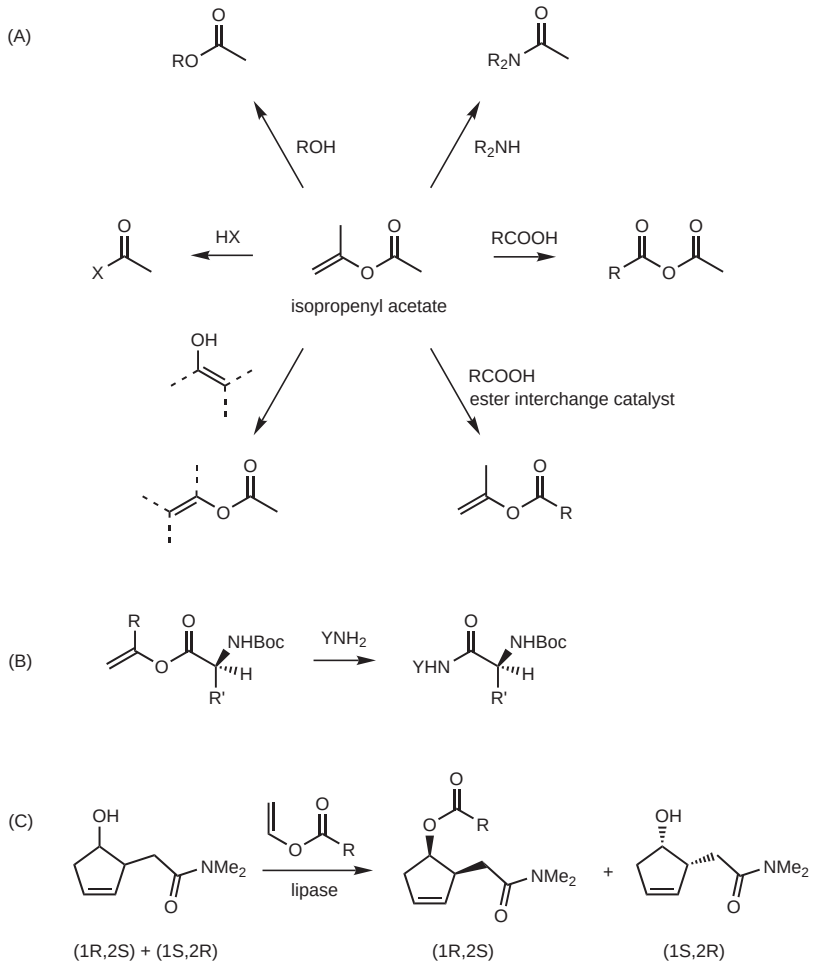


Figure 4.2: Applications of enol esters: examples of acylation.

(A) Isopropenyl acetate is a versatile and unique acylating agent.[267] In the reaction with an enolate, a new enol ester is generated, i.e. a vinyl acetate. Reactions with alcohols, amines, halogen acids and carboxylic acids give esters, amides, acid halides and mixed anhydrides respectively. Applying an ester interchange reagent in the reaction with carboxylic acids results in new isopropenyl esters.

All these reactions are also applicable to other enol esters.[268] Lactones were synthesized by an intramolecular acyltransfer[269] and α-dicarbonyl compounds such as oxamides and oxalates could be prepared from oxalic acid.[270] 1,3-Diketones result from the reaction of carbanions with enol esters.[271]

(B) Dixneuf et al. used enol ester intermediates of amino acids for easy conversion into amides and dipeptides.[5,272] This allowed for a clean and mild acylation, avoiding the use of toxic phosgenes for carboxylic acid activation.

(C) The lipase-catalyzed acylation of racemic alcohols was applied for the resolution of chiral alcohols into their enantiomers with high optical purity. The acyl group performed the function of stereochemical controller.[273,274]

Other uses of enol esters include the conversion into α-halogenated ketones,[275–278] α,β-unsaturated ketones[279,280] or aldehydes[281,282] and the selective acylation of unsymmetrical ketones.[283,284] Enol ester monomers have been used to synthesize polymers bearing tertiary ester functionalities for applications in lithographic films.[285] Exocyclic enol lactones constitute a moiety that is present in several natural products exhibiting biological activity. Examples of these compounds are cyanobacterins,[286] obtusilactones[287–289] and acetoxyfimbrolides[290–292] (Figure 4.3).

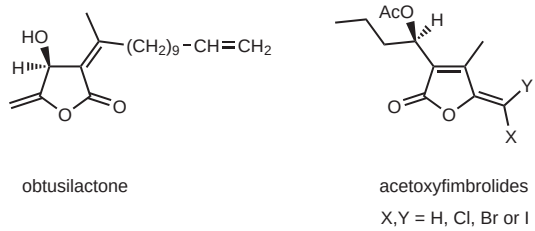


Figure 4.3: Naturally occurring obtusilactones and acetoxyfimbrolides.

Vinyl acetate is a very important industrial compound.[293] It is used as monomer in the synthesis of poly(vinyl acetate), an essential polymer for a range of industrial and consumer products such as paints, concrete additives, adhesives, textiles, and plastics. Hydrolysis of poly(vinyl acetate) leads to the water soluble, biocompatible polymer poly(vinyl alcohol).[294] The production of vinyl acetate monomers was 4.5 million tons worldwide in 2003 and it still increases each year.[295] Figure 4.4 illustrates the described reactions.

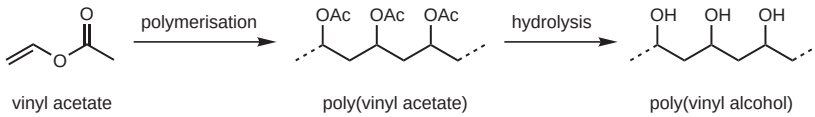


Figure 4.4: Vinyl acetate, poly(vinyl acetate) and poly(vinyl alcohol).

4.3 Synthesis of enol esters

Enol esters can be prepared in several ways. The two most widely practiced techniques involve

- the direct addition of carboxylic acids to alkynes.
- the treatment of enolates from aldehydes or ketones with acid anhydrides, acid halides or ketenes under acidic or basic conditions.

4.3.1 Addition of carboxylic acids to alkynes

The direct addition of carboxylic acids to 1-alkynes is the most efficient route towards enol esters in terms of atom economy, a goal that every chemist strives for.[296,297] Effectively every atom from the starting reagents is accounted for in the enol ester products. The general reaction scheme for this method is presented in Figure 4.5. Essentially three enol ester products can be formed. Markovnikov

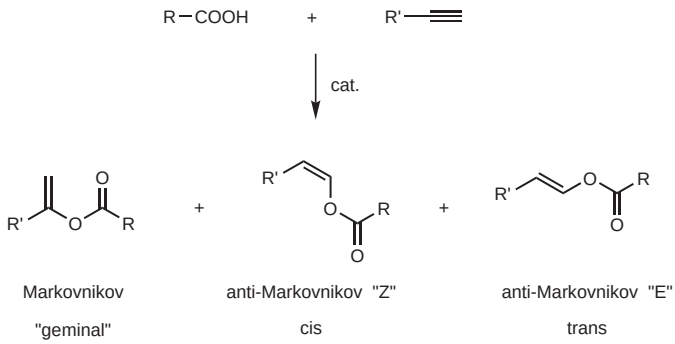


Figure 4.5: General reaction scheme for the addition of carboxylic acids to alkynes.

addition results in “geminal” enol esters while anti-Markovnikov addition affords either Z (cis) or E (trans) enol esters.
A molecule that has both an alkyne and a carboxylic acid functionality can undergo an intramolecular cyclization reaction that leads to lactones. Depending on which alkyne carbon the addition takes place, either “exo” enol lactones with an external double bond or “endo” enol lactones with an internal double bond are produced, as shown in Figure 4.6.
Because of the high activation energy, the reaction requires the presence of a transition metal catalyst.

Mercury

The use of mercury salts dates back to the 1950’s and this metal is probably the first that was ever used for the addition of carboxylic acids to alkynes. $Hg(OAc)_2$ was used by Lemaire and Lucas to catalyze the addition of acetic acid to 3-hexyne,[298] and 1-methoxyvinyl esters were prepared from ethoxyacetylene and carboxylic

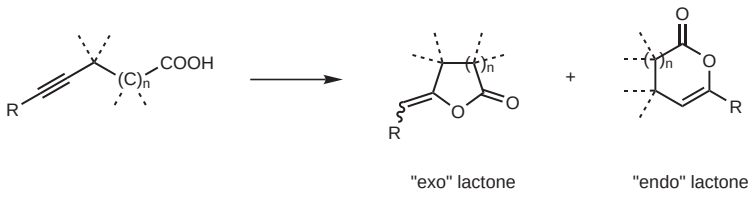


Figure 4.6: Synthesis of enol lactones.

acids.[268] Also cyclic enol esters such as naturally occurring lactones or mimics of these compounds have been synthesized using $Hg(OAc)_2$,[299,300] HgO[301,302] or $Hg(OTFA)_2$.[300,303–305] The latter mercury salt, mercury trifluoroacetate, was substantially more effective than mercury acetate.
The reaction mechanism involves the acid facilitated addition of HgX (X = OAc, OTFA) to the triple bond. Subsequent addition of a carboxylic acid gives the enol ester (Figure 4.7). Bach et al. devoted a study to the stereochemistry of the ace-

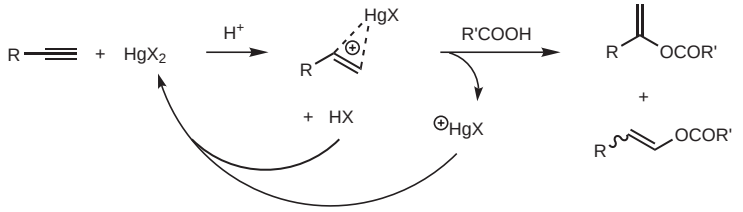


Figure 4.7: Reaction mechanism of mercury-catalyzed enol ester synthesis.

toxymercuration of alkynes.[306]
Other mercury-mediated methods are based on the use of vinylmercurials[307,308] or chloromercurio aldehydes[309] or they apply a solvomercuration-demercuration strategy.[310]
Although it is an excellent metal for this reaction, the toxic nature of mercury has severely limited its use and research is now focussed on other less toxic transition metals.

Ruthenium

A wide variety of ruthenium complexes has been used for the synthesis of enol esters (Figure 4.8). The first application of ruthenium was reported by Rotem and Shvo in 1983.[311] They used $Ru_3(CO)_{12}$ (**29**) to generate vinyl esters with variable stereoselectivity: both Markovnikov and anti-Markovnikov (cis + trans) enol esters were formed.
Mitsudo and Watanabe applied the bis(η^5-cyclooctadienyl)ruthenium complex **30** for the coupling of unsaturated acids with alkynes, resulting in a mixture of the three enol ester isomers. The addition of phosphine ligands such as nBu_3P pro-

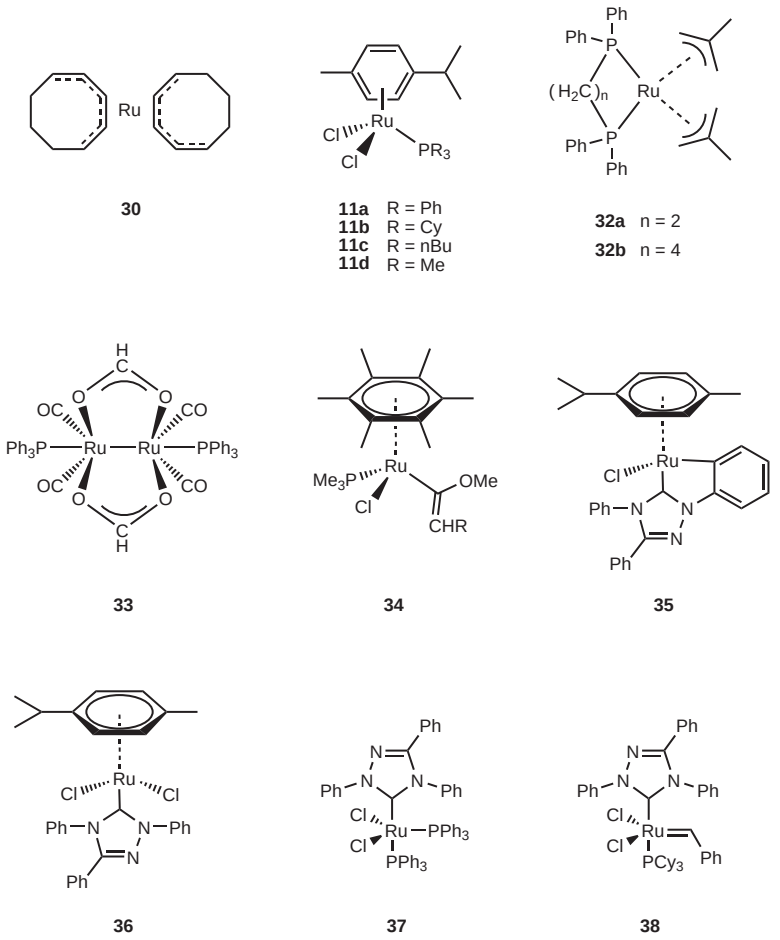


Figure 4.8: Ruthenium catalysts used for enol ester synthesis.

duced mainly the Markovnikov adduct.[312] The coupling of saturated acids was made possible with the supplemental addition of maleic anhydride.[313] Also functionalized acids and alkynes such as propargyl alcohols were coupled using this catalytic system.[314,315]

The research group of Dixneuf has performed an extensive study of various ruthenium catalysts for the synthesis of enol esters. Terminal alkynes were coupled with carboxylic acids using $RuCl_3.xH_2O$ (**31**), affording both Markovnikov and anti-Markovnikov products.[316] The addition of 2 equivalents of phosphine ligands PR_3 or the use of the phosphine complex $RuCl_2(PR_3)$(p-cymene) (**11a-d**) resulted in selective Markovnikov addition. Catalyst **11d** was also used in the reaction of carboxylic acids with butenynes, affording 2-acyloxy-1,3-dienes which are potential Diels-Alder substrates (Figure 4.9).[317] Enol formates were produced by coupling formic acid with alkynes[318] and enol ester intermediates of N-protected amino

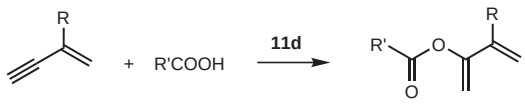


Figure 4.9: Synthesis of 2-acyloxy-1,3-dienes.

acids could be prepared with retention of optical activity and protecting groups for further synthetic applications towards amides or dipeptides (Figure 4.10).[272,319] Careful tuning of phosphine complexes of the type $Ru(Ph_2P(CH_2)_nPPh_2)(\eta^3\text{-}CH_2\text{-}$

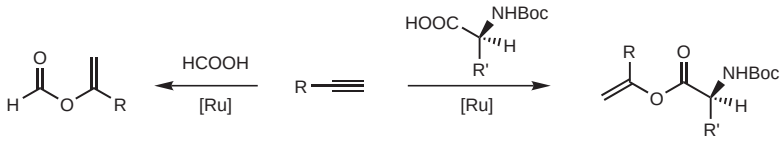


Figure 4.10: Formation of enol formates and enol ester intermediates of amino acids.

$C(Me)=CH_2)_2$ (**32a,b**) made it possible to reverse the stereoselectivity from geminal enol esters for **11a-d** to almost exclusively anti-Markovnikov Z enol esters for catalyst **32b**.[320,321] It was found that both the nature of the chelating phosphine ligand and the nature of the alkyne had a crucial influence on the selectivity. Also functionalized alkynes, such as prop-2-ynylic ethers, were coupled with carboxylic acids using catalyst **32b**, but now Markovnikov adducts were obtained. The use of **32a** or **32b** with additional PPh_3 ligand resulted in anti-Markovnikov Z adducts.[322] Similarly, the reaction of propargyl alcohols with benzoic acid in the presence of catalyst **32a** resulted in the anti-Markovnikov (Z + E) products 3-hydroxy-1-propen-1-ylbenzoates that undergo rapid transformation into α,β-unsaturated aldehydes upon treatment with acids such as PTSA or HBF_4 (Figure 4.11).[281,282]

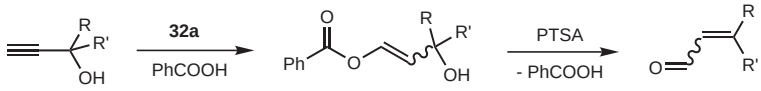


Figure 4.11: Reaction of propargyl alcohols with benzoic acid.

The complex $[Ru(\mu\text{-}O_2CH)(CO)_2(PPh_3)]_2$ (**33**) was used for the coupling of halogenated aromatic acids with alkynes which was difficult to achieve with **11a-d**.[323] Polymer supported **33** was a reusable catalyst for the synthesis of enol diesters from di-carboxylic acids and alkynes (Figure 4.12).[324] Diisopropenyl oxalate was synthesized from oxalic acid and propyne with **11a-d**-type catalysts.[270] Further acylation with alcohols or amines leads to α-dicarbonyl compounds such as oxalates and oxamides, which are useful synthons in organic chemistry. Also the coupling of diynes with carboxylic esters leads to enol diesters. Catalysts **11a-d**

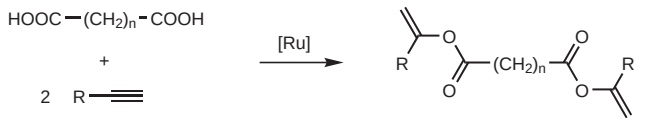


Figure 4.12: Synthesis of enol diesters from di-carboxylic acids.

and **33** give geminal/geminal enol esters whereas **32b** leads to Z/Z enol esters (Figure 4.13).[325,326] Complex **34** has proven to be an excellent catalyst for the

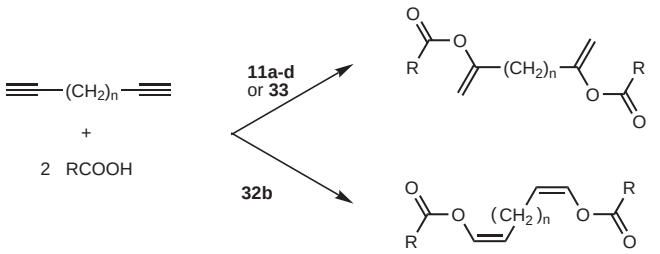


Figure 4.13: Synthesis of enol diesters from diynes.

reaction between hydroxy- or unsaturated acids with alkynes where other complexes failed.[327] The resulting products were either dioxolanones or methacrylates as shown in Figure 4.14.

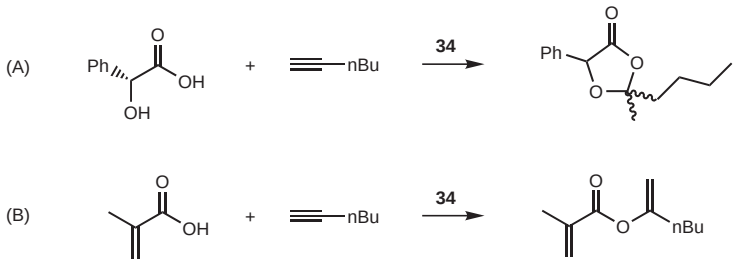


Figure 4.14: Reaction of (A) hydroxy acids and (B) unsaturated acids.

Not only carboxylic acids could be coupled with alkynes. Vinylcarbamates were produced from the reaction between alkynes, carbon dioxide and amines, promoted by **29**, **31** or **11a-d** (Figure 4.15).[328,329] Dienylcarbamates were formed from 2-methylbut-1-en-3-yne using **32a**.[330]
Other groups also made contributions to ruthenium catalyzed enol ester synthesis. Kita et al. prepared 1-ethoxyvinylesters from ethoxyacetylene and carboxylic acids. The use of **3** as catalyst gave the best results.[331]

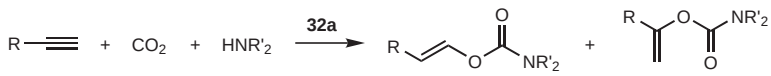


Figure 4.15: Synthesis of vinylcarbamates from alkynes, CO_2 and amines.

Leadbeater et al. immobilized **3** on polymer supported triphenylphosphine, which gave similar results as the homogeneous catalyst **11a-d**.[332] The catalyst retains its activity after several consecutive runs.
Goosen et al. found that the addition of a catalytic amount of base to a mixture of **3** and phosphine ligands increased the yield of enol esters.[333] Furthermore, the nature of the base had an influence on the stereoselectivity. The use of inorganic bases resulted in mainly Markovnikov enol esters, while the use of organic bases such as pyridine produced the cis anti-Markovnikov enol esters. This difference was explained by possible complexation of the organic base with ruthenium.
Le Paih and co-workers discovered that RuCl(cyclooctadiene)(C_5Me_5) catalyzed the addition reaction of 2 equivalents of alkyne with a carboxylic acid, selectively producing (1E,3E)-1,4-disubstituted-1,3-dienes (Figure 4.16).[334,335]

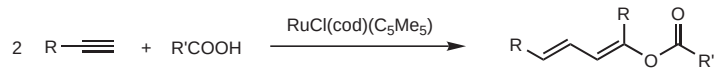


Figure 4.16: Formation of dienylesters from 2 equivalents of alkyne and carboxylic acid.

Dicationic ruthenium complexes developed by Doherty et al.,[336] $CpRu(CO)_2Cl$ and $[CpRu(CO)_2]_2$ complexes by Ye and Leong[337] and Ru complexes with PNO tridentate ligands by Pelegatti et al[338] all produced anti-Markovnikov Z enol ester with high stereoselectivity.
In the research group of Verpoort, Melis investigated several ruthenium catalysts for enol ester synthesis. Thermolyzed Grubbs 1st generation catalyst **1** produced mainly Markovnikov enol esters.[339] Triazol complexes **35** and **36** derived from **3** afforded anti-Markovnikov enol esters as major products, but the cis/trans selectivities were not always high.[340] Triazol complex **37** was shown to be a highly active catalyst that generated enol esters in good yields in a short time-period of 30 minutes.[11] Also the Ru-alkylidene complex **38** was a good catalyst precursor. After thermal treatment, predominantly Markovnikov enol esters were produced.[341]
Bimetallic complexes containing a ruthenium center were reported by Moise[342] and Leong[343] but their scope is at present rather limited.
Enynes are commonly observed side-products in the ruthenium-catalyzed coupling reaction of carboxylic acids with alkynes (Figure 4.17). They result from the dimerization of alkynes. Especially aromatic alkynes such as phenylacetylene are prone to dimerization. The occurrence of this side-reaction is not surprising, as several ruthenium catalysts have been developed especially for the dimerization of alkynes.[344–351] In the absence of a carboxylic acid, the catalytic systems of Melis (**35**, **36** and **38**) are also dimerization catalysts.

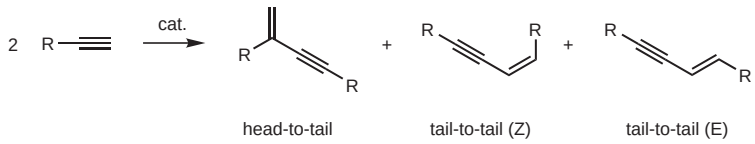


Figure 4.17: Formation of enynes.

Palladium

In the presence of $Pd(OAc)_2$, alkynes react with lithium or sodium acylates forming Markovnikov enol esters.[352] Heterogeneous Pd/C particles are also good catalysts and the addition of phosphine ligands further improves their activity. Again geminal enol esters were obtained.[353] Exocyclic enol lactones were synthesized by the intramolecular coupling reaction of either lithiumalkynoates using $PdCl_2(MeCN)_2$[354] or alkynoic acids using $PdCl_2(PhCN)_2$.[355]
The very diverse chemistry of palladium makes it possible to perform complex coupling reactions. Tsuda et al. reacted alkynoic esters or a lithium alkynoate/allylic acetate mixture in the presence of $Pd_2(dba)_3.CHCl_3$ and trimethylolpropanephosphite, giving substituted enol lactones.[356] Ynenol lactones were prepared by Bouyssi et al. from alkynoic acids and 1-bromo-1-alkynes, using a $Pd(0)/[PR_3]_n$ catalyst.[357] Similar addition/cyclization reactions were developed by Arcadi,[358] using $Pd(OAc)_2(PPh_3)_2$ or $Pd(PPh_3)_4$ and Kundu[359] using $PdCl_2(PPh_3)_2$. An example of the latter method is shown in Figure 4.18.

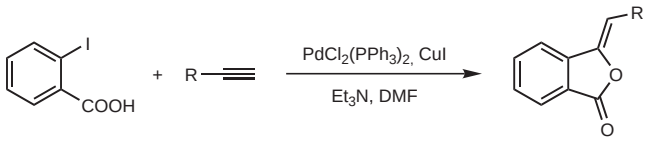


Figure 4.18: Pd-catalyzed lactone synthesis.

Other transition metals

In some occasions, silver salts replaced the toxic mercury salts, especially for the synthesis of natural lactones. Silver nitrate performed the intramolecular lactonization reaction in the total synthesis of cyanobacterin.[286] Also silver carbonate has been used.[360,361]
The rhodium complex $[Rh(Cy_2PCH_2CH_2PCy_2)Cl]_2$ produced exocyclic enol lactones with Z-stereochemistry selectively (Figure 4.19). Even internal alkynes were converted into lactones.[362,363]
Hidai et al. employed cubane-type molybdenum clusters of the types $PdMo_3S_4$ and Mo_3NiS_4 for the previously difficult to achieve coupling of carboxylic acids with alkynes that are substituted with electron withdrawing groups. Anti-Markovnikov

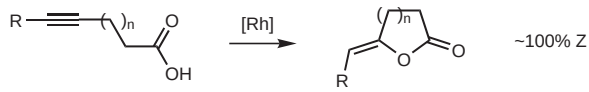


Figure 4.19: Rhodium catalyzed synthesis of enol lactones with Z-geometry.

adducts of cis geometry were obtained selectively.[364] Intramolecular cyclization of alkynoic acids afforded exocyclic enol lactones.[365,366]
Iridium systems based on $[Ir(cod)Cl]_2$ were reported by Ishii.[367] Mainly Markovnikov adducts were produced. The addition of $P(OMe)_3$ and the base Na_2CO_3 increased the yield substantially.
Quite recently, Hua used the rhenium complex $Re(CO)_5Br$ for the synthesis of anti-Markovnikov enol esters.[368] When n-heptane was used as solvent, the catalyst could be partially recovered.

4.3.2 Enol esters via enolates

Through the so-called keto-enol equilibrium, ketones and aldehydes can act as nucleophiles in the form of their corresponding enols. The acylating agent isopropenyl acetate is prepared from the reaction of acetone with ketene in the presence of sulfuric acid catalyst (Figure 4.20).[267] To facilitate this type of reaction,

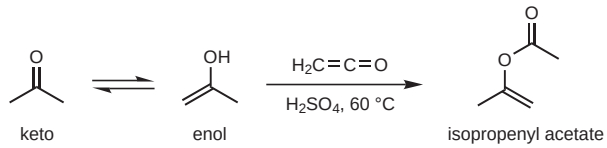


Figure 4.20: The synthesis of isopropenylacetylene.

metal enolates of the ketones are often used. They can be generated by bases such as Ph_3CK, Ph_3CLi or NaH. This way, sodium and potassium enolates were reacted with dimethyl ketene or acetyl chloride to afford geminal enol esters[369] and manganese-enolates were employed by Cahiez et al. affording the Z enol esters as major products in the reaction with acid anhydrides.[370]
The exact stereochemistry of the enolates and the resulting enol ester is not always easy to predict. Kosugi et al.[284] found that the reaction of 2-butanone with ketene resulted in the geminal enol ester 2-acetoxybut-2-ene while generating the Li-enolate with Ph_3CLi followed by the reaction with acetic anhydrides results in the Z enol ester 2-acetoxybut-1-ene (Figure 4.21).
Another difficulty is the control of O-acylation, leading to enol esters, versus C-acylation. A study by Gong[371] showed that at low temperatures Li-enolates react with simple ketenes via O-acylation giving enol esters. However, with bulkier ketenes or at higher temperatures, C-acylation occurs and β-diketones are obtained (Figure 4.22). The group of House performed two interesting studies on both the

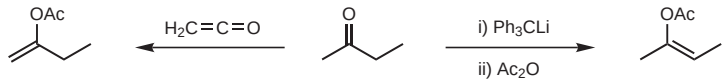


Figure 4.21: Different stereochemistry in different reactions.

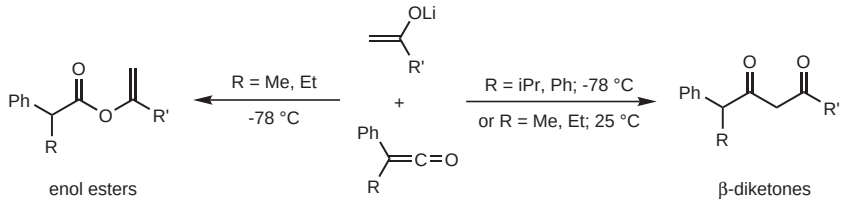


Figure 4.22: O-acylation versus C-acylation.

enolate equilibrium[372] and O-acylation versus C-acylation.[373]
Additional examples for the synthesis of enol esters that follow the enolate mechanism are the acylation of β-oxoalkyltetracarbonylferrates with acyl halides[374] and the reductive homologation of esters.[375] More recently, Schaefer and Fu used a chiral Fe complex for the asymmetric coupling of a ketene with an aldehyde,[376] that presumably proceeds via the enolate form of the aldehyde.[377]

4.3.3 Other methods for the synthesis of enol esters

The allylic oxidation of olefins by $Pd(OAc)_2$ produces a mixture of enol esters and other isomers (Figure 4.23).[378]

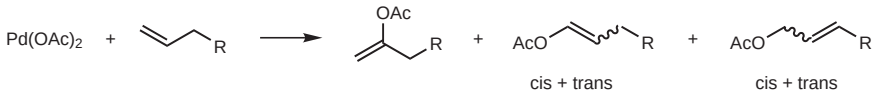


Figure 4.23: Allylic oxidation of olefins by $Pd(OAc)_2$.

Hudrlik et al. were able to selectively prepare cis or trans enol esters from epoxysilanes (Figure 4.24).[379] This synthetic approach involves the regio- and stereospe-

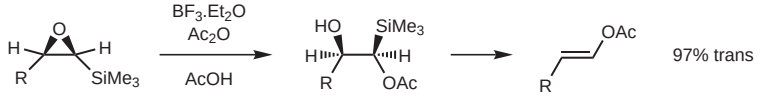


Figure 4.24: Selective synthesis of cis or trans enol esters from epoxysilanes.

cific acid catalyzed ring-opening reaction of the α,β-epoxysilanes, followed by a stereospecific β-elimination of the resulting β-hydroxysilanes.
The synthesis of halo enol lactones has been attempted via mercury-mediated lactonization but this procedure has certain shortcomings. The most efficient route to halo enol lactones involves halo-lactonization of the acetylenic acids applying N-halosuccinimide (NXS) and the base $KHCO_3$ in a biphasic system of water and dichloromethane using tetrabutylammonium hydroxide as phase-transfer catalyst (Figure 4.25).[300,304,305]

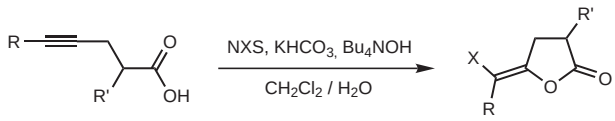


Figure 4.25: Halo enol lactones using N-halosuccinimide.

Chemla and Normant observed the unexpected formation of enol esters from acylzinc species of acid halides.[380] The reaction produced the Z-isomer almost exclusively.

4.3.4 Reaction mechanism of the ruthenium-catalyzed synthesis of enol esters

One of the first mechanisms that has been proposed is shown in (Figure 4.26). The first step is (a) the oxidative addition of a carboxylic acid to the Ru(II) complex, followed by (b) subsequent insertion of an acetylenic bond into the Ru-H bond. Reductive elimination (c) then affords the enol esters and the Ru(II) species again.[312] Inversion of steps (a) and (b) has also been suggested.[315] This proposed mecha-

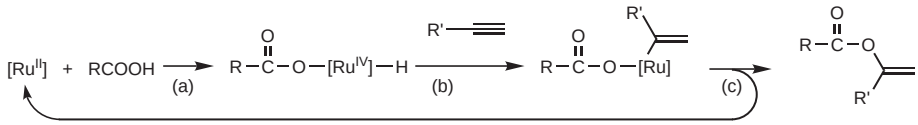


Figure 4.26: Enol ester synthesis via oxidative addition of carboxylic acids.

nism is however not widely supported and experimental results point in another direction as explained below.
Nowadays, there seems to be a general agreement that the reaction proceeds through the initial addition of the alkyne to ruthenium, followed by a nucleophilic attack of the carboxylic acid. Figure 4.27 presents one possible reaction pathway, proposed by Melis et al., for catalyst **1**.[339] Cycle A presents the synthesis of enol esters. The first step is the replacement of a phosphine ligand by an acetylene ligand that is rearranged to a vinylidene, generating the actual catalyst. Subsequent coordination of a carboxylic acid and internal addition to the acetylene ligand affords the enol esters. Addition of a new acetylene ligand releases the enol ester

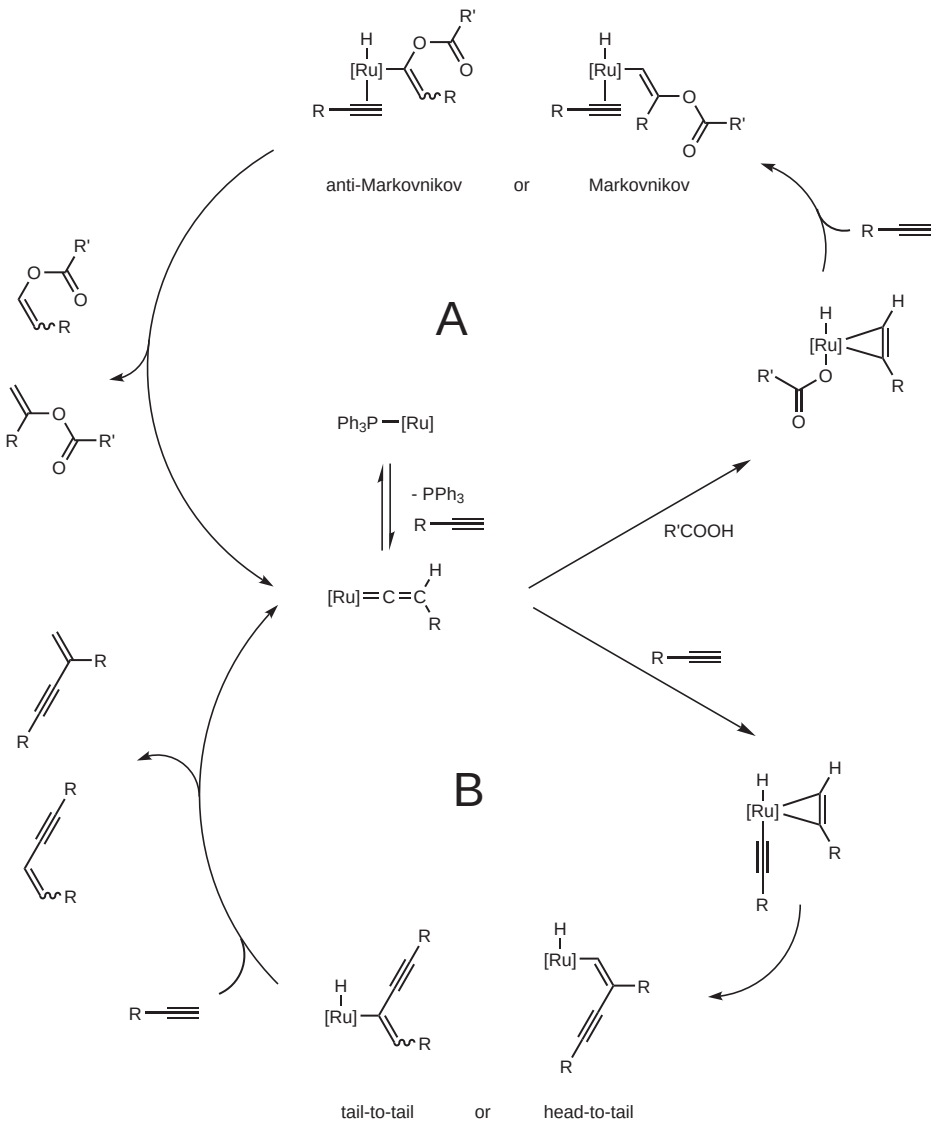


Figure 4.27: Enol ester synthesis via alkyne insertion.

from the ruthenium center and a new catalytic cycle can start. The formation of enynes is explained by cycle B. In the absence of carboxylic acids, a second alkyne coordinates to the metal vinylidene and the internal addition produces enynes.

5

Ruthenium catalyzed synthesis of enol esters

5.1 Introduction

The most direct way for the preparation of enol esters is the addition of carboxylic acids to alkynes. The overview of the existing literature in the previous chapter has shown that ruthenium complexes are without a doubt the most potent and versatile catalysts for this reaction. The transition metal ruthenium is able to "activate" the alkynes so that they become susceptible to the nucleophilic attack of a carboxylic acid. The general reaction scheme is presented in Figure 5.1. Theoretically, three

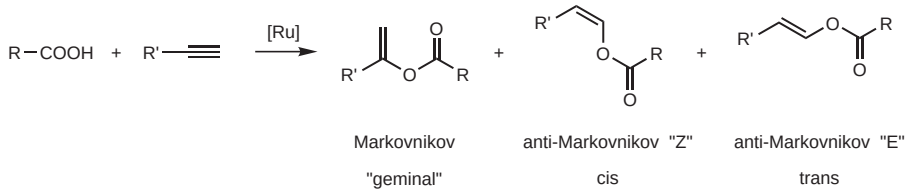


Figure 5.1: General reaction scheme for the addition of carboxylic acids to alkynes.

enol ester isomers can be formed: the Markovnikov adduct and the cis and trans anti-Markovnikov adducts. Careful selection and tuning of the ligands makes it possible to prepare enol esters with high stereoselectivities. For example, complexes of the type $RuCl_2(PR_3)$(p-cymene) are widely used for the selective synthesis of Markovnikov adducts. Almost all of the already described complexes have phosphine ligands and many of them also contain an η^6-arene ligand. However, to the

best of our knowledge, the application of ruthenium arene complexes with N,O-bidentate Schiff base ligands has not yet been explored. It was therefore our goal to establish the possibilities and limitations of these complexes for the synthesis of enol esters, and to compare them with other commercially available catalysts. The structure and synthesis of the Schiff base complexes **4a,b - 8a,b** has already been described previously.

5.2 Screening of ruthenium catalysts

5.2.1 Model reaction 1: phenylacetylene and acetic acid

The coupling of phenylacetylene (**PA**) with acetic acid was chosen as a model reaction for the screening of the activity of several commercial catalysts (**1**, **2**, **3**, **11a**, **11b**, **15**, **16**, **17** and **21**) and our own Schiff base catalysts. Figure 5.2 shows the possible reaction products. The general experimental procedure is as follows:

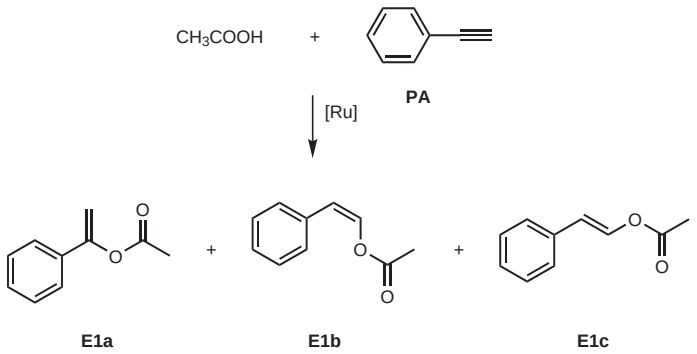


Figure 5.2: The addition of acetic acid to phenylacetylene.

the catalyst, alkyne and carboxylic acid are dissolved in toluene and the solution is stirred at 110 °C. At certain time intervals, samples are taken from the reaction mixture and purified by filtering the sample through a short silica gel column (ethyl acetate). The resulting solution is then analyzed by gas chromatography.
The conversion of phenylacetylene and the yield of the enol esters after five hours of reaction is summarized in Table 5.1. The reaction was monitored over time and the conversion of phenylacetylene is visualized in Figures 5.3 and 5.4. The experiment with catalyst **3** is included in both graphs as reference. One thing that immediately catches the eye is the irregular shape of all the curves. After the initial fast start, there is an inflection in the curve, whereafter the consumption of phenylacetylene continues. An overlay of the phenylacetylene conversion graph with the enol ester and enyne production using **3** in Figure 5.5 reveals the origin of this phenomenon: during the first part of the reaction, phenylacetylene is dimerized to enynes. Only after approximately 30 minutes the formation of enol esters starts and the dimerization slows down considerably or even stops completely. The total

Table 5.1: Enol ester synthesis from phenylacetylene and acetic acid[a]

	%conversion	Relative %			Yield (%)	
Catalyst	**PA**	**E1a**	**E1b**	**E1c**	∑**E1a-c**	enynes
1	89.9	91.1	8.9	0	32.4	66.0
2	93.6	75.0	17.9	7.1	47.2	43.7
3	100	3.7	27.2	69.1	51.8	41.2
11a	100	58.0	21.8	20.3	58.7	30.9
11b	100	64.0	17.6	18.4	51.1	36.4
15	36.7	12.5	51.0	36.5	10.6	0
16	97.8	66.9	18.8	14.3	60.2	23.8
17	94.9	13.6	31.4	55.1	52.9	23.8
21	95.7	76.9	16.7	6.3	58.8	27.3
4a	100	5.5	33.2	61.3	60.4	36.6
4b	94.2	11.8	37.6	50.7	55.2	34.5
5a	100	4.6	30.4	65.0	59.5	33.2
5b	89.2	7.3	31.5	61.1	45.7	36.2
6a	82.8	5.6	30.9	63.5	43.3	28.2
6b	56.3	11.3	33.6	55.1	11.5	31.4
7a	82.5	5.4	33.0	61.6	40.0	32.4
7b	59.3	13.9	37.6	48.5	12.6	35.1
8a	78.1	5.7	34.8	59.5	32.6	31.0
8b	53.8	12.7	35.8	51.5	11.7	30.7

[a] Reaction conditions: phenylacetylene (**PA**, 1.0 mmol), acetic acid (1.1 mmol), catalyst (0.01 mmol) and hexadecane (0.25 mmol) in toluene (1 mL) at 110 °C. Yields based on phenylacetylene and determined by GC analysis with hexadecane as internal standard. Reaction time: 5 h.

amount of dimerization products is for most catalysts situated around 30% (±5-10%). The highest enyne production is observed for the first generation Grubbs catalyst **1**. This was to be expected, since this catalyst was used by Melis as precursor in the dimerization of alkynes.[381] The second generation analogue **2** still produces a lot of enynes (43.7%) but not as much as **1**. Little or no dimerization products were found for **15**, but this is most probably due to the limited overall conversion of phenylacetylene. The lowest amount of enynes (23.8%) were observed for the Hoveyda catalysts **16** and **17**. While the parent complex **3** produces 41.2% enynes, the derived arene-type catalysts all had lower and roughly comparable amounts of dimerization products, ranging from 28% to 36%.

What can also be concluded from Figure 5.3 is that ruthenium arene complexes **3**, **11a** and **11b** are more active for the conversion of phenylacetylene than the carbene complexes **1**, **2**, **15**, **16**, **17** and **21**. With **11a**, **3** and **11b** full conversion is reached after 3, 4 and 5 hours respectively, where the other catalysts need longer reaction times (typically around 7 hours). Strangely enough, **15** shows very little activity towards enol ester synthesis, while it is structurally not so different from **1** and **2**.

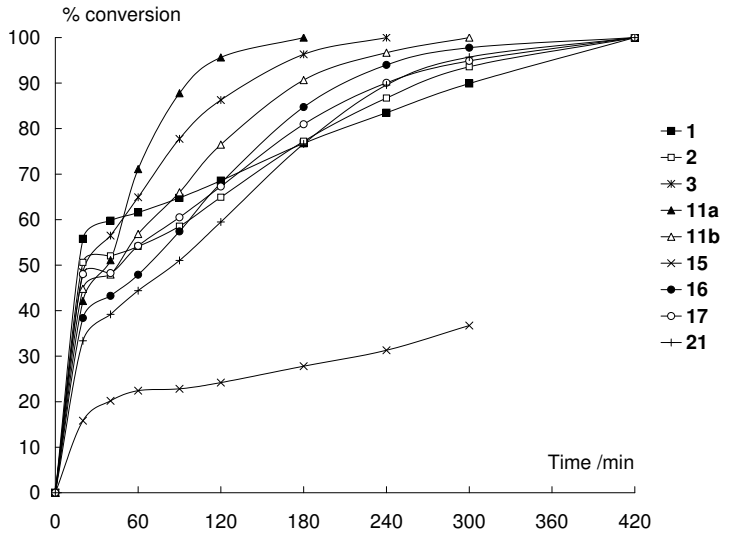


Figure 5.3: Conversion of phenylacetylene with commercial catalysts.

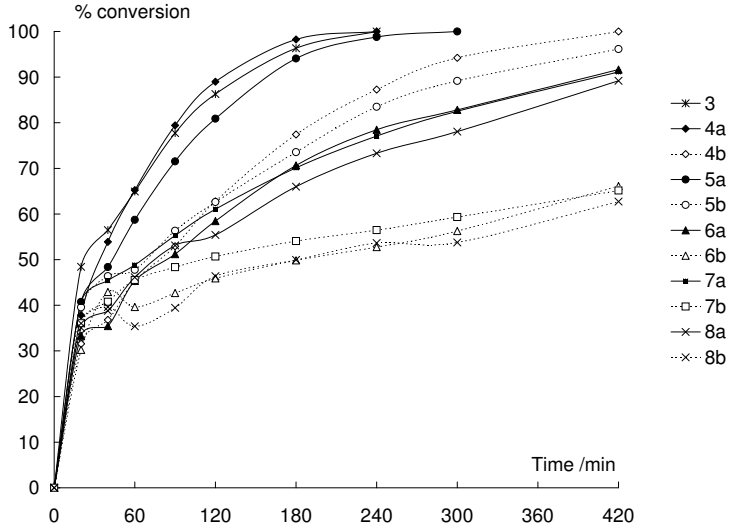


Figure 5.4: Conversion of phenylacetylene with Schiff base catalysts.

In the series of Schiff base catalysts, the complexes with an aliphatic group on the nitrogen of the Schiff base (**4a,b** and **5a,b**) performed remarkably better than the

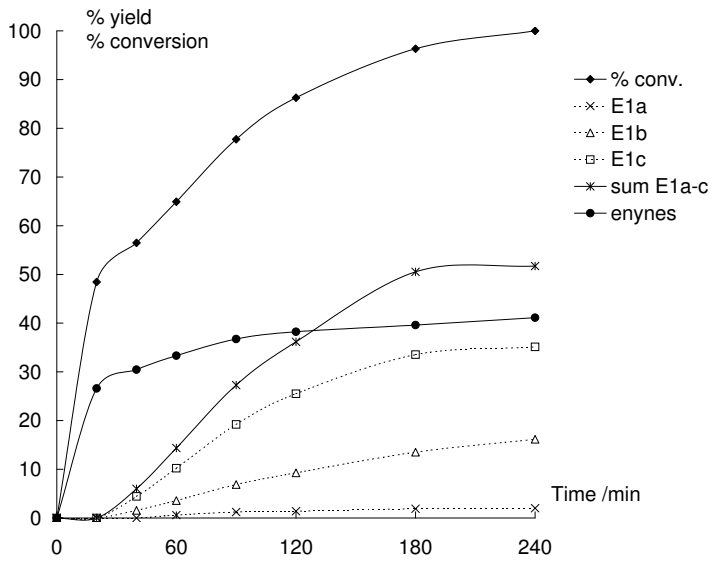


Figure 5.5: Overlay of phenylacetylene conversion and enol ester / enyne production with **3**.

complexes with an aromatic group (**6a,b** - **8a,b**). Furthermore, there is an obvious trend that non-nitro complexes (**4a** - **8a**) are more active than their corresponding nitro-containing complexes (**4b** - **8b**). The nature of the aromatic group on the Schiff base seems to be less important as the difference between the three complexes **6a**, **7a** and **8a** is small. Likewise, **6b**, **7b** and **8b** perform nearly identically. From the Schiff base complexes with an aliphatic group, **4a** seems to perform slightly better than **5a**, indicating that a small side-group gives the best results. The bulkier cyclohexyl group might cause some steric hindrance resulting in a slightly slower reaction. The corresponding complexes **4b** and **5b** with a nitro group show a similar trend.

These results show that Schiff base complexes **4a** and **5a** are able to compete with **3**, **11a** and **11b** with regard to the reaction rate. This is, however, not the only important parameter. Some amount of alkyne is consumed in the dimerization reaction, limiting the maximum yield of enol esters. Figures 5.6 and 5.7 show the formation of enol esters for all catalysts. Again, the reaction with catalyst **3** is included in both graphs as reference. For the commercial catalysts, after 5 hours the highest yields of enol esters are obtained with **11a** (58.2%), **16** (60.2%) and **21** (58.8%). These catalysts also have the lowest amount of dimerization. Catalyst **1** only produces 32.4% enol esters in conjunction with 66.0% enynes. The best results with Schiff base catalysts are established with complexes **4a** and **5a** with 60.4% and 59.5% enol esters respectively. Other Schiff base catalysts were less efficient.

There is also a sharp contrast between the catalysts regarding the distribution of enol ester isomers. Complexes **1**, **2**, **11a,b**, **16** and **21** containing phosphine

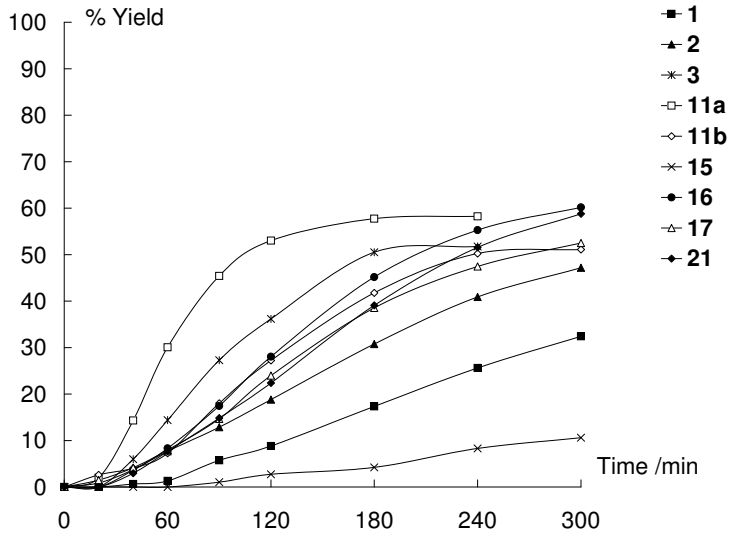


Figure 5.6: Cumulative enol ester yields with commercial catalysts.

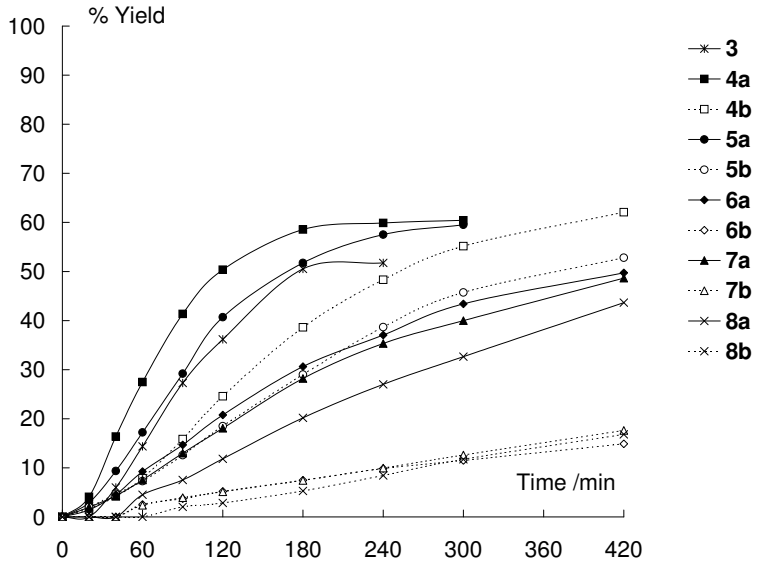


Figure 5.7: Cumulative enol ester yields with Schiff base catalysts.

ligands preferentially produce Markovnikov adducts. The Schiff base catalysts **4a,b-8a,b**, **3**, and **17** on the other hand, produce mainly anti-Markovnikov adducts

with mostly trans geometry.
Figure 5.8 shows the enol ester distribution during the reaction with catalyst **4a**. The bars represent the relative ratios of the three isomers and the curves show the yield. All enol ester isomers are produced simultaneously from the beginning and the relative amounts do not change during the reaction. This indicates that there is no conversion of one isomer into another. Distillation of the compounds for purification purposes did not change the ratios either.

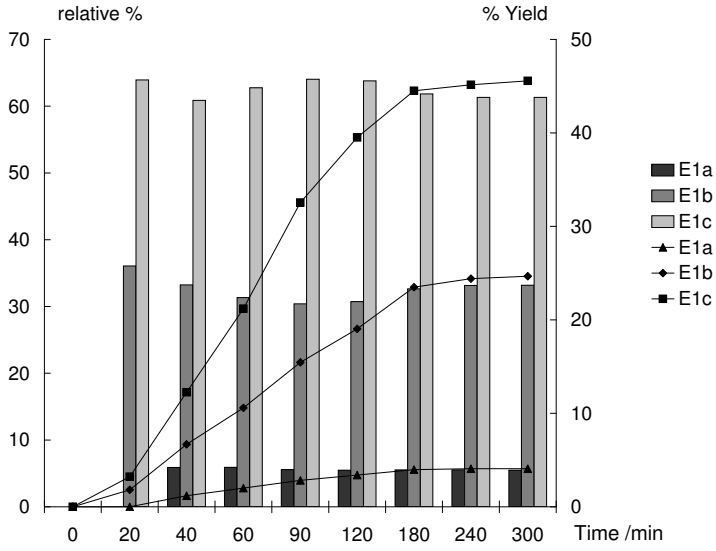


Figure 5.8: Enol ester distribution during the reaction. **E1a** = Markovnikov, **E1b** = anti-Markovnikov cis, **E1c** = anti-Markovnikov trans.

5.2.2 Model reaction 2: 1-octyne and acetic acid

To verify whether the results of the reaction with phenylacetylene and acetic acid are representative for other alkynes, also the reaction of 1-octyne (**OC**) with acetic acid was investigated. The reaction scheme is depicted in Figure 5.9. The results of the tested catalysts are presented in Table 5.2. Figure 5.10 shows the conversion of 1-octyne for some selected catalysts and Figure 5.11 shows the formation of enol esters.
The first important observation is the absence of enynes in all the reactions. No dimerization products were observed in the chromatograms or NMR spectra. Strangely enough, some of the curves are still irregular, comparable to the curves with phenylacetylene. Furthermore, there is a difference of 15% or higher between the percent conversion of the alkyne and the cumulative yield of the enol esters. The most logical explanation would be the loss of product during the work-up, but this can be ruled out as both the analysis of the original reaction mixture and

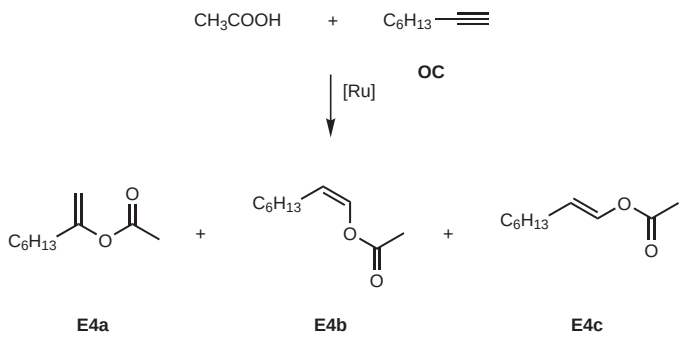


Figure 5.9: Addition of acetic acid to 1-octyne.

Table 5.2: Enol ester synthesis from 1-octyne and acetic acid[a]

	%conversion	time	Relative %			Yield (%)
Catalyst	1-octyne	(min)	**E4a**	**E4b**	**E4c**	**∑E4a-c**
1	100	180	94.9	5.1	0	83.2
2	100	240	79.4	13.3	7.3	78.8
3	100	300	15.7	38.1	46.3	60.7
11a	100	90	79.2	14.3	6.4	85.7
11b	100	180	62.9	18.6	18.5	78.7
15			not tested			
16	100	180	82.2	11.2	6.6	82.6
17	100	300	43.3	31.2	25.5	64.3
21			not tested			
4a	100	180	14.4	57.6	28.0	77.1
4b	100	300	18.8	61.4	19.8	82.2
5a	100	240	15.3	47.5	37.3	70.5
5b	100	420	18.2	50.3	31.5	75.3
6a	100	420	14.7	52.8	32.4	71.2
6b	70.7	420	17.7	53.1	29.2	44.3
7a	100	420	15.4	52.4	32.2	73.9
7b	72.4	420	17.8	56.6	25.6	47.8
8a	100	420	15.1	54.9	29.9	79.8
8b	77.5	420	17.7	60.9	21.4	55.9

[a] Reaction conditions: 1-octyne (1.0 mmol), acetic acid (1.1 mmol), catalyst (0.01 mmol) and hexadecane (0.25 mmol) in toluene (1 mL) at 110 °C. Yields based on 1-octyne and determined by GC analysis with hexadecane as internal standard.

the purified sample gave nearly identical results. Other explanations, such as the partial evaporation of 1-octyne or the formation of higher oligomers are unlikely.

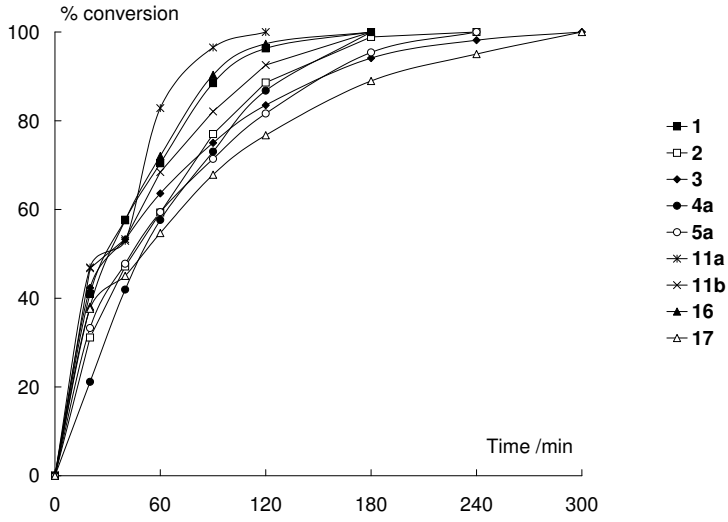


Figure 5.10: Conversion of 1-octyne with different catalysts.

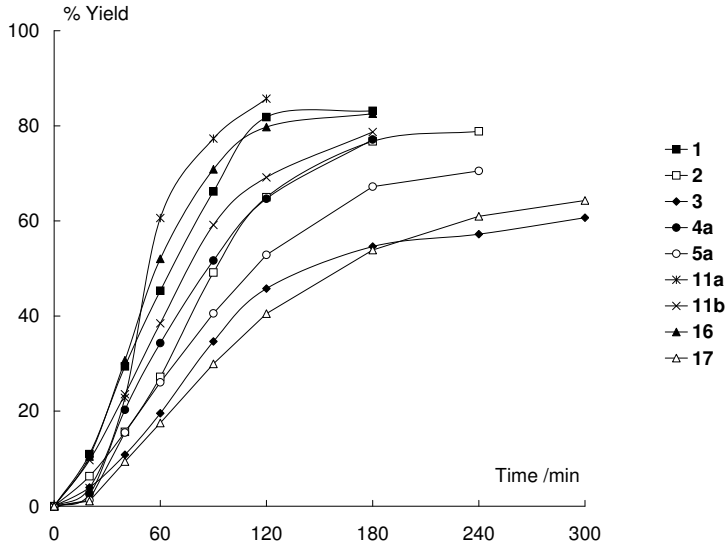


Figure 5.11: Cumulative enol ester yield with different catalysts.

The boiling point of 1-octyne (127 °C) is higher than that of toluene (110 °C) and the formation of oligomers or polymers should be accompanied by the formation of

detectable amounts of dimers or trimers and a change in viscosity, neither of which are observed. The reason for this discrepancy between the total yield of enol esters and 1-octyne conversion and the irregular shape of some conversion curves remains yet unexplained.
Compared to the results of phenylacetylene, the yields with 1-octyne are always higher, which can easily be explained by the absence of enynes. The trends among the catalysts are roughly the same. Catalysts with phosphine ligands produce predominantly Markovnikov enol esters and the catalysts with Schiff base ligands produce mainly anti-Markovnikov enol esters. The exception to this rule is **17** which now also produces Markovnikov adducts, opposed to the reaction with phenylacetylene.
While the anti-Markovnikov enol esters of phenylacetylene had mainly trans stereochemistry, the reaction with 1-octyne produces mostly the cis-isomer. Again, complexes **4a** and **5a**, with an aliphatic chain on the Schiff base nitrogen, perform better than the complexes with an aromatic group. Complexes without nitro group are more efficient than their nitro-containing counterparts.

5.2.3 Phenylacetylene and the dimerization problem

The enyne formation in the reaction of phenylacetylene with acetic acid is further investigated. The first set of experiments explores the variation of phenylacetylene / acetic acid ratios. Table 5.3 presents the results; **4a** was used as catalyst. Only

Table 5.3: Enol ester synthesis from phenylacetylene and acetic acid[a]

Entry	**PA** (mmol)	CH_3COOH (mmol)	%conversion **PA**	time (min)	Total yield (%)[b] enol esters	enynes
1	1	1.1	100	180	61.5	32.1
2	1	2	100	120	61.8	37.0
3	2	1	93.7	420	>99	56.8
4	2	0.1	35.7	420	8.2	20.4
5	2	0	32.5	420	0	0

[a] Reaction conditions: phenylacetylene (**PA**), acetic acid, **4a** (0.01 mmol) and hexadecane (0.25 mmol) in toluene (1 mL) at 110 °C. Yields determined by GC analysis with hexadecane as internal standard.
[b] based upon 1 equivalent of phenylacetylene, i.e. 100% equals 1.0 mmol

the total yield of enol esters is given because the relative ratios of stereoisomers were identical for all experiments: 5% Markovnikov, 35% cis and 60% trans anti-Markovnikov. With a 1 : 1.1 ratio of phenylacetylene versus acetic acid, 61.5% enol esters and 32.1 % enynes are produced. Doubling the amount of acetic acid does increase the quantity of enynes to 37%, but the yield of enol esters remains the same. Thus, increasing the amount of acid does not prevent the formation of enynes, on the contrary, even more enynes are produced.
With two equivalents of phenylacetylene, the amount of enynes increases to 56.8%. Additionally, all of the acetic acid is consumed in the formation of enol esters,

with a total yield of >99%. When only 0.1 mmol of acetic acid is used, again nearly all of the acid is consumed in the formation of enol esters, but only 20% enynes are produced. In the absence of an acid, no enynes could be detected by gas chromatography, although 32.5% of phenylacetylene was consumed. Further experiments will be required to provide an adequate explanation for this result.
Figure 5.12 shows the conversion of phenylacetylene and the formation of enynes and enol esters for entry 2 in Table 5.3. From this graph, it can be concluded that

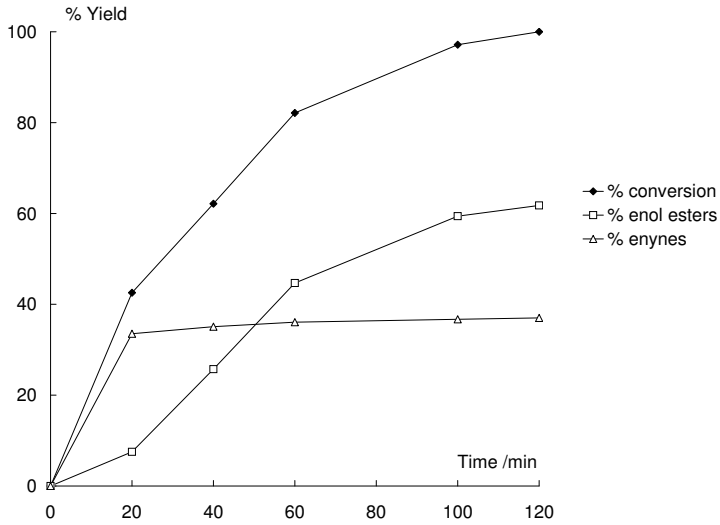


Figure 5.12: Conversion of phenylacetylene and cumulative yields of enol esters and enynes.

the formation of enynes stops after approximately 20 minutes and the formation of enol esters takes over. The reason for this sudden change is unclear. One hypothesis is the slow formation of a ruthenium-acetate complex as the actual catalyst that is responsible for the synthesis of enol esters. To verify this hypothesis, **4a** is reacted with acetic acid for three hours, before phenylacetylene is added. However, dimerization still takes place in comparable amounts to simultaneous addition. Also the distribution of stereoisomers remains the same. Hence, the complexation of acetic acid with **4a** is unlikely to be the key step in the formation of the active catalyst. Additionally, an NMR experiment shows no change in the spectrum of **4a** when acetic acid is added, ruling out the coordination of acetic acid with the original catalyst **4a**.
Another attempt to prevent dimerization was made by slowly adding phenylacetylene to a toluene solution of **4a** and acetic acid in small portions over a two hour time period. Again, dimerization occurs first and enol esters are only formed after 1 hour of reaction (after the 4th addition of phenylacetylene). Apparently, the presence of acid promotes the synthesis of enynes.

In the next set of experiments, the reasoning was reversed: the acid was used in an attempt to selectively prepare enynes and no enol esters. Figure 5.12 shows that the production of enynes stops after 20 minutes. Supplemental additions of one extra equivalent phenylacetylene after 20 and 40 minutes might repress the formation of enol esters. Figure 5.13 shows the result. Although it is clear that

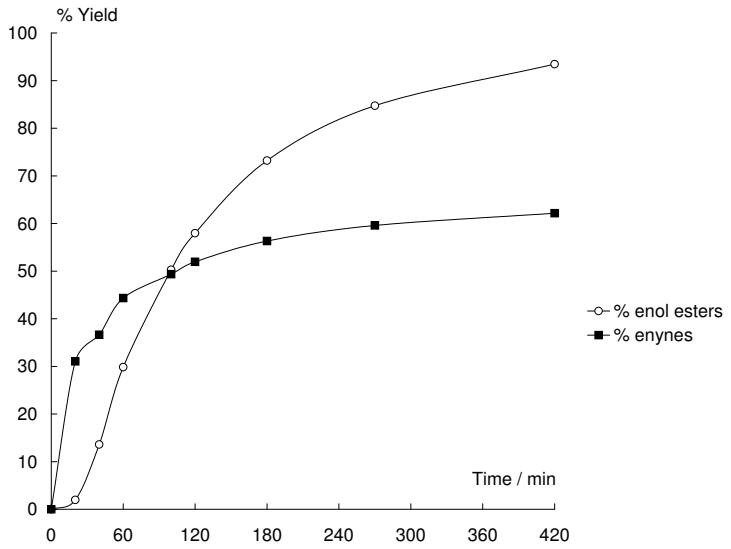


Figure 5.13: Cumulative yields of enol esters and enynes with the addition of extra equivalents of phenylacetylene after 20 and 40 minutes.

some additional dimerization takes place, eventually the enol ester formation takes the upper hand and after 7 hours, almost all acetic acid is consumed in the formation of enol esters with a total yield of 93.4%. In conclusion, we were unable to eliminate the dimerization reaction of phenylacetylene. Also enynes could not be prepared selectively.

5.3 Broadening the scope of the reaction

The scope of the reaction and the general applicability of complexes **4a** and **5a** is investigated using a variety of alkynes and carboxylic acids:

Alkynes: phenylacetylene (**PA**), 1-octyne (**OC**), 3,3-dimethyl-1-butyne (**BU**), 4-octyne, 2-methyl-3-butyn-2-ol

Carboxylic acids: acetic acid, trichloroacetic acid, benzoic acid, 4-pentynoic acid

5.3.1 Phenylacetylene and trichloroacetic acid

Figure 5.14 depicts the general reaction scheme. The results are presented in table 5.4. Phenylacetylene is completely consumed during the reaction and good yields

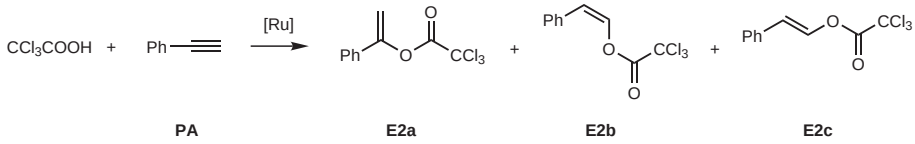


Figure 5.14: Addition of trichloroacetic acid to phenylacetylene.

Table 5.4: Enol ester synthesis from phenylacetylene and trichloroacetic acid[a]

	% conversion	time	Relative %			Yield (%)	
catalyst	**PA**	(min)	**E2a**	**E2b**	**E2c**	∑**E2a-c**	enynes
4a	100	40	75.7	24.3	0	81.7	0
5a	100	40	78.2	21.8	0	81.9	0

[a] Reaction conditions: phenylacetylene (**PA**, 1.0 mmol), trichloroacetic acid (1.1 mmol), catalyst (0.01 mmol) and dodecane (0.25 mmol) in toluene (1 mL) at 110 °C. Yields determined by GC analysis with dodecane as internal standard.

of enol esters were obtained. Enynes were not observed, but the chromatograms showed some other unidentified side-products.
The reaction is very fast: full conversion is already reached within 40 minutes. The higher acidity of trichloroacetic acid ($pK_a = 0.65$) versus acetic acid ($pK_a = 4.76$) is most likely the reason for this increase in speed. Because of the lower pK_a value, trichloroacetic acid will give a higher concentration of nucleophilic acetate anions, resulting in a faster reaction.
The distribution of enol esters is remarkable. Mainly Markovnikov adducts are formed with trichloroacetic acid where acetic acid produces the anti-Markovnikov adducts. The reason for the inversion of stereochemistry is unclear, but may be related to the kinetics of the reaction (vide infra). There is little or no difference between catalysts **4a** and **5a**.

5.3.2 Phenylacetylene and benzoic acid

The reaction of phenylacetylene and benzoic acid is presented in Figure 5.15. Table 5.5 summarizes the results. The conversion of phenylacetylene and the formation of enol esters and enynes is shown in Figure 5.16.
The trends that are observed here are comparable to the trends in the reaction of phenylacetylene with acetic acid. The reaction is a little bit faster, but otherwise there are no major differences. A lot of dimerization occurs ($\approx 40\%$) and the enol

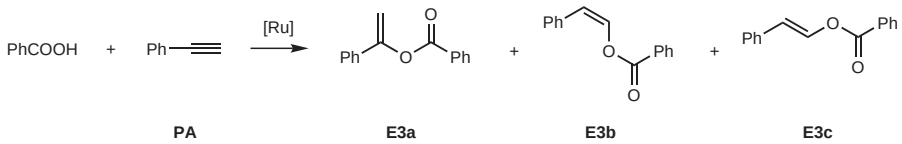


Figure 5.15: Addition of benzoic acid to phenylacetylene.

Table 5.5: Enol ester synthesis from phenylacetylene and benzoic acid[a]

	% conversion	time	Relative %			Yield (%)	
catalyst	**PA**	(min)	**E3a**	**E3b**	**E3c**	∑**E3a-c**	enynes
4a	100	180	7.5	36.7	55.8	59.1	40.3
5a	100	270	6.5	37.0	56.5	57.6	38.2

[a] Reaction conditions: phenylacetylene (**PA**, 1.0 mmol), benzoic acid (1.1 mmol), catalyst (0.01 mmol) and hexadecane (0.25 mmol) in toluene (1 mL) at 110 °C. Yields determined by GC analysis with hexadecane as internal standard.

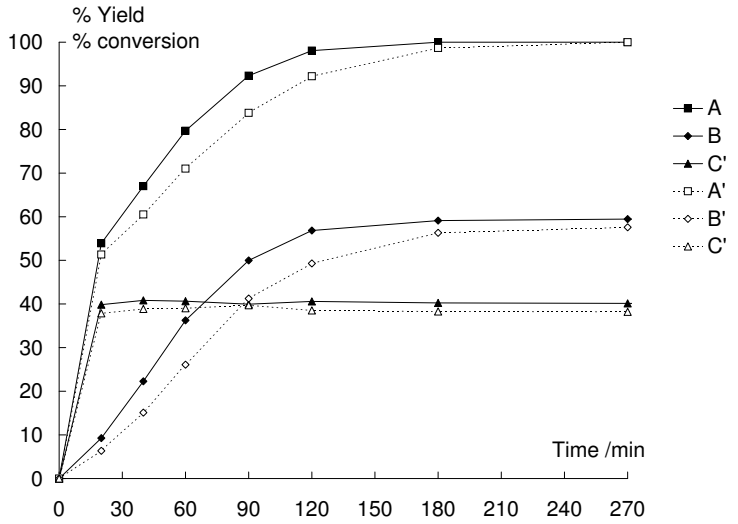


Figure 5.16: Conversion of phenylacetylene and formation of enol esters and enynes. Catalyst **4a**: A = %conversion **PA**, B = enol ester yield, C = enyne yield Catalyst **5a**: A' = %conversion **PA**, B' = enol ester yield, C' = enyne yield

esters have mainly anti-Markovnikov stereochemistry, of which the trans isomer is more abundant than the cis isomer. Catalyst **4a** performs the reaction faster than **5a**, but the yields obtained with both catalysts are similar.

5.3.3 1-Octyne and trichloroacetic acid

The general scheme of the reaction between 1-octyne and trichloroacetic acid is depicted in Figure 5.17. Table 5.6 summarizes the results. The reaction of 1-

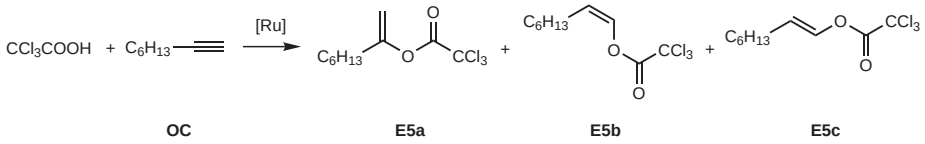


Figure 5.17: Addition of trichloroacetic acid to 1-octyne.

Table 5.6: Enol ester synthesis from 1-octyne and trichloroacetic acid[a]

	% conversion	time	Relative %			Yield (%)
catalyst	1-octyne	(min)	**E5a**	**E5b**	**E5c**	∑**E5a-c**
4a	100	20	63.7	34.3	1.9	90.1
5a	100	20	63.5	34.5	1.8	88.6

[a] Reaction conditions: 1-octyne (1.0 mmol), trichloroacetic acid (1.1 mmol), catalyst (0.01 mmol) and hexadecane (0.25 mmol) in toluene (1 mL) at 110 °C. Yields determined by GC analysis with hexadecane as internal standard.

octyne with trichloroacetic acid is extremely fast. Complete conversion of 1-octyne is already achieved after 20 minutes. Catalysts **4a** and **5a** perform equally well with excellent total yields and also the enol ester distribution is identical. Similar to the reaction of phenylacetylene with trichloroacetic acid, mainly Markovnikov enol esters are produced. Also a sizeable amount of cis enol esters is present, but the quantity of the trans isomer is minimal.

5.3.4 1-Octyne and benzoic acid

Figure 5.18 shows the general reaction of 1-octyne with benzoic acid. Table 5.7 presents the results and Figure 5.19 shows the 1-octyne conversion and enol ester yields as a function of time. Good yields of enol esters are obtained with both catalysts, though **4a** is superior to **5a**. Not only is the reaction faster with **4a**, also higher yields are obtained. Anti-Markovnikov enol esters with mainly cis configuration are the most abundant, but also a considerable amount of Markovnikov adducts is formed. The relative amount of Markovnikov products is higher than in

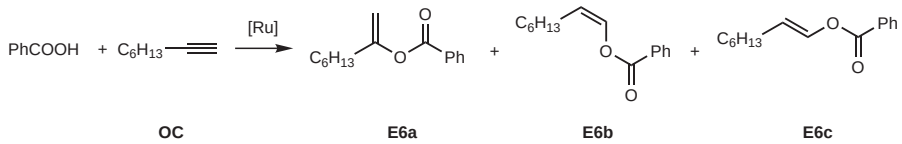


Figure 5.18: Addition of benzoic acid to 1-octyne.

Table 5.7: Enol ester synthesis from 1-octyne and benzoic acid[a]

	% conversion	time	Relative %			Yield (%)
catalyst	1-octyne	(min)	**E6a**	**E6b**	**E6c**	∑**E6a-c**
4a	100	180	25.2	50.6	24.2	84.2
5a	100	270	32.4	40.3	27.3	77.2

[a] Reaction conditions: 1-octyne (1.0 mmol), benzoic acid (1.1 mmol), catalyst (0.01 mmol) and hexadecane (0.25 mmol) in toluene (1 mL) at 110 °C. Yields determined by GC analysis with hexadecane as internal standard.

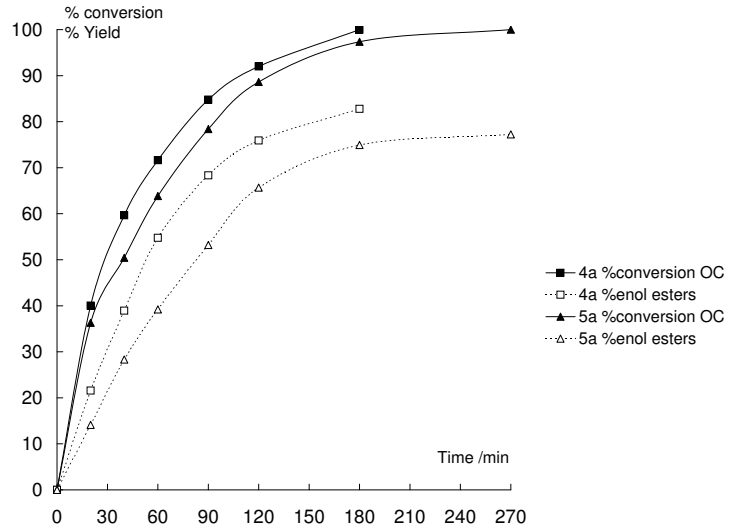


Figure 5.19: Conversion of 1-octyne and enol ester yield.

the reaction with acetic acid. The possible relationship between the pK_a value of the acid and the stereochemistry of enol esters will be discussed later in this work.

5.3.5 3,3-Dimethyl-1-butyne and acetic acid

The reaction of 3,3-dimethyl-1-butyne with acetic acid (Figure 5.20) is monitored over time and the results are summarized in Table 5.8. Because the solvent peak overlaps with the peak of 3,3-dimethyl-1-butyne in the chromatogram, only the formation of enol esters is shown in Figure 5.21. The total yield reaches a plateau after 270 minutes. Moderate to good yields were obtained and again **4a** proved to be

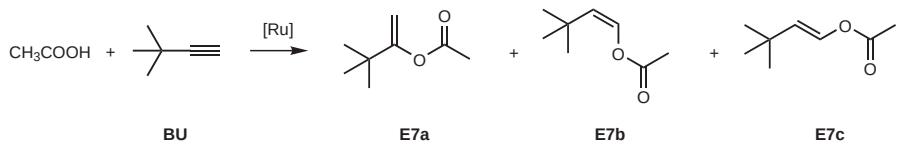


Figure 5.20: Addition of acetic acid to 3,3-dimethyl-1-butyne.

Table 5.8: Enol ester synthesis from 3,3-dimethyl-1-butyne and acetic acid[a]

	time	Relative %			Yield (%)
catalyst	(min)	**E7a**	**E7b**	**E7c**	∑**E7a-c**
4a	270	8.5	75.4	16.1	70.0
5a	270	9.8	69.5	20.7	64.6

[a] Reaction conditions: 3,3-dimethyl-1-butyne (1.0 mmol), acetic acid (1.1 mmol), catalyst (0.01 mmol) and hexadecane (0.25 mmol) in toluene (1 mL) at 110 °C. Yields determined by GC analysis with hexadecane as internal standard.

the better catalyst. The stereochemistry was predominantly cis anti-Markovnikov.

5.3.6 3,3-Dimethyl-1-butyne and trichloroacetic acid

3,3-Dimethyl-1-butyne reacts very fast with trichloroacetic acid (Figure 5.22). Very good maximum yields are reached after 20 minutes for **4a** and 30 minutes for **5a** (Table 5.9). Similar to the reaction of trichloroacetic acid with other alkynes, the geminal enol ester was the major compound.

5.3.7 3,3-Dimethyl-1-butyne and benzoic acid

The reaction of 3,3-Dimethyl-1-butyne with benzoic acid, depicted in Figure 5.23, produces enol esters in moderate yields (Table 5.10). A plateau is not yet reached after 420 minutes (Figure 5.24), making this reaction slower than that of 3,3-dimethyl-1-butyne with acetic acid. The main product is the cis anti-Markovnikov enol ester, but again, considerable amounts of Markovnikov enol esters are present, as was seen in the reaction of benzoic acid with the other alkynes.

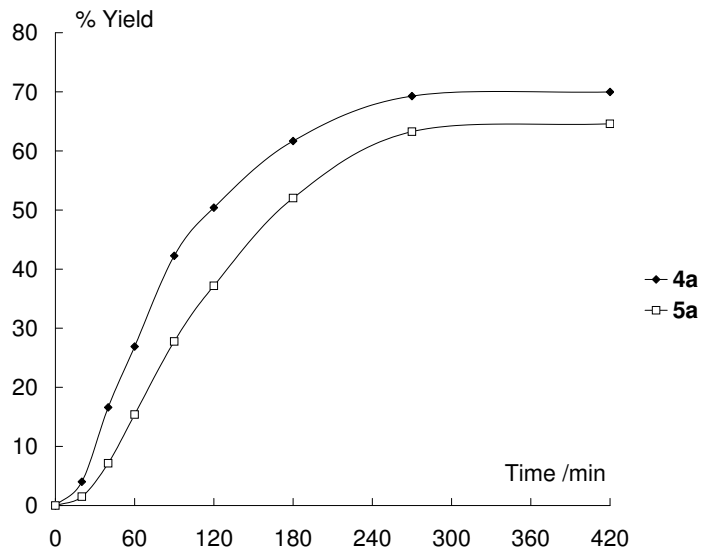


Figure 5.21: Yield of enol esters in the reaction of 3,3-dimethyl-1-butyne and acetic acid.

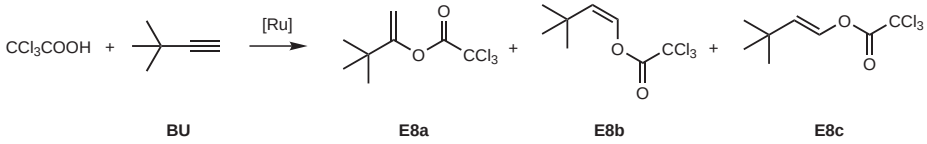


Figure 5.22: Addition of trichloroacetic acid to 3,3-dimethyl-1-butyne.

Table 5.9: Enol ester synthesis from 3,3-dimethyl-1-butyne and trichloroacetic acid[a]

	time	Relative %			Yield (%)
catalyst	(min)	**E8a**	**E8b**	**E8c**	∑**E8a-c**
4a	20	72.5	25.1	2.4	88.1
5a	30	74.9	22.3	2.9	84.9

[a] Reaction conditions: 3,3-dimethyl-1-butyne (1.0 mmol), trichloroacetic acid (1.1 mmol), catalyst (0.01 mmol) and hexadecane (0.25 mmol) in toluene (1 mL) at 110 °C. Yields determined by GC analysis with hexadecane as internal standard.

5.3.8 Cyclic enol esters from 4-pentynoic acid (Lactones)

Molecules that contain both an alkyne functionality and a carboxylic acid group can react either inter- or intramolecularly. An intermolecular reaction would pro-

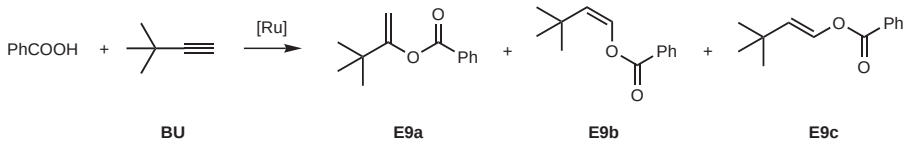


Figure 5.23: Addition of benzoic acid to 3,3-dimethyl-1-butyne.

Table 5.10: Enol ester synthesis from 3,3-dimethyl-1-butyne and benzoic acid[a]

	time	Relative %			Yield (%)
catalyst	(min)	**E9a**	**E9b**	**E9c**	∑**E9a-c**
4a	420	28.0	64.2	7.8	68.3
5a	420	32.3	54.9	12.8	65.9

[a] Reaction conditions: 3,3-dimethyl-1-butyne (1.0 mmol), benzoic acid (1.1 mmol), catalyst (0.01 mmol) and hexadecane (0.25 mmol) in toluene (1 mL) at 110 °C. Yields determined by GC analysis with hexadecane as internal standard.

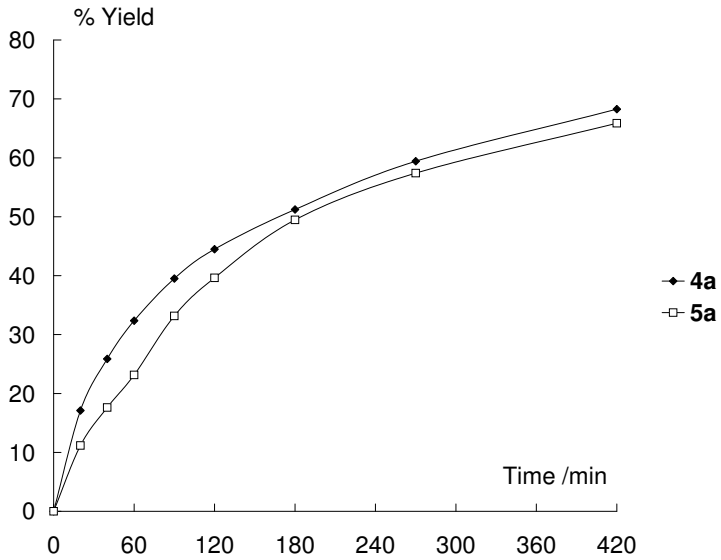


Figure 5.24: Yield of enol esters in the reaction of 3,3-dimethyl-1-butyne and benzoic acid.

duce polymers but this is never observed because the intramolecular reaction is much faster in the given reaction conditions. The substrate 4-pentynoic acid was chosen in the cyclization experiments. Two products can be formed: the five-

membered ring with an external double bond **E10a**, or the six-membered ring with an internal double bond **E10b** (Figure 5.25). Because of the high volatility

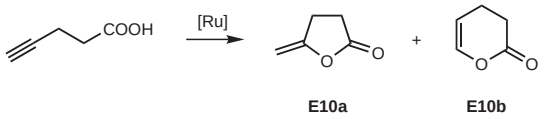


Figure 5.25: Intramolecular cyclization reaction of 4-pentynoic acid.

of the cyclic compound, the reaction was analyzed by ^{1}H-NMR spectroscopy. The substrate 4-pentynoic acid and the catalyst (**4a** or **5a**) were dissolved in deuterated toluene and the mixture was reacted at 110 °C. After 1 hour, the ^{1}H-NMR spectrum showed full conversion of the alkyne proton and carboxylic acid proton (Table 5.11). The only detectable product that was formed was the exocyclic five-

Table 5.11: Enol ester synthesis from 4-pentynoic acid[a]

		Yield (%)
catalyst	%conversion	**E10a**
4a	100	>95
5a	100	>95

[a] Reaction conditions: 4-pentynoic acid (1.0 mmol) and catalyst (0.01 mmol) in toluene-d8 (0.75 mL) at 110 °C for 1 h. Yields determined by ^{1}H-NMR spectroscopy and GC analysis.

membered γ-methylene-γ-butyrolactone **E10a**. Analysis of the reaction mixture by gas chromatography showed that less than 5% side-products were formed.

5.3.9 The alkynes 4-octyne and 2-methyl-3-butyn-2-ol

Both the substrates 4-octyne and 2-methyl-3-butyn-2-ol (Figure 5.26) did not react with carboxylic acids in the presence of **4a** or **5a**. They were recovered almost quantitatively after 7 hours of reaction. Apparently , complexes **4a** and **5a** are unable to activate internal triple bonds or the terminal triple bond of functionalized alkynes.

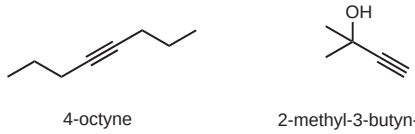


Figure 5.26: The alkynes 4-octyne and 2-methyl-3-butyn-2-ol.

5.3.10 Influence of the pK_a on the stereochemistry

The correlation between the pK_a value of the carboxylic acid and the stereochemistry of the enol esters can be deduced from Figure 5.27. Higher acidities (lower pK_a values) result in higher amounts of Markovnikov products. The pK_a may also be related to the reaction rate, as the reaction with trichloroacetic acid (pK_a = 0.62) is much faster than the reaction with benzoic acid (pK_a = 4.2) or acetic acid (pK_a = 4.76). The difference between benzoic acid and acetic acid is much less pronounced, but for the reaction with phenylacetylene and 1-octyne, the alkyne is consumed faster with benzoic acid than acetic acid.
The higher acidity results in a higher degree of dissociation of the acid and the resulting higher concentration of carboxylate anions enhances the reaction rate. Thus, the explanation for the correlation between the pK_a and stereochemistry

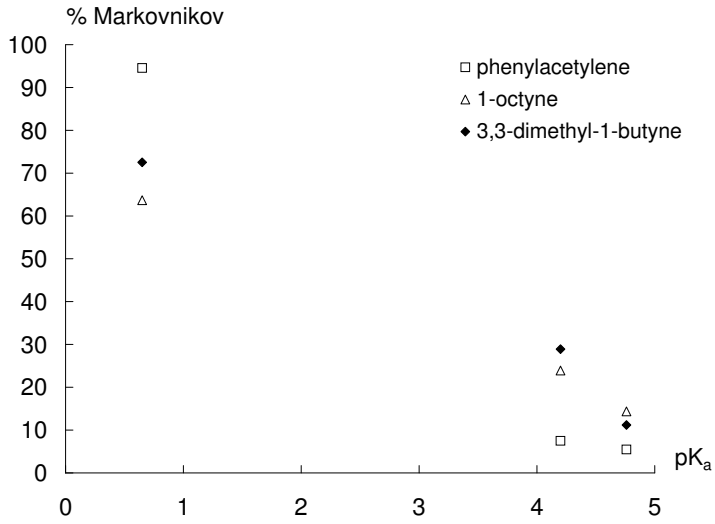


Figure 5.27: Relationship between pK_a and stereochemistry of enol esters.

may be found in the kinetics of the coupling reaction. Perhaps the formation of the geminal enol ester is kinetically favoured, resulting in higher amounts of Markovnikov addition in the fast reaction of trichloroacetic acid with alkynes. In the slower reactions with acetic acid and benzoic acid, the thermodynamically more stable cis and trans enol esters are preferably formed.

5.4 Tweaking the reaction conditions

5.4.1 Introduction

Thus far, all experiments have been performed under very straightforward reaction conditions: alkyne + acid + catalyst. This paragraph surveys the use of other reagents or additives in an attempt to improve the results. Some authors have described the use of bases for this reaction.[333] Another common modification is the addition of specific ligands to improve the catalytic activity.

5.4.2 Sodium acetate instead of acetic acid

The reaction of sodium acetate with phenylacetylene in the presence of **4a** only produces 0.9% enol esters. This result proves that the presence of an acid is required to succesfully perform the coupling reaction. When HCl (1.1 equivalents, 4 N solution in 1,4-dioxane) is added to the solution of sodium acetate, phenylacetylene and **4a**, the reaction is complete within 3 hours with 67% total yield of enol esters. Only 6% enynes were formed, but a lot of other unidentified side-products were also observed on the chromatograms. They might be attributed to Cl addition to the triple bond of the alkyne, but this is not yet confirmed.

5.4.3 The addition of NHC ligands

The beneficial effects that N-heterocyclic carbene (NHC) ligands often have on the catalytic activity has already been briefly described in a previous chapter (paragraph 2.2.1). The in situ addition of NHC's has also been explored for the synthesis of enol esters. First the HCl salt of the NHC is "activated" by the base KHMDS, to generate the free carbene. Then the carbene is added to a solution of the catalyst in toluene. This mixture is allowed to react for 30 minutes before the alkyne and the acid are added. Figure 5.28 shows the activation reaction and the used NHC's. The application of several NHC's has been tested for the reaction between

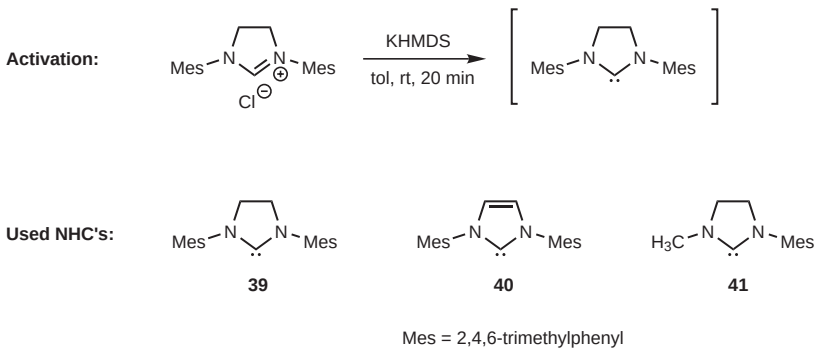


Figure 5.28: Activation reaction of the NHC and the used NHC ligands.

phenylacetylene and acetic acid with **3** as catalyst. The results are summarized in

Table 5.12. The addition of NHC's clearly has a beneficial effect on the total yield

Table 5.12: The use of NHC ligands for enol ester synthesis[a]

entry	catalyst	NHC	NHC equiv.[b]	%conv. **PA**	time (min)	% Yield ∑**E1a-c**	% Yield enynes
1	**3**	/	/	100	240	48.6	43.4
2	**3**	39	1	100	300	76.9	13.3
3	**3**	39	2	100	240	83.6	9.1
4	**3**	40	1	100	420	61.6	12.6
5	**3**	40	2	90.3	300	64.3	16.9
6	**3**	41	1	100	240	75.0	17.5
7	**3**	41	2	100	120	82.0	9.8
8	**12**	/	/	85.8	300	42.2	33.0

[a] Reaction conditions: phenylacetylene (**PA**, 1.0 mmol), acetic acid (1.1 mmol), activated NHC ligand, hexadecane (0.20 mmol) and **3** or **12** (0.01 mmol) in toluene (1.0 mL) at 110 °C. Yields determined by GC analysis with hexadecane as internal standard. [b] versus catalyst.

of enol esters and the dimerization reaction is suppressed to a great extent. Normally, **3** produces 43.4% enynes but with the use of NHC ligands, this amount can be reduced to values around 10%. The distribution of enol ester isomers remains unchanged and is therefore not shown. As an additional advantage, the reaction is faster when 2 equivalents of **41** are used. The use of saturated NHC's **39** and **41** results in higher yields than the use of unsaturated **40**.
To determine the generality of the enhanced reaction rate and yields obtained with the addition of NHC's, the approach was extended to all alkyne-carboxylic acid pairs with **4a** as catalyst. Table 5.13 presents the results. Again, the enol ester distributions are not included as they were nearly identical to the reactions without NHC addition. It appears that, compared to the reactions without NHC addition, improved yields are only obtained in certain reactions. General examples are the reactions where acetic acid is used. Also the coupling of phenylacetylene with benzoic acid greatly benefits from NHC addition. On the other hand, in the reactions with trichloroacetic acid, the yields are substantially lower. Additionally, in none of the reactions an enhanced reaction rate is observed. Thus the addition of NHC ligands does not necessarily lead to faster reactions with higher enol ester yields.
Complex **12** with the NHC coordinated to the metal center was also tested (entry 8 in Table 5.12), but the results are disappointing. The reaction rate is low (only 85.8% conversion after 5 hours), low enol ester yields are obtained and a considerable amount of enynes is formed. This leads to the question whether the improved performance can be attributed to the in situ complexation of the NHC with **3**, leading to an improved catalyst, or that the NHC has some other effect. Experiments with only the NHC in the absence of a catalyst did not afford any enol esters or enynes, thus the NHC itself has no catalytic activity. NHC's are strong bases[382,383] and perhaps their only fuction is to increase the pH of the solution to increase the

Table 5.13: The use of NHC ligands for all alkyne/carboxylic acid pairs[a]

entry			%conv.	time	% Yield	
n =	alkyne	acid	alkyne	(min)	$\sum$**E(n)a-c**	enynes
1	**PA**	CH_3COOH	100	270	85.1	6.6
2		CCl_3COOH	100	60	52.3	0
3		PhCOOH	100	420	87.3	11.2
4	**OC**	CH_3COOH	100	270	84.7	0
5		CCl_3COOH	100	40	77.3	0
6		PhCOOH	100	270	84.2	0
7	**BU**	CH_3COOH	100	420	82.1	0
8		CCl_3COOH	100	90	68.7	0
9		PhCOOH	100	420	63.6	0

[a] Reaction conditions: alkyne (1.0 mmol), carboxylic acid (1.1 mmol), activated **41** (0.02 mmol), hexadecane (0.25 mmol) and **4a** (0.01 mmol) in toluene (1.0 mL) at 110 °C. Yields determined by GC analysis with hexadecane as internal standard. **PA** = phenylacetylene, **OC** = 1-octyne, **BU** = 3,3-dimethyl-1-butyne.

amount of acetate anions in the reaction mixture, resulting in a higher reaction rate. The basic function also inhibits the acid-promoted dimerization reaction.

5.4.4 The addition of bases

The addition of bases has been reported by other authors[333] and was also investigated in this work. A catalytic amount (5% versus alkyne) of several organic and inorganic bases was added to the reaction of phenylacetylene with acetic acid in the presence of complex **4a**. The results are presented in Table 5.14. The use of a base has a similar effect as the addition of NHC ligands. The amount of enynes is greatly reduced and higher enol ester yields are obtained. With the exception of KOH, the inorganic bases all performed equally well: around 75% enol esters are obtained along with 6% enynes. The use of the organic bases Et_3N or DBU gave comparable enol ester yields but resulted in more dimerization. The strongest base, KHMDS, gave the best results.
Goossen et al. reported that there was a difference in enol ester stereochemistry when inorganic or organic bases were used.[333] However, this is not observed for complex **4a**. The use of all bases gave isomer ratios that were similar to the reaction without a base.
These results support the theory that the NHC's in fact behave as a base, and not as a ligand. Further confirmation is found when the NHC is added *last* to a reaction mixture of catalyst/alkyne/acid. Because of the 100-fold excess of acid versus catalyst, the NHC will react with the acid before it can coordinate with the catalyst. The results obtained this way are similar to the original results in Table 5.12.

Table 5.14: The addition of bases to the reaction of phenylacetylene with acetic acid[a]

		%conv.	time	relative %			% Yield	
entry	base	**PA**	(min)	**E1a**	**E1b**	**E1c**	∑**E1a-c**	enynes
1	/	100	180	5.8	36.8	57.4	57.1	36.4
2	KOH	89.1	420	6.0	40.4	53.6	57.5	7.6
3	NaOEt	100	270	4.9	40.4	54.7	76.9	6.6
4	KOtBu	100	420	4.6	40.9	54.5	77.3	6.1
5	Na_2CO_3	100	420	5.0	40.4	54.6	73.3	6.2
6	Et_3N	100	270	5.4	40.6	54.0	71.4	17.5
7	DBU	100	420	5.0	43.3	51.7	72.0	13.6
8	KHMDS	100	270	5.3	41.8	52.9	85.6	6.3

[a] Reaction conditions: phenylacetylene (**PA**, 1.0 mmol), acetic acid (1.1 mmol), base (0.05 mmol), hexadecane (0.25 mmol) and **4a** (0.01 mmol) in toluene (1.0 mL) at 110 °C. Yields determined by GC analysis with hexadecane as internal standard.

5.5 Mechanistical considerations for the synthesis of enol esters.

Many authors have proposed possible reaction mechanisms for the ruthenium-catalyzed synthesis of enol esters, but thus far none of these proposals has been backed up with sound proof. One fundamental part of a reaction mechanism is the explanation of the stereochemistry of the formed enol esters.

Let's start by stating the obvious: the ruthenium catalyst is somehow involved in the reaction. The coupling reaction does not proceed without the presence of a catalyst, but how and where exactly does it interfere? Ruthenium complexes are known to be able to coordinate triple bonds, but the addition of an alkyne to the ruthenium center can have several outcomes: η^2-coordination of the alkyne leads to **I** while oxidative addition of the C-H bond to the metal center gives **II** (Figure 5.29). Both **I** and **II** can rearrange to vinylidene complex **III**, either by 1,2-hydrogen migration over the triple bond, or by a 1,3-hydride shift to the alkynyl ligand respectively.[384–388] This coordination results in the activation of the alkyne triple bond, making it susceptible to a nucleophilic attack of a carboxylic acid, or more likely, a carboxylate anion.

The question then is, whether or not the carboxylate also coordinates with the metal center prior to reacting with the alkyne. This has been proposed by Melis[339] and Ye,[337] but no proof has been provided to support this assumption. Most other authors regard the addition as an intermolecular attack of a free carboxylate on the coordinated alkyne. The addition of carboxylic acids to ruthenium is certainly possible as was shown by Esteruelas et al.[389] Dixneuf et al. have shown that carboxylate addition even is a key step in the generation of the active catalyst from complex **32a,b**.[321] The coordinated carboxylates, however, do not participate in the enol ester synthesis. Ye and Leong based their proposal of carboxylate addition to catalyst

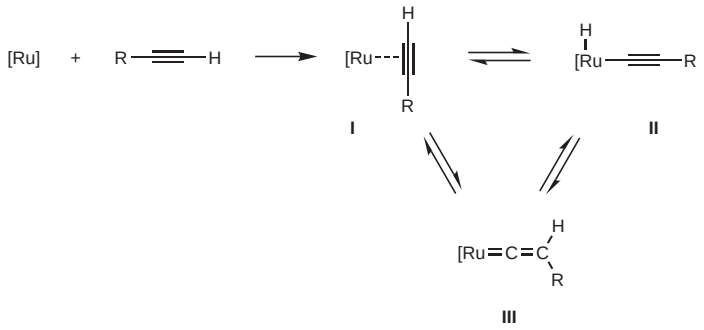


Figure 5.29: Possible ways of alkyne coordination.

$[CpRu(CO)_2)Cl]$ on the fact that the carboxylate complex $[CpRu(CO)_2(O_2CPh)]$ catalyzes the reaction with similar efficiency. Kawano and co-workers have synthesized what they claim to be a real intermediate in ruthenium-catalyzed synthesis of enol esters.[390] The reaction of complex **42** with alkynes produced complexes of the type **43**, containing a (Z)-enol ester like chelate ligand (Figure 5.30). Treatment

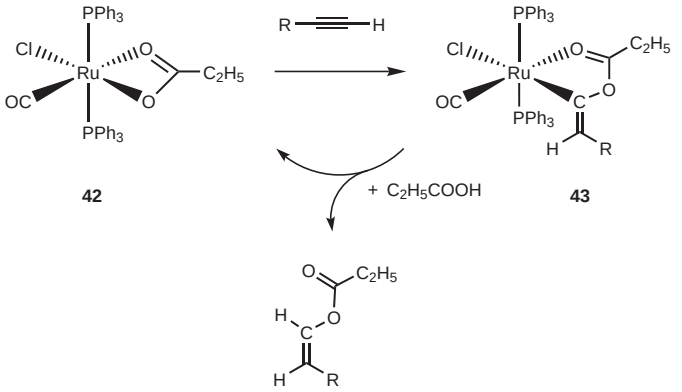


Figure 5.30: Synthesis of a complex with a (Z)-enol ester like chelate ligand.

of **43** with propanoic acid released the (Z)-enol ester and partially returned starting complex **42**, leading to the suggestion that **43** is a real intermediate in the synthesis of (Z)-enol esters. However, a real catalytic experiment with complex **43** did not only produce the (Z)-enol ester, but also a small amount of (E)-enol esters and large amounts of geminal enol esters. Furthermore, not only complex **42** was returned upon addition of propanoic acid, but also several other ruthenium compounds. It shows nonetheless, that carboxylic acid addition to the ruthenium catalyst is a possible step in the total reaction mechanism. It may very well be that carboxylate coordination is in fact catalyst-dependent and that no general conclusions can be made on this account.

The coupling of carboxylic acids with alkynes can result in three isomers. Anti-Markovnikov addition is usually explained by the generation of a vinylidene intermediate.[321,329,384,391] The α-carbon of the vinylidene is electrophilic[386,387] and a nucleophilic attack on this carbon results in anti-Markovnikov adducts as is illustrated in Figure 5.31. Melis et al.[339] have shown the actual formation of a vinylidene complex as reaction intermediate. Markovnikov addition on the other

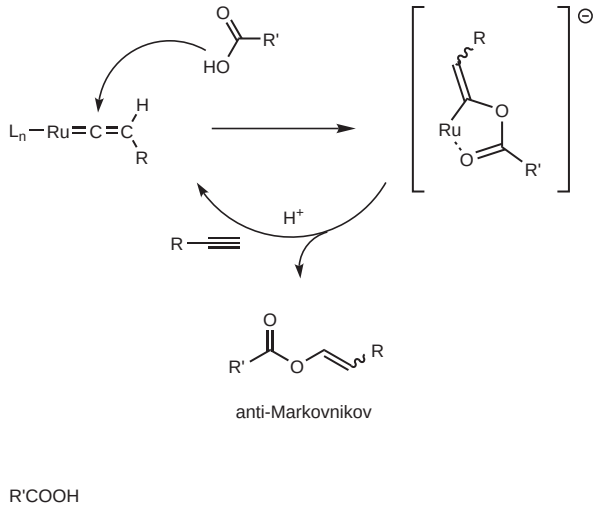


Figure 5.31: Synthesis of anti-Markovnikov enol esters via a vinylidene intermediate.

hand, might occur by carboxylate addition to the alkyne ligand in intermediates of the type **I** (see Figure 5.29).
We have been unable to determine the reaction mechanism that operates with Schiff base complexes **4a** and **5a**. The reaction of **4a** with an equimolar amount of acetic acid (5 hours at 60 °C in $CDCl_3$) did not result in any changes in the ^{1}H or ^{13}C-NMR spectrum. Likewise, the addition of 1-octyne to **4a** did not afford detectable amounts of vinylidene carbons. The experiments were repeated in deuterated toluene (5 hours at 110 °C), but the solubility of **4a** was too low to obtain clean NMR-spectra.

5.6 Conclusions on ruthenium-catalyzed synthesis of enol esters

Enol esters can be prepared by the ruthenium-catalyzed coupling reaction between alkynes and carboxylic acids. The application of some new ruthenium Schiff base complexes for this reaction was tested and they were shown to be able to compete with several commercially available catalysts. The nature of the Schiff base ligand proved to be very important. Nitro-containing complexes were less efficient than their non-nitro analogues. Furthermore, complexes with an aliphatic group on the

Schiff base nitrogen performed markedly better than complexes with an aromatic group.
Several alkynes (phenylacetylene, 1-octyne and 3,3-dimethyl-1-butyne) and carboxylic acids (acetic acid, benzoic acid, trichloroacetic acid and 4-pentynoic acid) were coupled using complexes **4a** and **5a**. The stereochemistry of the prepared enol esters was strongly dependent on the nature of the acid. Reactions with acetic acid or benzoic acid produced mainly anti-Markovnikov enol esters, while trichloroacetic acid resulted in Markovnikov adducts. The reactions with trichloroacetic acid were also much faster, which might be attributed to the stronger acidity resulting in a higher concentration of nucleophilic carboxylate anions.
The coupling reactions of phenylacetylene with acetic or benzoic acid produced a sizeable amount of enynes as side-products from the dimerization reaction of the alkyne. The addition of NHC's or bases greatly reduced this dimerization and resulted in higher enol ester yields. Again, the resulting higher carboxylate concentration may be responsible for the preference of enol ester formation over dimerization.

6

General conclusions and outlook

The main goal of this work was the synthesis of some new ruthenium complexes with Schiff base ligands and to explore their applicability in the synthesis of quinolines and enol esters. Several new ruthenium Schiff base catalysts were prepared from the dimeric ruthenium precursor $[RuCl_2(\text{p-cymene})]_2$. Although the general strategy towards these compounds had already been described, an important finding from our work was the need for an additional purification by column chromatography to obtain the Schiff base complexes as pure compounds.

In a modification of the Friedlander method, 2-aminobenzylalcohol is oxidatively cyclized with ketones in the presence of a base, affording quinolines. The key step in this method involves a ruthenium-catalyzed hydrogen transfer reaction for the *in situ* oxidation of 2-aminobenzylalcohol to 2-aminobenzaldehyde. While a literature overview suggests that ruthenium Schiff base complexes are active for transfer hydrogenation reactions, the use of ruthenium-arene Schiff base catalysts resulted in little or no quinolines. The incorporation of strong σ-donating ligands such as phosphines or NHC's substantially increased the quinoline yields. This proves that the coordination sphere of the transition metal is a determinant factor for catalytic activity. Not only the catalyst is important, also the base plays an important role. The second generation Grubbs catalyst, in combination with the strong *tert*-butoxide base from KOtBu gives the best results in terms of quinoline yield and reaction time. The presence of a hydrogen acceptor is necessary for the regeneration of the original catalyst.
The classic reaction mechanism often proposed in literature was subjected to a very close examination. The experimental data that were obtained in this work are clearly not in accordance with the proposed literature model. Based on the experimental results, we suggest that the reaction mechanism consists of two distinctively different pathways that can operate simultaneously. Due to the very complex na-

ture of the reaction mixture, the exact structure of the active catalytic ruthenium species could not be determined. However, combining a thorough literature report with the experimental data, a ruthenium-carbonyl-hydride complex is a credible suggestion. The elucidation of the active species remains a formidable challenge.
The newly developed synthetic strategy for the previously cumbersome synthesis of 3-substituted quinolines might be a valuable contribution to this research area. In a two-step reaction, first a 1,3-oxazine is formed in the reaction between 2-aminobenzylalcohol and the aldehyde. Via the well-documented ring-chain tautomerism, the oxazine is at equilibrium with the imine-tautomer. Subsequent addition of a ruthenium catalyst, the strongly basic potassium t-butoxide and a hydrogen acceptor (benzophenone) affords 3-substituted quinolines in excellent yields.
It was discovered that the presence of an expensive ruthenium catalyst is not mandatory. Quinolines could also be prepared in a purely base-mediated process. The best results were obtained with KOtBu. The reaction most likely proceeds via the Meerwein-Ponndorf-Verley-Oppenauer (MPVO) mechanism with a six-membered cyclic intermediate. This mechanism differs from the one in the ruthenium catalyzed process in the way the hydrogen atoms are transferred. In the case of transition metals, first a metal hydride is formed in the oxidation reaction of 2-aminobenzylalcohol. To regenerate the original catalyst, the hydrogen atoms are then transferred to a hydrogen acceptor that is reduced in the process. In the absence of transition metals, the hydrogen transfer is believed to occur through a cyclic intermediate. This base-mediated process could also be applied to the preparation of 3-substituted quinolines in nearly quantitative yields. In retrospect, one might wonder which mechanism is followed in the ruthenium-catalyzed process with KOtBu as a base.
Evaluating these results, it is remarkable that Grubbs-type complexes are good transfer hydrogenation catalysts in the modified Friedlander method and it would be interesting to find out if their application can be extended to other hydrogen transfer reactions. This is still an expanding research area and perhaps this type of complexes will prove to be a valuable extension of the vast arsenal of hydrogenation catalysts. Another extraordinary finding is the preparation of quinolines via a relatively mild MPVO reaction, mediated merely by the strong base KOtBu. Although it appears that the favourable reaction conditions for this process are provided by the specific nature of the reagents, it would still be worthwhile to investigate this method for other transfer hydrogenation reactions.

The second part of this work is devoted to the synthesis of enol esters in a ruthenium-catalyzed coupling reaction between carboxylic acids and terminal alkynes. From the prepared ruthenium Schiff base catalysts, only complexes without a nitro group and an aliphatic group on the Schiff base nitrogen showed high activity. Several alkynes and carboxylic acids were coupled using the two most promising catalysts. The stereochemistry of the obtained enol esters depends on several factors. A literature survey shows that most catalysts produce the geminal enol ester (Markovnikov addition). This is especially true for complexes containing phosphine ligands, which is confirmed by the experimental data in the present PhD-work. Anti-Markovnikov enol esters are less frequently reported, and as such it is interesting that the Schiff base catalysts mainly produce these anti-Markovnikov

adducts for most acid/alkyne combinations. However, the distribution of enol ester isomers is also strongly influenced by the nature of the carboxylic acid. The use of trichloroacetic acid results in Markovnikov enol esters, while acetic acid and benzoic acid lead to anti-Markovnikov adducts. The acidic strength might be the reason for this, even though this assumption still requires a more thorough investigation.
A frequently observed non-desired side-reaction in the coupling of phenylacetylene with acids is alkyne dimerization to enynes. The addition of N-heterocyclic carbenes or bases greatly reduces this dimerization and results in higher enol ester yields, while not affecting the stereochemistry. Likely, the resulting higher carboxylate concentration is responsible for this.
In summary, ruthenium Schiff base complexes catalyze the coupling of carboxylic acids with alkynes, but the reaction does not proceed with high regio- and stereoselectivity. Future research should focus on fine-tuning the ligand environment to selectively obtain one enol ester isomer as a major compound.

7 Experimental

7.1 General remarks

7.1.1 Chemical compounds and synthesis

All synthetic procedures involving organometallic compounds were conducted in oven-dried glassware under argon atmosphere using standard Schlenk techniques. The following solvents were distilled and dried under argon using standard techniques: THF (Na, Benzophenone), Toluene (Na), CH_2Cl_2 (CaH_2). Other solvents (Dioxane, Aldrasorb®and Ethyl Acetate, Rotisolv®Pestylise®) were used as received without further manipulations. Products that were obtained from commercial sources (Aldrich, Acros, VWR International, Fiers) were used as received. Argon was dried over a column of Drierite®.
Catalysts **1**, **16** and **17** were purchased from Sigma-Aldrich and **21** was generously supplied by Umicore. Compounds **2**,[243] **3**,[229] **11a,b**,[232,233] **12**,[239] **14**,[217] **15**,[244] **16**,[246] **17**,[247] **18-20**,[213] **22-23**,[7] **24-25**,[212] **26**,[251] **27**,[253] **39-40**,[240] and **41**[392,393] were prepared following literature procedures.

7.1.2 Experimental techniques and analysis

NMR spectra were recorded on a Varian Unity 300 MHz spectrometer equipped with a 300AutoSW probe (4NUC/30-122 MHz). Standard parameters for ^{1}H-NMR: frequency: 299.87 MHz, acquisition time: 1.0000 s, number of scans: 16, sweep width: 9000.90 Hz, room temperature, solvent as indicated in spectral data. Standard parameters for ^{13}C-NMR: frequency: 75.41 MHz, acquisition time: 1.8151 s, number of scans: 1024, sweep width: 16501.65 Hz, room temperature, solvent as indicated in spectral data.
GC measurements were performed on a Finnigan TraceGC Ultra with an Ultra Fast

Column Module. The quinoline experiments were analyzed using a 100% dimethyl polysiloxane column (0.32 mm × 5 m, 0.25 μm film thickness) with the following GC method. Temperature program: initial temperature 40 °C, 6 seconds; ramping with 100 °C min^{-1} to 250 °C; 250 °C, 1 minute. Carrier gas: helium, constant flow, 5 mL min^{-1}, inlet temperature: 250 °C, block temperature 260 °C, split flow: 100 mL min^{-1}. Detector: flame ionization detector, air: 300 mL min^{-1}, hydrogen: 30 mL min^{-1}, base temperature: 310 °C. The analysis of the enol ester experiments was conducted using a 5% diphenyl - 95% dimethyl polysiloxane column (0.10 mm × 10 m, 0.40 μm film thickness) with the following GC method. Temperature program: initial temperature 40 °C, 6 seconds; ramping with 75 °C min^{-1} to 250 °C; 250 °C, 4 minutes. Carrier gas: helium, constant flow, 0.5 mL min^{-1}, inlet temperature: 250 °C, block temperature 260 °C, split flow: 100 mL min^{-1}. Detector: flame ionization detector, air: 300 mL min^{-1}, hydrogen: 30 mL min^{-1}, base temperature: 310 °C.
GC-MS measurements were performed by Marc Schelfaut (Dept. Organic Chemistry, Separation Sciences) on a HP 5890 series II chromatograph coupled with a HP 5989A quadrupole mass spectrometer. Column: HP-5MS (crosslinked 5% Ph ME siloxane). Carrier gas: He, 8 psi. Temperature program: from room temperature to 80 °C at 50 °C min^{-1}, from 80 °C to 280 °C at 6 °C min^{-1}.

7.2 Synthesis of Schiff base ligands

All Schiff base ligands were obtained by a simple and straightforward condensation reaction of an aldehyde (salicyladehyde or 5-nitrosalicylaldehyde) with an amine. Schiff base **SB7** was synthesized by a procedure described by Allaert.[394]

7.2.1 Schiff base SB1

A 2.0 M solution of methylamine in THF (20.5 mL, 40.9 mmol) was added to 5.0 g (40.9 mmol) salicylaldehyde. The solution was refluxed for 4 h, cooled down to room temperature and dried on $MgSO_4$. After filtration, the solvent was evaporated to afford the Schiff base as a viscous yellow oil (Yield: 65%).
^{1}H-NMR ($CDCl_3$) δ(ppm): 13.17 (bs, 1H), 8.21 (s, 1H), 7.25 (t, 1H, ^3J(H,H) = 7.4 Hz), 7.16 (d, 1H, ^3J(H,H) = 7.7 Hz), 6.93 (d, 1H, ^3J(H,H) = 8.2 Hz), 6.84 (t, 1H, ^3J(H,H) = 7.1 Hz), 3.37 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 166.5, 161.5, 132.3, 131.3, 119.1, 118.7, 117.2, 46.1

7.2.2 Schiff base SBN1

A 2.0 M solution of methylamine in THF (15 mL, 30 mmol) was added to 5.0 g (30 mmol) 5-nitrosalicylaldehyde. The solution was refluxed for 4 h. Upon cooling to 0°C, a yellow precipitate formed. The precipitate was filtered, washed with ice cold THF and dried in vacuo to afford the Schiff base in good yield (82%).
^{1}H-NMR ($CDCl_3$) δ(ppm): 14.82 (bs, 1H), 8.36 (s, 1H), 8.23 (s, 2H), 6.98 (s, 1H), 3.55 (s, 3H); ^{13}C-NMR (DMSO-d_6) δ(ppm): 178.7, 168.9, 134.1, 133.4, 130.0, 123.6, 114.2, 39.7

7.2.3 Schiff base SB2

Cyclohexylamine (5.4 mL, 47 mmol) and salicylaldehyde (5.0 mL, 47 mmol) were dissolved in 25 mL THF. The solution was refluxed at 60 °C for 4 h, then cooled down to room temperature and dried on $MgSO_4$. After filtration, the solvent was evaporated, leaving the Schiff base as a viscous yellow oil. (Yield: 67 %)
^{1}H-NMR ($CDCl_3$) δ(ppm): 13.81 (s, 1H), 8.31 (s, 1H), 7.26 (t, 1H, ^3J(H,H) = 8.2 Hz), 7.20 (d, 1H, ^3J(H,H) = 7.7 Hz), 6.93 (d, 1H, ^3J(H,H) = 8.2 Hz), 6.83 (t, 1H, ^3J(H,H) = 7.7 Hz), 3.19 (m, 1H), 1.78 (m, 4H), 1.65-1.20 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 162.5, 161.8, 132.2, 131.4, 119.2, 118.6, 117.3, 67.7, 34.5, 25.8, 24.6.

7.2.4 Schiff base SB6

Tert-butylamine (4.9 mL, 47 mmol) and salicylaldehyde (5.0 mL, 47 mmol) were dissolved in 25 mL THF. The solution was refluxed at 60 °C for 4 h, then cooled down to room temperature and dried on $MgSO_4$. After filtration, the solvent was evaporated, leaving the Schiff base as a viscous yellow oil. (Yield: 64%)
^{1}H-NMR ($CDCl_3$) δ(ppm): 14.38 (bs, 1H), 8.31 (s, 1H), 7.25 (m, 2H), 6.95 (d, 1H, ^3J(H,H) = 8.2 Hz), 6.83 (t, 1H, ^3J(H,H) = 7.1 Hz), 1.32 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 162.4, 159.9, 132.3, 131.6, 119.1, 118.4, 117.5, 57.2, 29.8.

7.2.5 Schiff bases SBN2, SB3, SBN3, SB4, SBN4, SB5, SBN5 and SBN6

Equimolar quantities (typically 30 mmol) of amine and saliciylaldehyde or 5-nitro-saliciylaldehyde were dissolved in ethanol. After stirring for 4 h at 80 °C the solution was cooled to 0 °C. The yellow precipitate was filtered, washed with cold ethanol and dried in vacuo to afford the desired Schiff base ligand in good to excellent yields.
SBN2 (yellow solid, 72%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 15.16 (bs, 1H), 8.35 (s, 1H), 8.23 (s, 1H), 8.15 (d, 1H, ^3J(H,H) = 9.3 Hz), 6.87 (d, 1H, ^3J(H,H) = 9.3 Hz), 3.47 (m, 1H), 2.00-1.30 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 173.1, 162.3, 137.6, 129.5, 128.9, 120.8, 115.7, 64.4, 33.8, 25.3, 24.3.
SB3 (yellow solid, 88%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 13.12 (bs, 1H), 8.31 (s, 1H), 7.46-7.32 (m, 2H), 7.19 (bs, 3H), 7.08 (d, 1H, ^3J(H,H) = 8.2 Hz), 6.95 (t, 1H, ^3J(H,H) = 7.1 Hz), 2.98 (m, 2H, ^3J(H,H) = 6.6 Hz), 1.18 (d, 12H, ^3J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 166.9, 161.5, 146.5, 138.9, 133.6, 132.5, 125.8, 123.5, 119.3, 118.9, 117.6, 28.4, 23.8.
SBN3 (yellow solid, 95%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 14.31 (s, 1H), 8.39 (s, 1H), 8.35 (s, 1H), 8.32 (d, 1H, ^3J(H,H) = 9.3 Hz), 7.23 (s, 3H), 7.14 (d, 1H, ^3J(H,H) = 9.3 Hz), 2.93 (m, 2H, ^3J(H,H) = 6.6 Hz), 1,20 (d, 12H, ^3J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 167.3, 165.6, 144.8, 140.2, 138.9, 128.8, 128.7, 126.6, 123.8, 118.7, 117.8, 28.5, 23.8.
SB4 (yellow solid, 84%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 12.83 (s, 1H), 8.21 (s, 1H), 7.41 (t, 1H, ^3J(H,H) = 7.7 Hz), 7.33 (d, 1H, ^3J(H,H) = 7.3 Hz), 7.23 (s, 2H), 7.05 (d, 1H, ^3J(H,H) = 8.1 Hz), 6.95 (t, 1H, ^3J(H,H) = 7.7 Hz), 2.16 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 167.4, 161.4, 147.5, 133.8, 132.6, 131.2, 130.7, 119.4,

118.9, 118.0, 117.6, 18.6.
SBN4 (yellow solid, 90%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 13.95 (s, 1H), 8.41 (s, 1H), 8.34 (s, 1H), 8.31 (d, 1H, ^{3}J(H,H) = 9.3 Hz), 7.28 (s, 2H), 7.14 (d, 1H, ^{3}J(H,H) = 9.3 Hz), 2.19 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 166.9, 166.0, 146.1, 140.3, 131.5, 130.7, 128.9, 128.7, 119.0, 118.7, 117.8, 18.6.
SB5 (yellow solid, 92%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 13.28 (s, 1H), 8.36 (s, 1H), 7.45 (d, 1H, ^{3}J(H,H) = 6.9 Hz), 7.38 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 7.09 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 7.02-6.96 (m, 2H), 2.34 (s, 3H), 2.22 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 166.9, 161.5, 145.9, 134.7, 133.3, 132.4, 129.3, 128.5, 119.2, 119.1, 117.6, 21.1, 18.7.
SBN5 (yellow solid, 94%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 14.50 (s, 1H), 8.41 (s, 1H), 8.33 (s, 1H), 8.28 (d, 1H, ^{3}J(H,H) = 9.5 Hz), 7.11 (d, 1H, ^{3}J(H,H) = 9.5 Hz), 6.95 (s, 2H), 2.31 (s, 3H), 2.20 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 167.6, 165.4, 144.1, 140.0, 135.9, 129.6, 128.9, 128.7, 128.5, 118.7, 117.8, 21.1, 18.7.
SBN6 (yellow solid, 86%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 15.59 (s, 1H), 8.31 (s, 1H), 8.27 (s, 1H), 8.14 (d, 1H, ^{3}J(H,H) = 9.3 Hz), 6.83(d, 1H, ^{3}J(H,H) = 9.3 Hz), 1.47 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 175.2, 160.5, 136.9, 130.5, 129.3, 121.7, 114.7, 57.3, 29.5.

7.3 Synthesis of the Schiff base thallium salts

This step was performed under argon atmosphere due to the air-sensitivity of thallium ethoxide. Because of the highly toxic nature of thallium, all manipulations were carried out with extreme caution and waste products were collected and disposed with the highest care.
The Schiff base was dissolved in THF and an equimolar quantity of TlOEt was added. A yellow precipitate started to form almost instantaneously. After stirring for 2 hours at room temperature, the precipitation was filtered, dried in vacuo and used in the next step without further purification or characterization. For Schiff bases **SB1**, **SBN1**, **SB6** and **SBN6** it was necessary to reduce the solvent volume and/or to cool down the solution to 0°C before precipition occurred.

7.4 Synthesis of the catalysts

7.4.1 Synthesis of RuCl(p-cymene)SchiffBase complex

$[RuCl_2(p\text{-cymene})]_2$ and two equivalents of the Schiff base thallium salt were dissolved in THF and the solution was stirred for 4 h at room temperature. After evaporation of the majority of the solvent, the mixture was purified by column chromatography (silica gel) with aceton/dichloromethane (1:4). The red band containing the catalyst was collected and the solvent was evaporated. The catalyst was dissolved in a minimal amount of CH_2Cl_2, hexane was added and the solution was cooled to 0 °C to allow precipitation. The precipitate was filtered, washed with cold hexane and dried in vacuo to afford the pure catalyst in moderate to good yields. The reaction of the ruthenium dimer with the Schiff bases with a tertiary butyl (**SB6** and **SBN6**) or adamantyl (**SB7**) group did not afford the

desired ruthenium complexes due to rapid decomposition during purification by column chromatography. The initially red band quickly changed to dark brown and green on the silica column.
4a (orange-red powder, 62%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.68 (s, 1H), 7.17 (t, 1H, ^{3}J(H,H) = 6.9 Hz), 6.96 (d, 1H, ^{3}J(H,H) = 8.8 Hz), 6.91 (d, 1H, ^{3}J(H,H) = 7.3 Hz), 6.42 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 5.45 (d, 1H, ^{3}J(H,H) = 5.9 Hz), 5.40 (s, 2H), 5.17 (d, 1H, ^{3}J(H,H) = 5.1 Hz), 4.01 (s, 3H), 2.81 (m, 1H, ^{3}J(H,H) = 6.6 Hz), 2.20 (s, 3H), 1.24 (d, 3H, ^{3}J(H,H) = 6.6 Hz), 1.17 (d, 3H, ^{3}J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 165.7, 164.5, 134.8, 134.2, 122.8, 119.9, 114.4, 102.3, 97.4, 84.5, 82.8, 82.3, 80.8, 57.6, 31.0, 22.9, 22.1, 18.8.
4b (red powder, 74%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.01 (s + d, 2H), 7.79 (s, 1H), 6.88 (d, 1H, ^{3}J(H,H) = 9.5 Hz), 5.52 (s, 2H), 5.46 (d, 1H, ^{3}J(H,H) = 5.8 Hz), 5.21 (d, 1H, ^{3}J(H,H) = 5.1 Hz), 4.07 (s, 3H), 2.79 (m, 1H, ^{3}J(H,H) = 6.6 Hz), 2.23 (s, 3H), 1.26 (d, 3H, ^{3}J(H,H) = 6.6 Hz), 1.19 (d, 3H, ^{3}J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 171.0, 163.9, 135.9, 132.5, 129.4, 123.1, 118.6, 103.1, 98.0, 85.0, 83.6, 82.2, 81.3, 58.3, 31.0, 22.8, 22.1, 18.8.
5a (red-brown powder, 84%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.76 (s, 1H), 7.15 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 6.96 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 6.92 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 6.43 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 5.46 (d, 1H, ^{3}J(H,H) = 5.1 Hz), 5.40 (d, 1H, ^{3}J(H,H) = 5.9 Hz), 5.30 (d, 1H, ^{3}J(H,H) = 5.9 Hz), 5.07 (d, 1H, ^{3}J(H,H) = 5.9 Hz), 4.23 (m, 1H), 2.80 (m, 1H, ^{3}J(H,H) = 6.6 Hz), 2.50-1.25 (m, 10H), 2.16 (s, 3H) 1.23 (d, 3H, ^{3}J(H,H) = 6.6 Hz), 1.15 (d, 3H, ^{3}J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 165.4, 161.6, 134.5, 134.3, 123.0, 120.6, 114.3, 102.4, 97.0, 83.9, 83.4, 82.7, 80.7, 76.3, 36.0, 35.1, 30.9, 26.5 (2C), 25.9, 22.8, 22.1, 18.6.
5b (yellow-orange powder, 92%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.02 (s, 1H), 8.00 (d, 1H, ^{3}J(H,H) = 8.5 Hz), 7.86 (s, 1H), 6.90 (d, 1H, ^{3}J(H,H) = 8.5 Hz), 5.51 (d+d, 2H), 5.36 (d, 1H, ^{3}J(H,H) = 5.5 Hz), 5.08 (d, 1H, ^{3}J(H,H) = 4.9 Hz), 4.22 (m, 1H), 2.78 (m, 1H, ^{3}J(H,H) = 6.7 Hz), 2.50-1.30 (m, 10H), 2.20 (s, 3H), 1.25 (d, 3H, ^{3}J(H,H) = 6.7 Hz), 1.17 (d, 3H, ^{3}J(H,H) = 6.7 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 170.8, 161.3, 135.9, 132.6, 129.1, 123.2, 119.4, 103.1, 97.6, 84.6, 83.6, 83.1, 81.1, 77.3, 36.0, 34.9, 31.0, 26.4 (2C), 25.7, 22.8, 22.1, 18.7.
6a (red powder, 79%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.49 (s, 1H), 7.39-7.25 (m, 3H), 7.20 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 6.97 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 6.85 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 6.43 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 5.45 (d, 1H, ^{3}J(H,H) = 5.9 Hz), 5.31 (d, 1H, ^{3}J(H,H) = 5.1 Hz), 4.94 (d, 1H, ^{3}J(H,H) = 5.1 Hz), 4.25 (d, 1H, ^{3}J(H,H) = 5.9 Hz), 4.22 (m, 1H, ^{3}J(H,H) = 6.6 Hz), 3.19 (m, 1H, ^{3}J(H,H) = 6.6 Hz), 2.81 (m, 1H, ^{3}J(H,H) = 6.6 Hz), 1.96 (s, 3H), 1.48 (d, 3H, ^{3}J(H,H) = 6.6 Hz), 1.40 (d, 3H, ^{3}J(H,H) = 6.6 Hz), 1.37 (d, 3H, ^{3}J(H,H) = 6.6 Hz), 1.29 (d, 3H, ^{3}J(H,H) = 6.6 Hz), 1.07 (d, 3H, ^{3}J(H,H) = 6.6 Hz), 1.03 (d, 3H, ^{3}J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 167.5, 166.8, 152.8, 142.9, 141.8, 135.6, 135.2, 127.7, 124.5, 123.6, 122.2, 119.5, 114.7, 104.9, 94.5, 87.9, 84.9, 81.9, 77.3, 30.8, 28.1, 27.7, 27.0, 26.3, 23.5, 22.8, 22.6, 22.2, 17.9.
6b (orange powder, 88%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.01 (d, 1H, ^{3}J(H,H) = 9.5 Hz), 7.91 (s, 1H), 7.55 (s, 1H), 7.40-7.30 (m, 3H), 6.89 (d, 1H, ^{3}J(H,H) = 9.5 Hz), 5.46 (d, 1H, ^{3}J(H,H) = 5.9 Hz), 5.33 (d, 1H, ^{3}J(H,H) = 5.9 Hz), 5.00 (d, 1H, ^{3}J(H,H) = 5.9 Hz), 4.28 (d, 1H, ^{3}J(H,H) = 5.9 Hz), 4.03 (m, 1H, ^{3}J(H,H) = 5.9 Hz), 3.12 (m, 1H, ^{3}J(H,H) = 6.6 Hz), 2.79 (m, 1H, ^{3}J(H,H) = 6.6 Hz), 1.95 (s,

3H), 1.49 (d, 3H, ^3J(H,H) = 5.9 Hz), 1.38 (d, 6H, ^3J(H,H) = 6.6 Hz), 1.31 (d, 3H, ^3J(H,H) = 6.6 Hz), 1.06 (d, 3H, ^3J(H,H) = 5.9 Hz), 1.01 (d, 3H, ^3J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 173.1, 166.6, 158.5, 152.1, 142.2, 141.0, 132.9, 130.0, 128.4, 124.9, 123.8, 122.8, 119.2, 105.6, 94.9, 88.2, 84.9, 82.2, 78.7, 31.0, 28.3, 27.7, 26.9, 26.3, 23.4, 22.9, 22.5, 22.2, 18.0.

7a (deep red powder, 71%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.39 (s, 1H), 7.36 (s, 2H), 7.19 (t, 1H, ^3J(H,H) = 6.6 Hz), 6.93 (d, 1H, ^3J(H,H) = 8.1 Hz), 6.87 (d, 1H, ^3J(H,H) = 6.6 Hz), 6.42 (t, 1H, ^3J(H,H) = 7.3 Hz), 5.38 (d, 1H, ^3J(H,H) = 5.1 Hz), 5.16 (d, 1H, ^3J(H,H) = 5.1 Hz), 4.92 (d, 1H, ^3J(H,H) = 5.1 Hz), 4.23 (d, 1H, ^3J(H,H) = 5.1 Hz), 2.77 (m, 1H, ^3J(H,H) = 6.6 Hz), 2.56 (s, 3H), 2.25 (s, 3H), 2.00 (s, 3H), 1.33 (d, 3H, ^3J(H,H) = 6.6 Hz), 1.27 (d, 3H, ^3J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 167.5, 166.1, 154.2, 135.9, 135.2, 135.0, 133.1, 132.1, 130.9, 122.3, 120.0, 119.8, 114.7, 105.7, 93.9, 88.2, 85.9, 81.8, 77.8, 31.0, 22.5 (2C), 19.8, 18.8, 17.8.

7b (yellow-orange powder, 82%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.02 (d, 1H, ^3J(H,H) = 9.7 Hz), 7.95 (s, 1H), 7.48 (s, 1H), 7.41 (s, 1H), 7.39 (s, 1H), 6.88 (d, 1H, ^3J(H,H) = 9.7 Hz), 5.44 (d, 1H, ^3J(H,H) = 5.9 Hz), 5.22 (d, 1H, ^3J(H,H) = 5.9 Hz), 5.01 (d, 1H, ^3J(H,H) = 5.1 Hz), 4.27 (d, 1H, ^3J(H,H) = 5.1 Hz), 2.76 (m, 1H, ^3J(H,H) = 6.8 Hz), 2.52 (s, 3H), 2.27 (s, 3H), 2.01 (s, 3H), 1.34 (d, 3H, ^3J(H,H) = 6.8 Hz), 1.29 (d, 3H, ^3J(H,H) = 6.8 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 172.9, 166.3, 153.5, 136.3, 134.3, 133.1, 132.4, 132.3, 131.2, 130.1, 122.9, 120.5, 119.5, 106.3, 94.3, 88.6, 85.9, 82.1, 79.0, 31.2, 22.5, 22.4, 19.6, 18.7, 17.9.

8a (orange-red powder, 81%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.41 (s, 1H), 7.18 (t, 1H, ^3J(H,H) = 7.3 Hz), 7.03 (s, 1H), 6.99 (s, 1H), 6.95 (d, 1H, ^3J(H,H) = 7.3 Hz), 6.87 (d, 1H, ^3J(H,H) = 7.3 Hz), 6.42 (t, 1H, ^3J(H,H) = 6.6 Hz), 5.38 (d, 1H, ^3J(H,H) = 5.9 Hz), 5.17 (d, 1H, ^3J(H,H) = 5.9 Hz), 4.94 (d, 1H, ^3J(H,H) = 5.1 Hz), 4.23 (d, 1H, ^3J(H,H) = 5.1 Hz), 2.78 (m, 1H, ^3J(H,H) = 6.6 Hz), 2.53 (s, 3H), 2.38 (s, 3H), 2.23 (s, 3H), 1.99 (s, 3H), 1.32 (d, 3H, ^3J(H,H) = 6.6 Hz), 1.27 (d, 3H, ^3J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 167.2, 166.0, 153.1, 136.3, 135.5, 135.2, 132.2, 130.5, 130.0, 128.7, 120.2, 114.5, 105.5, 93.8, 88.2, 86.2, 81.8, 77.7, 30.9, 22.5, 22.4, 21.1, 19.8, 18.8, 17.7.

8b (yellow-orange powder, 90%): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.00 (d, 1H, ^3J(H,H) = 9.5 Hz), 7.94 (s, 1H), 7.49 (s, 1H), 7.05 (s, 1H), 7.02 (s, 1H), 6.87 (d, 1H, ^3J(H,H) = 9.5 Hz), 5.43 (d, 1H, ^3J(H,H) = 5.9 Hz), 5.20 (d, 1H, ^3J(H,H) = 5.9 Hz), 5.01 (d, 1H, ^3J(H,H) = 5.1 Hz), 4.25 (d, 1H, ^3J(H,H) = 5.1 Hz), 2.76 (m, 1H, ^3J(H,H) = 6.6 Hz), 2.49 (s, 3H), 2.38 (s, 3H), 2.24 (s, 3H), 2.00 (s, 3H), 1.33 (d, 3H, ^3J(H,H) = 6.6 Hz), 1.29 (d, 3H, ^3J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 172.8, 166.0, 152.5, 137.0, 136.2, 133.0, 131.5, 130.2, 129.8, 129.6, 129.0, 122.7, 119.7, 106.1, 94.1, 88.6, 86.3, 82.1, 79.0, 31.1, 22.5, 22.4, 21.1, 19.6, 18.7, 17.8.

7.5 Ru-catalyzed quinoline synthesis from ketones

7.5.1 General experimental procedure

A mixture of 2-aminobenzylalcohol (0.1232 g, 1.0 mmol), ketone (2.0 mmol), base (1.0 mmol, KOH: 250 μl of a 4 M solution in MeOH, other bases in their original

form) and Ru-catalyst (0.01 mmol) in 3 mL dioxane was placed in a 7 mL screw-capped vial and allowed to react at 80 °C for 1 h. The catalyst and inorganic salts were removed from the reaction mixture by filtration through a short silica gel column (ethyl acetate). The reported quinoline yields correspond to the reaction using **2** and KOtBu. Yields and retention times (RT) were determined by GC with the method described in paragraph 7.1.2.

7.5.2 Isolation of quinolines

To isolate the quinoline, the resulting solution was concentrated and passed through a second silica gel column (ethyl acetate/hexane mixture, 1:4). The solvent was evaporated and the resulting product was dissolved again in a minimal amount of ethyl acetate. A pale yellow precipitate formed upon addition of HCl (4 N solution in dioxane, Aldrich), which was filtered and suspended in an aqueous 1 M NaOH solution (15 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL) and after evaporation of the combined CH_2Cl_2 phases, the quinoline was obtained in good yield (typically 5-10% lower than GC yields). Quinolines **Q8** - **Q12** did not precipitate upon addition of HCl. For their isolation, a small modification was applied. After addition of HCl, the ethyl acetate solution was extracted three times with 15 mL of water. To the combined water phases were added a few pellets of KOH and the water phase was extracted with CH_2Cl_2 (2 × 15 mL). Evaporation of the combined CH_2Cl_2 phases yielded the quinoline.
Quinolines **Q9** and **Q10** were separated by careful column chromatography (ethyl acetate/hexane, 1:4). **Q9** eluated first, followed by **Q10**. The same technique was unsuitable for the mixture of **Q11** and **Q12**. Although **Q11** started to eluate slightly before **Q12** and could be collected as a pure compound, it was impossible to obtain pure **Q12** as it was always accompanied by the other isomer **Q11**.

7.5.3 Properties and spectral data of quinolines

2-Phenylquinoline (**Q1**, white powder, 100%, RT = 104.80 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 8.34 (t, 1H, ^3J(H,H) = 8.5 Hz), 8.27-8.15 (m, 3H), 7.90-7.71 (m, 3H), 7.58-7.46 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 157.6, 148.6, 139.9, 137.0, 130.0, 129.9, 129.6, 129.1 (2C), 127.8 (2C), 127.7, 127.4, 126.5, 119.2.
2-(2-Methylphenyl)quinoline (**Q2**, pale yellow powder, 100%, RT = 104.85 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 8.10-8.00 (m, 2H), 7.74 (m, 1H), 7.62 (m, 1H), 7.43 (m, 3H), 7.22 (m, 3H), 2.32 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 160.5, 148.2, 141.0, 136.3, 136.2, 131.1, 130.0, 129.9 (2C), 128.8, 127.8, 127.0, 126.7, 126.3, 122.6, 20.6.
2-(3-MethylPhenyl)quinoline (**Q3**, white powder, 100%, RT = 110.45 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 8.51 (m, 1H), 8.24 (m, 1H), 7.96 (s, 1H), 7.87-7.66 (m, 4H), 7.48 (m, 1H), 7.33 (m, 1H), 7.23 (m, 1H), 2.38 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 157.1, 148.5, 139.5, 139.2, 136.9, 131.6, 131.4, 129.3, 129.2, 127.9, 127.8, 127.5, 127.4, 125.7, 119.9, 21.8.
2-(4-MethylPhenyl)quinoline (**Q4**, pale yellow powder, 100%, RT = 111.05 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 8.59 (m, 1H), 8.36 (t, 1H, ^3J(H,H) = 9.5 Hz), 8.14 (d+d, 2H, ^3J(H,H) = 8.8 Hz), 7.95-7.77 (m, 3H), 7.60 (m, 1H), 7.38 (d+d, 2H, ^3J(H,H) = 8.8 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 156.0, 146.2, 138.9, 136.5, 134.7,

129.1, 128.7 (2C), 127.9, 126.7 (2C), 126.4, 126.1, 125.4, 118.0, 20.4.
2-Methoxyphenylquinoline (**Q5**, pale yellow oil, 100%, RT = 113.40 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 8.15 (m, 2H), 7.90-7.80 (m, 3H), 7.71 (m, 1H), 7.52 (m, 1H), 7.42 (m, 1H), 7.13 (m, 1H), 7.03 (m, 1H), 3.87 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 157.5, 157.4, 148.6, 135.3, 131.8, 130.6, 130.0, 129.9, 129.5, 127.7, 127.3, 126.4, 123.7, 121.5, 111.7, 55.9.
4-Methoxyphenylquinoline (**Q6**, pale yellow powder, 95%, RT = 120.10 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 8.16 (m, 4H), 7.86-7.67 (m, 3H), 7.50 (m, 1H), 7.05 (d+d, 2H, ^{3}J(H,H) = 8.8 Hz), 3.89 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 161.1, 157.1, 148.4, 137.0, 132.4, 129.9, 129.7, 129.2 (2C), 127.7, 127.1, 126.2, 118.8, 114.5 (2C), 55.6.
2-Methylquinoline (**Q8**, pale yellow oil, 68%, RT = 59.25 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 8.05-8.00 (m, 2H, ^{3}J(H,H) = 7.3 Hz), 7.75 (dd, 1H, ^{3}J(H,H) = 7.7 Hz), 7.67 (t, 1H, ^{3}J(H,H) = 7.7 Hz), 7.46 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 7.25 (dd, 1H, ^{3}J(H,H) = 8.5 Hz), 2.74 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 159.2, 148.0, 136.4, 129.7, 128.8, 127.7, 126.7, 125.9, 122.2, 25.6.
2-Pentylquinoline (**Q9**, pale yellow oil, 65%, RT = 86.35 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 7.98-7.95 (m, 2H), 7.67 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 7.59 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 7.38 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 7.20 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 2.88 (t, 2H, ^{3}J(H,H) = 7.3 Hz), 1.71 (m, 2H), 1.29 (m, 4H), 0.82 (t, 3H, ^{3}J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 162.1, 146.9, 135.2, 128.2, 127.8, 126.4, 125.6, 124.6, 120.3, 38.3, 30.7, 28.8, 21.6, 13.0.
3-Butyl-2-methylquinoline (**Q10**, pale yellow powder, 22%, RT = 89.00 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 7.98 (d, 1H, ^{3}J(H,H) = 8.8 Hz), 7.82 (s, 1H), 7.66 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 7.61 (t, 1H, ^{3}J(H,H) = 7.7 Hz), 7.46 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 2.79-2.72 (m, 5H), 1.65 (m, 2H), 1.45 (m, 2H), 0.99 (t, 3H, ^{3}J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 157.6, 145.3, 133.5, 133.4, 127.4, 127.2, 126.4, 125.9, 124.6, 31.6, 30.8, 22.2, 21.6, 13.0.
2-Butyl-3-methylquinoline (**Q11**, pale yellow oil, 62%, RT = 86.35 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 7.91 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 7.64 (s, 1H), 7.55-7.43 (m, 2H), 7.29 (t, 1H, ^{3}J(H,H) = 6.9 Hz), 2.98 (m, 2H), 2.48 (s, 3H), 1.76 (m, 2H), 1.50 (m, 2H), 0.98 (t, 3H, ^{3}J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 161.5, 145.6, 134.7, 128.5, 127.2, 126.4, 126.2, 125.6, 124.5, 35.2, 30.0, 22.0, 18.2, 13.0.
2-Ethyl-3-propylquinoline (**Q12**, pale yellow oil, 23%, RT = 87.35 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 8.01 (d, 1H), 7.82 (s, 1H), 7.70 (t, 1H), 7.60 (d, 1H), 7.44 (t, 1H), 2.97 (m, 2H), 2.66 (m, 2H), 1.76 (m, 2H), 1.39 (m, 2H), 1.04 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 162.0, 145.5, 133.8, 132.6, 127.8, 127.4, 127.3, 126.2, 125.8, 33.3, 27.8, 22.5, 13.0, 12.6.
3-Methyl-2-phenylquinoline (**Q13**, pale yellow oil, 100%, RT = 104.10 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 8.06 (t, 1H, ^{3}J(H,H) = 7.7 Hz), 7.92 (d, 1H, ^{3}J(H,H) = 6.6 Hz), 7.69 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 7.59-7.33 (m, 7H), 2.38 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 160.8, 146.9, 141.1, 136.9, 129.6, 129.5, 129.1 (2C), 129.0, 128.6 (2C), 128.4, 127.8, 127.0, 126.7, 20.9.
5,6,7,8-Tetrahydroacridine (**Q14**, pale yellow powder, 100%, RT = 90.75 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 7.98 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 7.81 (s, 1H), 7.70 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 7.61 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 7.43 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 3.14 (m, 2H), 2.98 (m, 2H), 2.00 (m, 2H), 1.91 (m, 2H); ^{13}C-NMR ($CDCl_3$)

δ(ppm): 159.6, 146.8, 135.2, 131.2, 128.8, 128.5, 127.4, 127.1, 125.8, 33.8, 29.5, 23.5, 23.1.
2-Methyl-1,2,3,4-tetrahydroacridine (**Q15**, pale yellow powder, 100%, RT = 91.15 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 7.98 (d, 1H, ^3J(H,H) = 8.1 Hz), 7.69 (s, 1H), 7.61 (d, 1H, ^3J(H,H) = 8.1 Hz), 7.52 (t, 1H, ^3J(H,H) = 7.7 Hz), 7.34 (t, 1H, ^3J(H,H) = 7.7 Hz), 3.20-2.90 (m, 3H), 2.50 (m, 1H), 1.98 (m, 1H), 1.90 (m, 1H), 1.52 (m, 1H), 1.04 (d, 3H, , ^3J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 159.3, 146.9, 135.2, 130.8, 128.7, 127.4, 127.1, 125.8, 38.0, 33.4, 31.7, 29.3, 21.9.
11*H*-indeno[1,2-b]quinoline (**Q16**, white powder, 22%, RT = 115.65 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 8.31 (s, 1H), 8.19 (m, 2H), 7.83 (m, 1H), 7.70 (m, 1H), 7.61 (m, 1H), 7.51 (m, 3H), 4.05 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 161.9, 148.3, 145.3, 140.6, 134.9, 131.4, 130.2, 129.9, 129.4, 129.1, 128.0, 127.8, 125.9, 125.7, 122.3, 34.3.

7.5.4 Synthesis of 3-phenylpropiophenone

1 (0.0082 g, 0.01 mmol), benzyl alcohol (0.1081 g, 1.0 mmol), acetophenone (0.1201 g, 1.0 mmol) and KOH powder (0.0561 g, 1.0 mmol) in 3 mL of 1,4-dioxane were placed in a screw-capped vial and allowed to react for 1 h at 80 °C. The mixture was passed through a silica gel column (ethyl acetate) and the solvent was evaporated. 3-Phenylpropiophenone was obtained as an orange solid (0.1982 g, 94%).
^{1}H-NMR ($CDCl_3$) δ(ppm): 7.95 (d, 2H, ^3J(H,H) = 7.3 Hz), 7.55 (t, 1H, ^3J(H,H) = 7.3 Hz), 7.44 (t, 2H, ^3J(H,H) = 7.7 Hz), 7.24-7.36 (m, 5H), 3.30 (t, 2H, ^3J(H,H) = 7.7 Hz), 3.07 (t, 2H, ^3J(H,H) = 7.7 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 199.5, 141.6, 137.1, 133.3, 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.3 (2C), 126.4, 40.7, 30.4.

7.6 Ruthenium-catalyzed synthesis of 3-substituted quinolines

7.6.1 Method A: slow addition of the aldehyde

2-Aminobenzylalcohol (0.1232 g, 1.0 mmol), **2** (0.0085 g, 0.01 mmol) and KOtBu (0.1347 g, 1.2 mmol) are dissolved in 2 mL dioxane. Every 15 minutes, 100 μL of a solution of octanal (0.2564 g, 2.0 mmol) in 1 mL dioxane is added to the stirring reaction mixture at 80 °C. Before every addition, a sample is taken from the reaction mixture and analyzed by GC. After the last addition, the reaction is allowed to react for an additional hour. Via an acidic/basic extraction the quinoline was isolated and characterized (**Q19**, vide infra).

7.6.2 Method B: oxazine formation followed by ring closing

2-Aminobenzylalcohol (0.1232 g, 1.0 mmol), aldehyde (1.0 mmol) and dodecane (internal standard, 0.0426 g, 0.25 mmol) are dissolved in dioxane and reacted for 1 hour at 80 °C to allow complete conversion into the oxazine (verified by GC analysis). Then, **2** (0.0085 g, 0.01 mmol), KOtBu (0.1347 g, 1.2 mmol) and benzophenone (0.2004 g, 1.1 mmol) were added and the reaction was stirred at 80

°C for 2 hours. The yields of the 3-substituted quinolines were determined by GC analysis using dodecane as internal standard. All quinolines were isolated by an acidic/basic extraction as described earlier and fully characterized by ^{1}H and ^{13}C-NMR. Retention times (RT) are characteristic for the GC method described in paragraph 7.1.2.

7.6.3 Spectral data of oxazines

2-propyl-2,4-dihydro-1*H*-benzo[d][1,3]oxazine (**O1**, RT = 75.20 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 7.06 (t, 1H, ^{3}J(H,H) = 5.9 Hz), 6.90 (d, 1H, ^{3}J(H,H) = 5.1 Hz), 6.80 (t, 1H, ^{3}J(H,H) = 5.9 Hz), 6.67 (d, 1H, ^{3}J(H,H) = 5.1 Hz), 4.93 (d, 1H, ^{2}J(H,H) = -13.9 Hz), 4.80 (d, 1H, ^{2}J(H,H) = -13.9 Hz), 4.54 (t, 1H, ^{3}J(H,H) = 5.1 Hz), 3.85 (bs, 1H), 1.70 (m, 2H, ^{3}J(H,H) = 5.9 Hz), 1.54 (m, 2H, ^{3}J(H,H) = 5.9 Hz), 0.98 (t, 3H, ^{3}J(H,H) = 5.9 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 141.8, 127.6, 125.2, 122.9, 119.9, 117.5, 84.4, 67.9, 37.5, 18.1, 14.2.
2-butyl-2,4-dihydro-1*H*-benzo[d][1,3]oxazine (**O2**, RT = 82.70 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 7.06 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 6.90 (d, 1H, ^{3}J(H,H) = 7.3 Hz), 6.79 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 6.66 (d, 1H, ^{3}J(H,H) = 7.3 Hz), 4.93 (d, 1H, ^{2}J(H,H) = -14.7 Hz), 4.80 (d, 1H, ^{2}J(H,H) = -14.7 Hz), 4.53 (t, 1H, ^{3}J(H,H) = 5.1 Hz), 3.57 (bs, 1H), 1.72 (m, 2H), 1.50 (m, 2H), 1.39 (m, 2H), 0.94 (t, 3H, ^{3}J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 141.8, 127.6, 125.2, 122.8, 119.9, 117.5, 84.6, 67.9, 35.1, 26.9, 22.8, 14.2.
2-heptyl-2,4-dihydro-1*H*-benzo[d][1,3]oxazine (**O3**, RT = 102.96 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 7.05 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 6.90 (d, 1H, ^{3}J(H,H) = 7.3 Hz), 6.78 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 6.65 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 4.93 (d, 1H, ^{2}J(H,H) = -14.7 Hz), 4.79 (d, 1H, ^{2}J(H,H) = -14.7 Hz), 4.52 (t, 1H, ^{3}J(H,H) = 5.1 Hz), 3.69 (bs, 1H), 1.72 (m, 2H), 1.50 (m, 2H), 1.35-1.20 (m, 8H), 0.89 (t, 3H, ^{3}J(H,H) = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 141.9, 127.6, 125.2, 122.8, 119.9, 117.5, 84.7, 67.9, 35.4, 32.0, 29.7, 29.4, 24.8, 22.9, 14.3.
2-isobutyl-2,4-dihydro-1*H*-benzo[d][1,3]oxazine (**O4**, RT = 79.20 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 7.09 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 6.93 (d, 1H, ^{3}J(H,H) = 6.6 Hz), 6.83 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 6.69 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 4.96 (d, 1H, ^{2}J(H,H) = -13.9 Hz), 4.82 (d, 1H, ^{2}J(H,H) = -13.9 Hz), 4.61 (dd, 1H, ^{3}J(H,H) = 5.1 + 6.6 Hz), 3.80 (bs, 1H), 1.94 (m, 1H, ^{3}J(H,H) = 6.6 Hz), 1.71 (m, 1H), 1.54 (m, 1H), 1.01 (d, 6H, ^{3}J(H,H) = 5.9 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 141.8, 127.6, 125.3, 123.0, 120.0, 117.7, 83.4, 67.9, 44.4, 24.5, 23.3, 22.9.
2-benzyl-2,4-dihydro-1*H*-benzo[d][1,3]oxazine (**O5**, RT = 105.25 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 7.40-7.15 (m, 5H), 7.01 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 6.86 (d, 1H, ^{3}J(H,H) = 6.6 Hz), 6.75 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 6.56 (d, 1H, ^{3}J(H,H) = 7.3 Hz), 4.90 (d, 1H, ^{2}J(H,H) = -14.7 Hz), 4.79 (d, 1H, ^{2}J(H,H) = -14.7 Hz), 4.57 (s, 1H), 3.30 (bs, 1H), 3.10 (m, 1H), 2.94 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 141.8, 136.3, 129.9, 129.0, 128.4, 127.6, 127.2, 125.2, 122.9, 119.9, 117.2, 84.7, 67.9, 41.8.
2-phenethyl-2,4-dihydro-1H-benzo[d][1,3]oxazine (**O6**, RT = 112.99 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 7.30-7.09 (m, 5H), 7.04 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 6.88 (d, 1H, ^{3}J(H,H) = 6.6 Hz), 6.78 (t, 1H, ^{3}J(H,H) = 7.3 Hz), 6.62 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 4.91 (d, 1H, ^{2}J(H,H) = -14.7 Hz), 4.81 (d, 1H, ^{2}J(H,H) = -14.7 Hz), 4.51

(s, 1H), 3.47 (bs, 1H), 2.92-2.75 (m, 2H), 2.02 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 141.8, 128.9 (2C), 128.8 (2C), 127.7, 126.6, 126.4, 125.3, 122.9, 120.1, 117.6, 83.9, 67.9, 36.9, 31.0.

2-(2-phenylpropyl)-2,4-dihydro-1*H*-benzo[d][1,3]oxazine (**O7**, RT = 112.45 s)

^{1}H-NMR ($CDCl_3$) δ(ppm): 7.29-7.18 (m, 5H), 7.02 (t, 1H, ^3J(H,H) = 7.3 Hz), 6.84 (d, 1H, ^3J(H,H) = 7.3 Hz), 6.77 (t, 1H, ^3J(H,H) = 7.3 Hz), 6.68 (d, 1H, ^3J(H,H) = 7.3 Hz), 4.79 (m, 2H), 4.23 (m, 1H), 3.48 (bs, 1H), 3.09 (m, 1H), 2.12-1.90 (m, 2H), 1.31 (d, 3H, ^3J(H,H) = 5.9 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 146.5, 141.9, 128.8 (2C), 127.5, 127.3 (2C), 126.6, 125.2, 123.0, 120.0, 117.6, 83.2, 67.8, 43.9, 36.2, 23.1.

7.6.4 Properties and spectral data of quinolines

3-Ethylquinoline (**Q17**, pale yellow oil, 94%, RT = 70.30 s)

^{1}H-NMR ($CDCl_3$) δ(ppm): 8.79 (s, 1H), 8.07 (d, 1H, ^3J(H,H) = 8.1 Hz), 7.92 (s, 1H), 7.76 (d, 1H, ^3J(H,H) = 7.3 Hz), 7.65 (t, 1H, ^3J(H,H) = 7.3 Hz), 7.51 (t, 1H, ^3J(H,H) = 7.3 Hz), 2.85 (m, 2H), 1.36 (t, 3H, ^3J(H,H) = 7.3 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 152.1, 146.9, 136.9, 133.6, 129.4, 128.7, 128.5, 127.5, 126.8, 26.5, 15.5.

3-Propylquinoline (**Q18**, pale yellow oil, 95%, RT = 77.05 s)

^{1}H-NMR ($CDCl_3$) δ(ppm): 8.76 (s, 1H), 8.07 (d, 1H, ^3J(H,H) = 8.1 Hz), 7.89 (s, 1H), 7.75 (d, 1H, ^3J(H,H) = 7.3 Hz), 7.64 (t, 1H, ^3J(H,H) = 7.3 Hz), 7.49 (t, 1H, ^3J(H,H) = 7.3 Hz), 2.75 (t, 2H, ^3J(H,H) = 7.3 Hz), 1.72 (m, 2H), 0.98 (t, 3H, ^3J(H,H) = 7.3 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 152.3, 146.9, 135.4, 134.5, 129.3, 128.8, 128.4, 127.6, 126.8, 35.5, 24.5, 13.9.

3-Hexylquinoline (**Q19**, pale yellow oil, >99%, RT = 97.60 s)

^{1}H-NMR ($CDCl_3$) δ(ppm): 8.77 (s, 1H), 8.08 (d, 1H, ^3J(H,H) = 8.1 Hz), 7.92 (s, 1H), 7.76 (d, 1H, ^3J(H,H) = 8.1 Hz), 7.65 (t, 1H, ^3J(H,H) = 7.3 Hz), 7.52 (t, 1H, ^3J(H,H) = 7.3 Hz), 2.78 (t, 2H, ^3J(H,H) = 7.3 Hz), 1.70 (m, 2H), 1.32 (bm, 6H), 0.88 (bs, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 152.0, 146.5, 135.7, 129.3, 128.9, 128.5, 127.5, 126.9, 33.4, 31.9, 29.1, 22.8, 14.3.

3-Isopropylquinoline (**Q20**, pale yellow oil, >99%, RT = 74.95 s)

^{1}H-NMR ($CDCl_3$) δ(ppm): 8.82 (s, 1H), 8.08 (d, 1H, ^3J(H,H) = 8.8 Hz), 7.93 (s, 1H), 7.76 (d, 1H, ^3J(H,H) = 8.1 Hz), 7.65 (t, 1H, ^3J(H,H) = 7.0 Hz), 7.51 (t, 1H, ^3J(H,H) = 7.3 Hz), 3.13 (m, 1H, ^3J(H,H) = 7.0 Hz), 1.36 (d, 6H, ^3J(H,H) = 7.3 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 151.2, 146.9, 141.4, 132.3, 129.1, 128.8, 128.5, 127.7, 126.8, 32.1, 23.9.

3-Phenylquinoline (**Q21**, pale yellow solid, 84%, RT = 104.90 s)

^{1}H-NMR ($CDCl_3$) δ(ppm): 9.17 (s, 1H), 8.24 (s, 1H), 8.14 (d, 1H, ^3J(H,H) = 8.8 Hz), 7.83 (d, 1H, ^3J(H,H) = 8.1 Hz), 7.71-7.66 (m, 3H), 7.56-7.38 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 150.2, 147.6, 138.1, 134.0, 133.3, 129.6, 129.5, 129.4, 128.6, 128.4, 128.3, 127.7, 127.2.

3-Benzylquinoline (**Q22**, light brown oil, 85%, RT = 110.58 s)

^{1}H-NMR ($CDCl_3$) δ(ppm): 8.81 (s, 1H), 8.07 (d, 1H, ^3J(H,H) = 8.8 Hz), 7.87 (s, 1H), 7.72 (d, 1H, ^3J(H,H) = 8.1 Hz), 7.65 (t, 1H, ^3J(H,H) = 7.3 Hz), 7.50 (t, 1H, ^3J(H,H) = 7.3 Hz), 7.34-7.21 (m, 5H), 4.15 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ(ppm):

152.4, 147.1, 139.9, 135.1, 134.1, 129.4, 129.2, 129.1, 129.0, 128.6, 127.7, 127.0, 126.8, 39.5.
3-(1-Phenylethyl)quinoline (**Q23**, light brown solid, 71%, RT = 108.35 s)
^{1}H-NMR ($CDCl_3$) δ(ppm): 8.80 (s, 1H), 8.07 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 7.93 (s, 1H), 7.75 (d, 1H, ^{3}J(H,H) = 8.1 Hz), 7.65 (t, 1H, ^{3}J(H,H) = 7.0 Hz), 7.51 (t, 1H, ^{3}J(H,H) = 7.0 Hz), 7.33-7.20 (m, 5H), 4.36 (q, 1H, ^{3}J(H,H) = 7.3 Hz), 1.75 (d, 3H, ^{3}J(H,H) = 7.3 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 152.0, 146.9, 145.1, 139.2, 133.4, 129.2, 129.1, 128.9, 128.3, 127.9, 127.8, 126.9, 126.8, 42.8, 21.9.

7.7 Base-mediated quinoline synthesis

7.7.1 Procedure for quinoline synthesis from ketones

A mixture of 2-aminobenzylalcohol (0.1232 g, 1.0 mmol), ketone (2.0 mmol, unless otherwise stated) and base (1.5 mmol) in 3 mL dioxane was placed in a 7 mL screw-capped vial. When KOtBu or NaOEt was used, the solution could immediately be allowed to react at 80 °C for 1 h. Addition of NaH however, resulted in the evolution of hydrogen gas. After approximately 20 minutes, the bubbling ceased and the solution was also allowed to react at 80 °C for 1 h. The inorganic salts were removed from the reaction mixture by filtration through a short silica gel column (ethyl acetate). The reported quinoline yields were determined by GC with dodecane as internal standard. To isolate the quinolines, the same procedure as described for the ruthenium-catalyzed process could be applied.

7.7.2 Procedure for the synthesis of 3-substituted quinolines

2-Aminobenzylalcohol (0.1232 g, 1.0 mmol), aldehyde (1.0 mmol) and dodecane (internal standard, 0.0426 g, 0.25 mmol) were dissolved in 1,4-dioxane and reacted for 1 hour at 80 °C to allow complete conversion into the oxazine (verified by GC analysis). Then, KOtBu (0.1347 g, 1.2 mmol) and benzophenone (0.2004 g, 1.1 mmol) were added and the reaction was stirred at 80 °C for 2 hours. The yields of the 3-substituted quinolines were determined by GC analysis using dodecane as internal standard.

7.7.3 Synthesis of 2-acetamidobenzyl acetate (ABA")

2-Aminobenzylalcohol (0.1232 g, 1.0 mmol) and triethylamine (695 μL, 5.0 mmol) are dissolved in 6 mL diethylether and acetyl chloride (0.1963 g, 2.5 mmol) is added dropwise. The solution is stirred overnight at room temperature. After removing the amine salt by filtration, the solvent is removed in vacuo. The crude product was purified by column chromatography (ethyl acetate) and after evaporation of the solvent the title compound was isolated as a white solid (Yield: 77%).
^{1}H-NMR ($CDCl_3$) δ(ppm): 8.79 (bs, 1H), 7.96 (d, 1H, ^{3}J(H,H) = 7.3 Hz), 7.35 (m, 2H), 7.13 (t, 1H, ^{3}J(H,H) = 6.6 Hz), 5.11 (s, 2H), 2.23 (s, 3H), 2.10 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 172.7, 169.0, 136.9, 132.0, 130.3, 126.0, 125.0, 123.9, 63.7, 24.6, 21.2.

MS m/z: [M^+] 207; [M^+ - CH_3CO] 164; [M^+ - CH_3CO - CH_2CO] 122; [M^+ - CH_3CO - CH_2CO - OH] 105; [CH_3CO^+] 43.
The mono-acylated 2-aminobenzylalcohol (**ABA'**) could not be synthesized as a pure compound.
MS m/z: [M^+] 165; [M^+ - CH_3CO] 122; [M^+ - CH_3CO - OH] 105; [CH_3CO^+] 43.

7.7.4 Self-condensation of 2-heptanone

2-Heptanone (0.1142 g, 1.0 mmol) and KOtBu (0.1346 g, 1.2 mmol) are dissolved in 1 mL 1,4-dioxane and stirred for 1 h at 80 °C. After filtration over a short silica gel column (ethyl acetate) the solution was analyzed by GC-MS.
MS m/z: [M^+] 210 (dimers); 306 (trimers).

7.8 Ruthenium-catalyzed synthesis of enol esters

7.8.1 General experimental procedure

A mixture of alkyne (1.0 mmol), carboxylic acid (1.1 mmol), hexadecane (0.25 mmol) and Ru-catalyst (0.01 mmol) in 1 mL toluene was placed in a 7 mL screw-capped vial and allowed to react at 110 °C. At certain time intervals, a 20 μl sample was taken out of the solution with a microsyringe. The catalyst was removed from this sample by filtration through a short silica gel column (ethyl acetate). The reported alkyne conversion and enol ester yields were determined by GC, with hexadecane as internal standard. For the reaction of phenylacetylene with trichloroacetic acid, dodecane was used as internal standard because the peaks of the formed enol esters overlapped with the peak hexadecane.

7.8.2 Procedure for the addition of NHC ligands

Activation of the NHC ligand

Typically, a 0.2 M stock solution is prepared. The procedure for **41** is given here as an example, but for the other NHC's similar procedures were followed. The NHC **41** (0.0573 g, 0.24 mmol) was suspended in 720 μl toluene and 480 μl KHMDS solution (1 M in toluene) was added to obtain a total volume of 1.2 mL. Stirring for 20 minutes resulted in a pale yellow solution with colorless KCl precipitation. 100 μl of this solution contains 0.02 mmol "active" NHC (2 equivalents versus the catalyst).

Setting up the reaction

The catalyst (0.01 mmol) was weighed in a 7 mL screw-capped vial. The appropriate volume of activated NHC is added and the mixture is stirred for 30 minutes at room temperature. Then the alkyne, carboxylic acid and hexadecane are added and the reaction is performed as usual.

7.8.3 Procedure for the addition of bases

The general experimental procedure as described above was followed. The base (0.05 mmol) was added last. Solid inorganic bases were weighed, organic bases were added volumetrically. KHMDS was added as a 1 M solution in toluene.

7.8.4 Isolation of enol esters

Enol esters **E1a-c**, **E4a-c**, **E7a-c**, and **E8a-c** were isolated by vacuum distillation. The other enol esters were purified by column chromatography (ethyl acetate/hexane 1:4). It was impossible to separate the three isomers.

7.8.5 Properties and spectral data of enol esters

The reported yields correspond to the reaction using standard reaction conditions and **4a** as catalyst. Reaction times are indicatied in parentheses. Retention times (RT) are characteristic for the GC method described in paragraph 7.1.2.
1-Phenylvinyl acetate (**E1a**, yellow oil, 3.3% (300 min), RT = 148.85 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.50-7.25 (m, 5H), 5.54 (s, 1H), 5.09 (s, 1H), 2.23 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 169.3, 168.2, 153.5, 129.7, 129.2, 128.8 (2C), 125.2 (2C), 102.4, 21.2.
(*Z*)-Styryl acetate (**E1b**, 20.1% (300 min), RT = 155.30 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.64 (d, 1H, ^{3}J(H,H) = 7.3 Hz), 7.50-7.25 (m, 5H), 5.75 (d, 1H, ^{3}J(H,H) = 7.3 Hz), 2.23 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 167.7, 134.4, 134.2, 129.4 (2C), 128.7 (2C), 127.6, 112.1, 21.1.
(*E*)-Styryl acetate (**E1c**, 37.1% (300 min), RT = 158.80 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.91 (d, 1H, ^{3}J(H,H) = 13.9 Hz), 7.50-7.25 (m, 5H), 6.44 (d, 1H, ^{3}J(H,H) = 13.9 Hz), 2.23 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 168.2, 136.5, 134.4, 129.0 (2C), 127.7, 126.5 (2C), 115.5, 20.9.
1-Phenylvinyl 2,2,2-trichloroacetate (**E2a**, yellow/brown oil, 61.8% (40 min), RT = 185.45 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.61 (d, 2H, ^{3}J(H,H) = 7.3 Hz), 7.44-7.36 (m, 3H), 5.65 (s, 1H), 5.29 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 160.2, 153.5, 130.0, 129.1 (2C), 125.2 (2C), 102.8, 90.0.
(*Z*)-Styryl 2,2,2-trichloroacetate (**E2b**, 19.9% (40 min), RT = 191.35 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.61 (d, 2H, ^{3}J(H,H) = 7.3 Hz), 7.44-7.36 (m, 3H), 7.30 (d, 1H, ^{3}J(H,H) = 7.3 Hz), 6.00 (d, 1H, ^{3}J(H,H) = 7.3 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 160.2, 133.9, 132.9, 129.9 (2C), 128.9 (2C), 128.6, 116.0, 90.0.
1-Phenylvinyl benzoate (**E3a**, orange oil, 5.0% (180 min), RT = 234.10 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.19 (m, 2H), 7.70-7.20 (m, 8H), 5.58 (s, 1H), 5.16 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 165.1, 153.5, 133.9, 130.4 (2C), 129.5, 129.3, 129.0, 128.9 (2C), 128.8 (2C), 125.2 (2C), 102.6.
(*Z*)-styryl benzoate (**E3b**, 24.3% (180 min), RT = 246.15 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.15 (m, 2H), 7.70-7.20 (m, 9H), 5.85 (d, 1H, ^{3}J(H,H) = 7.3 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 162.4, 133.2, 133.0, 132.7, 129.1 (2C), 128.7, 128.2 (2C), 127.7 (2C), 127.5 (2C), 126.3, 111.6.
(*E*)-styryl benzoate (**E3c**, 29.8% (180 min), RT = 267.75 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.15 (m, 2H), 8.09 (d, 1H, ^{3}J(H,H) = 14.4 Hz), 7.70-7.20 (m, 8H), 6.58 (d, 1H, ^{3}J(H,H) = 14.4 Hz); ^{13}C-NMR ($CDCl_3$) δ(ppm): 162.6, 135.4, 133.1, 132.6,

129.0 (2C), 128.7, 127.7 (2C), 127.5 (2C), 126.4, 125.3 (2C), 114.8.
Oct-1-en-2-yl acetate (**E4a**, colorless oil, 11.1% (180 min), RT = 132.55 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 4.72 (s, 1H), 4.71 (s, 1H), 2.11 (s, 3H), 2.00 (m, 2H), 1.45-1.20 (m, 8H), 0.89 (bs, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 169.3, 156.8, 101.2, 33.5, 31.8, 28.8, 26.6, 22.8, 21.2, 14.2.
(Z)-Oct-1-enyl acetate (**E4b**, 44.4% (180 min), RT = 137.70 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.00 (d, 1H, ^{3}J(H,H) = 6.6 Hz), 4.88 (m, 1H), 2.11 (s, 3H), 2.00 (m, 2H), 1.45-1.20 (m, 8H), 0.89 (bs, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 168.3, 134.1, 114.4, 31.8, 29.3, 29.0, 24.6, 22.8, 20.8, 14.2.
(*E*)-Oct-1-enyl acetate (**E4c**, 21.6% (180 min), RT = 141.95 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.06 (d, 1H, ^{3}J(H,H) = 12.5 Hz), 5.41 (m, 1H), 2.11 (s, 3H), 2.00 (m, 2H), 1.45-1.20 (m, 8H), 0.89 (bs, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 168.4, 135.6, 115.2, 31.8, 29.7, 28.9, 27.4, 22.8, 20.8, 14.2.
Oct-1-en-2-yl 2,2,2-trichloroacetate (**E5a**, yellow oil, 57.4% (20 min), RT = 174.05 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 4.95 (s, 1H), 4.88 (s, 1H), 2.31 (m, 2H), 1.52 (m, 2H), 1.40-1.20 (m, 6H), 0.89 (bs, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 156.9, 153.5, 102.3, 90.0, 32.7, 31.7, 28.7, 26.4, 22.7, 14.3.
(*Z*)-Oct-1-enyl 2,2,2-trichloroacetate (**E5b**, 30.9% (20 min), RT = 177.65 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 6.99 (d, 1H, ^{3}J(H,H) = 6.6 Hz), 5.18 (m, 1H), 2.31 (m, 2H), 1.52 (m, 2H), 1.40-1.20 (m, 6H), 0.89 (bs, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 160.2, 134.8, 118.6, 90.0, 31.7, 29.0, 28.9, 24.5, 22.8, 14.3.
Oct-1-en-2-yl benzoate (**E6a**, orange oil, 21.2% (180 min), RT = 202.90 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.08 (d, 2H, ^{3}J(H,H) = 6.6 Hz), 7.58 (m, 1H), 7.45 (m, 2H), 4.85 (s, 1H), 4.83 (s, 1H), 2.35 (m, 2H), 1.52 (m, 2H), 1.38-1.22 (m, 6H), 0.88 (bs, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 165.0, 157.1, 133.5, 130.2 (2C), 129.6, 128.7 (2C), 101.5, 33.7, 31.8, 28.9, 26.8, 22.8, 14.3.
(*Z*)-Oct-1-enyl benzoate (**E6b**, 42.6% (180 min), RT = 211.35 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.08 (d, 2H, ^{3}J(H,H) = 6.6 Hz), 7.58 (m, 1H), 7.45 (m, 2H), 7.16 (d, 1H, ^{3}J(H,H) = 6.6 Hz), 5.00 (m, 1H), 2.35 (m, 2H), 1.52 (m, 2H), 1.38-1.22 (m, 6H), 0.88 (bs, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 163.8, 134.4, 133.6, 130.1 (2C), 129.7, 128.8 (2C), 115.2, 31.9, 29.4, 29.1, 24.9, 22.9, 14.3.
(*E*)-Oct-1-enyl benzoate (**E6c**, 20.4% (180 min), RT = 223.90 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.08 (d, 2H, ^{3}J(H,H) = 6.6 Hz), 7.58 (m, 1H), 7.45 (m, 2H), 7.23 (d, 1H, ^{3}J(H,H) = 11.7 Hz), 5.59 (m, 1H, ^{3}J(H,H) = 11.7 Hz), 2.35 (m, 2H), 1.52 (m, 2H), 1.38-1.22 (m, 6H), 0.88 (bs, 3H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 164.1, 135.8, 133.6, 130.1 (2C), 129.7, 128.8 (2C), 115.9, 31.9, 29.8, 29.0, 27.6, 22.9, 14.3.
3,3-Dimethylbut-1-en-2-yl acetate (**E7a**, colorless liquid, 7.8% (270 min), RT = 94.65 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 4.78 (s, 1H), 4.55 (s, 1H), 2.04 (s, 3H), 0.98 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 169.3, 162.7, 99.3, 36.3, 28.0 (3C), 21.6.
(*Z*)-3,3-Dimethylbut-1-enyl acetate (**E7b**, 49.1% (270 min), RT = 97.35 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 6.74 (d, 1H, ^{3}J(H,H) = 16.6 Hz), 4.66 (d, 1H, ^{3}J(H,H) = 6.6 Hz), 2.04 (s, 3H), 1.07 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 167.8, 132.2, 123.5, 32.1, 30.6 (3C), 21.2.
(*E*)-3,3-Dimethylbut-1-enyl acetate (**E7c**, 13.0% (270 min), RT = 101.40 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 6.98 (d, 1H, ^{3}J(H,H) = 12.5 Hz), 5.39 (d, 1H, ^{3}J(H,H) = 12.5 Hz), 2.04 (s, 3H), 1.02 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 168.5, 133.5, 126.3, 31.3, 29.9 (3C), 21.0

3,3-Dimethylbut-1-en-2-yl 2,2,2-trichloroacetate (**E8a**, yellow oil, 63.9% (20 min), RT = 143.05 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 4.99 (s, 1H), 4.88 (s, 1H), 1.17 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 163.6, 160.3, 99.7, 90.4, 36.7, 27.7 (3C).
(*Z*)-3,3-Dimethylbut-1-enyl 2,2,2-trichloroacetate (**E8b**, 22.1% (20 min), RT = 146.00 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 6.85 (d, 1H, ^{3}J(H,H) = 6.6 Hz), 5.04 (d, 1H, ^{3}J(H,H) = 6.6 Hz), 1.17 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 163.6, 132.6, 127.2, 90.4, 32.2, 30.6 (3C).
(*E*)-3,3-Dimethylbut-1-enyl 2,2,2-trichloroacetate (**E8c**, 2.1% (20 min), RT = 148.91 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 7.00 (d, 1H, ^{3}J(H,H) = 12.5 Hz), 5.78 (d, 1H, ^{3}J(H,H) = 12.5 Hz), 1.17 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 163.6, 130.2, 126.5, 90.4, 31.2, 29.7 (3C).
3,3-Dimethylbut-1-en-2-yl benzoate (**E9a**, orange oil, 19.7% (420 min), RT = 169.60 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.13 (d, 2H, ^{3}J(H,H) = 6.6 Hz), 7.62 (t, 1H, ^{3}J(H,H) = 6.6 Hz), 7.50 (t, 2H, ^{3}J(H,H) = 7.3 Hz), 5.01 (s, 1H), 4.84 (s, 1H), 1.21 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 165.0, 162.9, 133.5, 130.2 (2C), 129.7, 128.7 (2C), 99.5, 36.7, 28.1 (3C).
(*E*)-3,3-Dimethylbut-1-enyl benzoate (**E9b**, 40.2% (420 min), RT = 174.15 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.13 (d, 2H, ^{3}J(H,H) = 6.6 Hz), 7.62 (t, 1H, ^{3}J(H,H) = 6.6 Hz), 7.50 (t, 2H, ^{3}J(H,H) = 7.3 Hz), 7.19 (d, 1H, ^{3}J(H,H) = 7.3 Hz), 4.92 (d, 1H, ^{3}J(H,H) = 7.3 Hz), 1.28 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 163.8, 133.7, 132.4, 130.1 (2C), 129.6, 128.9 (2C), 124.1, 32.3, 30.9 (3C).
(*Z*)-3,3-Dimethylbut-1-enyl benzoate (**E9c**, 8.4% (420 min), RT = 177.75 s): ^{1}H-NMR ($CDCl_3$) δ(ppm): 8.13 (d, 2H, ^{3}J(H,H) = 6.6 Hz), 7.62 (t, 1H, ^{3}J(H,H) = 6.6 Hz), 7.50 (t, 2H, ^{3}J(H,H) = 7.3 Hz), 7.34 (d, 1H, ^{3}J(H,H) = 13.2 Hz), 5.71 (d, 1H, ^{3}J(H,H) = 13.2 Hz), 1.15 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 164.3, 133.6, 130.2 (2C), 129.8, 128.9 (2C), 128.7, 31.5, 30.1.
γ-Methylene-γ-butyrolactone (**E10a**, >95 %): ^{1}H-NMR ($CDCl_3$) δ(ppm): 4.59 (s, 1H), 3.97 (s, 1H), 2.11 (m, 2H), 1.93 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ(ppm): 173.9, 156,5 87.3, 27.3, 24.7.

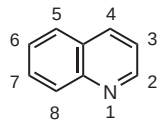
8

Nederlandse samenvatting

8.1 Quinoline synthese

8.1.1 Inleiding

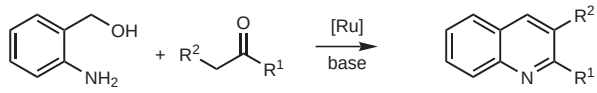
Het quinoline skelet is aanwezig in verschillende natuurlijke medicinale alkaloiden. Ze vinden onder andere toepassingen als geneesmiddel tegen malaria, astma en kanker. Verder worden quinolines gebruikt in kleurstoffen, agrochemische producten en polymeren. De basistructuur van quinoline wordt voorgesteld in Figuur 8.1.



Figuur 8.1: De algemene structuur van quinoline.

Veel klassieke methoden om quinolines te synthetiseren hebben het nadeel van moeilijke reactieomstandigheden of lage opbrengsten. Daarom zijn er de laatste jaren verschillende organometaal-gekatalyseerde procedures ontwikkeld. In dit proefschrift wordt gebruik gemaakt van een gemodificeerde Friedlander methode, voor het eerst voorgesteld door de onderzoeksgroep van Cho en Shim. Traditioneel vertrekt men in de Friedlander synthese van aminobenzaldehydes, maar de prijs en instabiliteit van deze producten en de neiging tot zelfcondensatie vormden lange tijd een rem op de ontwikkeling van deze methode. In de gemodificeerde versie vertrekt men van het stabiele 2-aminobenzylalcohol dat met behulp van een ru-

thenium katalysator in-situ geoxideerd wordt tot het aminobenzaldehyde. In de aanwezigheid van een base wordt dan via een aldol-type cyclo-additiereactie met een keton het quinoline bekomen. Figuur 8.2 stelt het globale reactieschema voor.

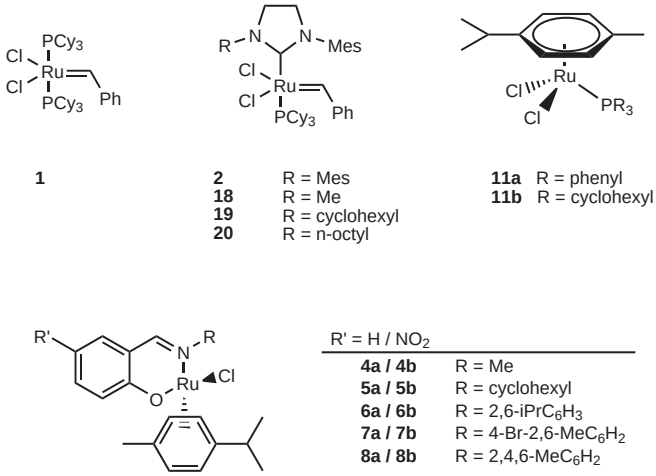


Figuur 8.2: Globale reactie van de gemodificeerde Friedlander methode.

Ook koper, palladium en iridium katalysatoren werden ontwikkeld voor de gemodificeerd Friedlander methode. Andere methoden voor de synthese van quinolines zijn onder andere gebaseerd op ringsluiting metathese, multi-component koppelingsreacties of Diels Alder reacties.

8.1.2 Ruthenium katalysatoren voor quinoline synthese

De eerste generatie Grubbs katalysator (**1**) werd beschreven als beste katalysator voor de gemodificeerde Friedlander methode, maar het aantal geteste ruthenium complexen is vrij beperkt. Daarom werd in dit werk een systematische studie ondernomen van verschillende ruthenium katalysatoren met een gevarieerde ligand-omgeving. De belangrijkste complexen staan weergegeven in Figuur 8.3. Ruthenium-arene complexen en complexen met Schiffse base liganden werden reeds



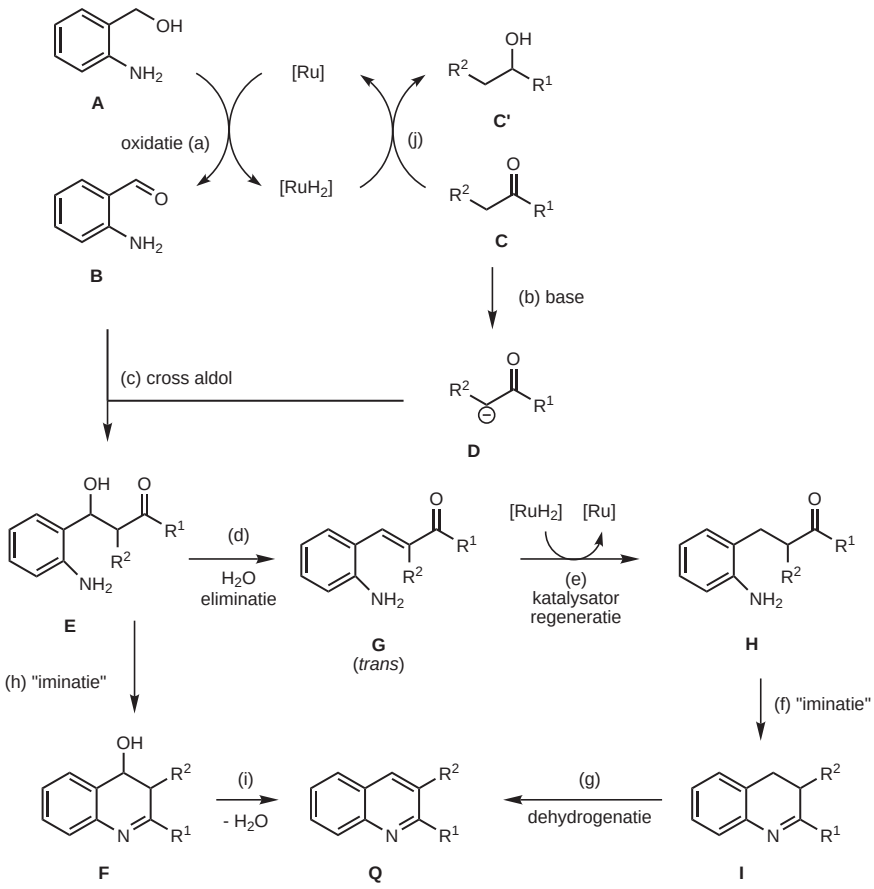
Figuur 8.3: Katalysatoren voor quinoline synthese.

beschreven in katalytische oxidatiereacties. Vandaar dat een reeks ruthenium-Schiffse base complexen **4a,b-8a,b** werd gesynthetiseerd en getest voor quinoline

synthese. Daarnaast werd ook variaties op de Grubbs katalysator onderzocht.
Als modelreactie werd gekozen voor de koppeling tussen 2-aminobenzylalcohol en acetofenon. De tweede generatie Grubbs katalysator (**2**) kwam duidelijk naar voor als beste katalysator. Het ruthenium dimeer $[RuCl_2(\text{p-cymene})]_2$ en Schiffse base complexen **4a,b-8a,b** waren weinig of niet actief terwijl complexen **11a** en **11b** een matige activiteit vertoonden.
De tweede generatie Grubbs katalysator werd gebruikt om een gamma aan ketonen te koppelen met 2-aminobenzylalcohol, en over het algemeen werden goede tot uitstekende quinoline opbrengsten verkregen. Wanneer er in het keton twee α-protonen aanwezig zijn, zoals bvb bij 2-heptanon, worden er twee quinoline isomeren gevormd.
Niet alleen de katalysator heeft een invloed op de reactie. Ook de keuze van de base is zeer belangrijk. De functie van de base is immers het onttrekken van het α-proton van het keton, in de cross-aldol reactie met het in-situ gevormde 2-aminobenzaldehyde. Klassiek wordt KOH in poedervorm gebruikt. Het toevoegen van KOH als oplossing in methanol is niet alleen handiger, door de hogere homogeniteit zorgt het ook voor een snellere reactie. De sterke base KOtBu gaf de hoogste quinoline opbrengsten in de kortste tijd. Organische basen zoals Et_3N, die het voordeel hebben van goede oplosbaarheid, bleken inefficiënt.
Het reactiemechanisme, voorgesteld in Figuur 8.4, is vrij complex en bestaat wellicht uit twee verschillende reactiewegen. De ruthenium katalysator bewerkstelligt de oxidatie van 2-aminobenzylalcohol (**A**) tot 2-aminobenzaldehyde (**B**). Hierbij wordt een $[RuH_2]$ species gevormd, die de oorspronkelijke katalysator regenereert door afgifte van de waterstofatomen aan het aanwezige keton **C**. Hierbij wordt het corresponderende alcohol **C'** gevormd, wat bevestigd wordt via gas chromatografie. Een tweede equivalent van het keton ondergaat in de aanwezigheid van een base een cross-aldol reactie met het benzaldehyde ter vorming van **E**. Deze molecule kan via een cyclocondensatie reactie ("iminatie") omgevormd worden tot een cyclish imine **F**. Eliminatie van water levert vervolgens het quinoline **Q**.
In een tweede mogelijke reactieweg gebeurt de eliminatie van water al bij component **E**, ter vorming van het α,β-onverzadigd keton **G**. Directe ringsluiting vanuit **G** is onwaarschijnlijk omdat voornamelijk het trans-isomeer gevormd wordt. Echter, de dubbele binding kan gehydrogeneerd worden door het $[RuH_2]$ species waarbij **H** gevormd wordt. Cyclocondensatie gevolgd door dehydrogenatie resulteert dan in het quinoline.

8.1.3 Synthese van 3-gesubstitueerde quinolines

De reactie van 2-aminobenzylalcohol met ketonen levert 2- of 2,3-gesubstitueerde quinolines. In principe kunnen 3-gesubstitueerde quinolines gevormd worden door een analoge reactie met aldehydes, maar in de praktijk blijkt dit niet zo eenvoudig. Daarom werd een nieuwe methode ontwikkeld voor de synthese van 3-gesubstitueerde quinolines, voorgesteld in Figuur 8.5. In een eerste stap reageert 2-aminobenzylalcohol met een aldehyde, wat aanleiding geeft tot 1,3-oxazines. Via het zogenoemde ring-keten tautomerisme staat deze oxazine-ring in evenwicht met de imine-keten. Toevoegen van een ruthenium katalysator, KOtBu en benzofenon resulteert in 3-gesubstitueerde quinolines. Op deze manier werden verschillende

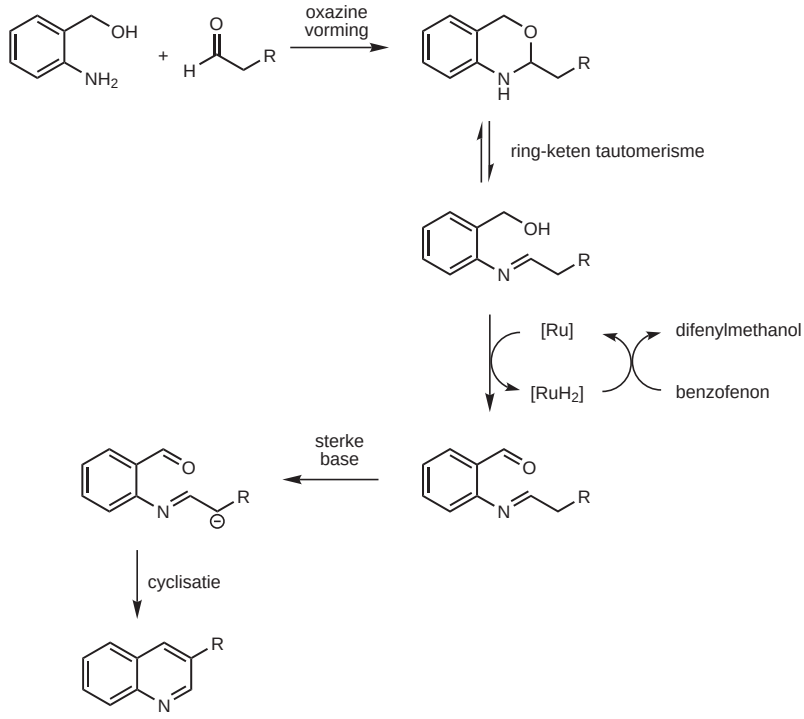


Figuur 8.4: Voorgesteld reactiemechanisme voor quinoline synthese.

aldehyden gekoppeld met 2-aminobenzylalcohol. De 3-gesubstitueerde quinolines werden bekomen met uitstekende opbrengsten.

8.1.4 Base gemediëerde quinoline synthese

Er werd vastgesteld dat de gemodificeerde Friedlander reactie ook doorgaat in enkel de aanwezigheid van een base en zonder het toevoegen van een dure ruthenium katalysator. Van de verschillende basen die getest werden, gaf het gebruik van KOtBu de beste resultaten. Ook natriumhydride is een geschikte base, maar de reactie gaat gepaard met de ontwikkeling van potentieel gevaarlijk waterstof gas. Een mogelijke nevenreactie die wordt waargenomen bij 2-heptanon is de zelf-aldol reactie, wat de quinoline opbrengst limiteert.
Het voorgestelde reactiemechanisme voor het base gemediëerde proces, dat getoond wordt in Figuur 8.6, vertoont grote gelijkenissen met de klassieke Meerwein-Ponndorf-Verley reductie of Oppenauer oxidatie (MPVO). Om de figuur niet no-

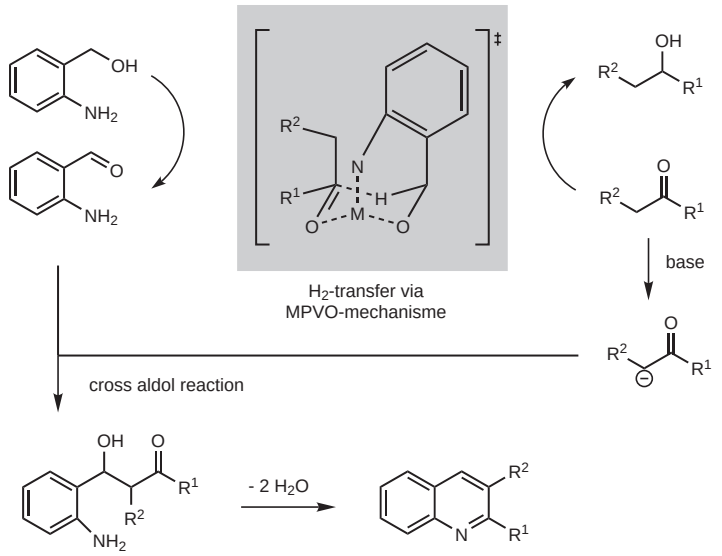


Figuur 8.5: Reactiemechanisme voor de synthese van 3-gesubstitueerde quinolines.

deloos te compliceren, worden overbodige atomen weggelaten. De waterstoftransfer gebeurt via een cyclisch intermediair, waarbij het extra stikstofatoom van 2-aminobenzylalcohol een bijkomende stabilisatie kan geven van het alkali metaal.
Deze strategie kan ook toegepast worden op de synthese van 3-gesubstitueerd quinolines. Wanneer enkel KOtBu als base en benzofenon als waterstofacceptor worden toegevoegd aan de voorgevormde oxazines, worden bijna kwantitatieve opbrengsten aan quinolines verkregen.

8.1.5 Conclusies

Quinolines kunnen gesynthetiseerd worden met behulp van een ruthenium gekatalyseerde modificatie van de Friedlander methode, waarbij 2-aminobenzylalcohol oxidatief gekoppeld wordt met ketonen. Verschillende ruthenium complexen werden getest voor deze reactie, evenals een reeks basen. De tweede generatie Grubbs katalysator in combinatie met de base KOtBu geeft de beste resultaten, zowel qua opbrengst als reactietijd. Het reactiemechanisme verloopt wellicht via twee verschillende reactiewegen.
Er werd een nieuwe methode ontwikkeld voor de problematische synthese van 3-gesubstitueerde quinolines. De reactie van 2-aminobenzylalcohol met aldehydes produceert oxazines. Het toevoegen van een ruthenium katalysator en een base



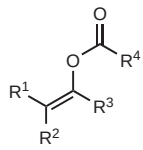
Figuur 8.6: Voorgesteld reactiemechanisme voor base-gemediëerde quinoline synthese.

resulteert in het quinoline.
Beide voorgaande procedures kunnen ook gerealiseerd worden met enkel een base. De aanwezigheid van een dure katalysator is niet noodzakelijk. Het reactiemechanisme verloopt dan wellicht analoog aan dat van de Meerwein-Ponndorf-Verley reductie of Oppenaur oxidatie.

8.2 Ruthenium gekatalyseerde synthese van enol esters

8.2.1 Inleiding

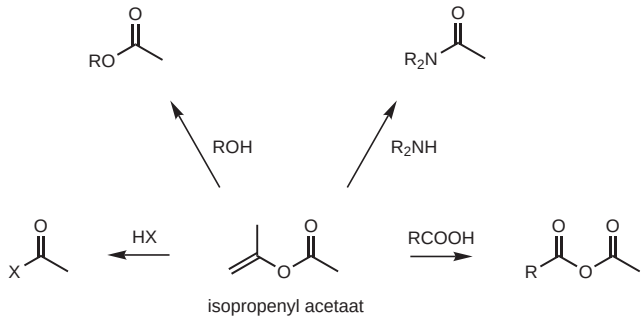
Enol esters zijn moleculen die een enol groep combineren met een ester via een gemeenschappelijk zuurstofatoom (Figuur 8.7). Deze producten zijn zeer interessante



Figuur 8.7: De algemene structuur van enol esters.

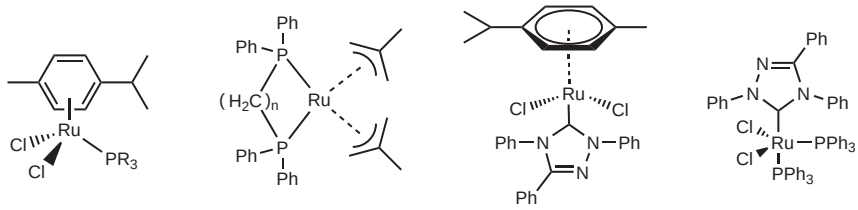
intermediairen om koolstof-koolstof of koolstof-heteroatoom bindingen te genere-

ren. Het zijn goede acylerende reagentia, waarvan een voorbeeld wordt gegeven in Figuur 8.8. Reacties met alcoholen, amines, halogeenzuren en carbonzuren geven respectievelijk esters, amides, zuurhalides en gemengde anhydrides.



Figuur 8.8: Toepassingen van enol esters: acylatie.

De synthese van enol esters gebeurt voornamelijk via twee wegen: door de reactie van enolaten van aldehydes of ketonen met zuuranhydrides, zuurhalides of ketenen in zuur of basisch milieu, of door directe additie van carbonzuren aan de drievoudige binding van alkynes. In dit werk wordt enkel gebruik gemaakt van de tweede methode.
De reactie van carbonzuren met alkynes is een zeer atoomeconomische reactie: 100% van de atomen van de beginproducten is terug te vinden in de eindproducten. Wegens de hoge activeringsenergie is een katalysator vereist om de reactie te laten doorgaan. De beste en meest veelzijdige katalysatoren zijn gebaseerd op het transitiemetaal ruthenium. Enkele voorbeelden van katalysatoren worden getoond in Figuur 8.9.

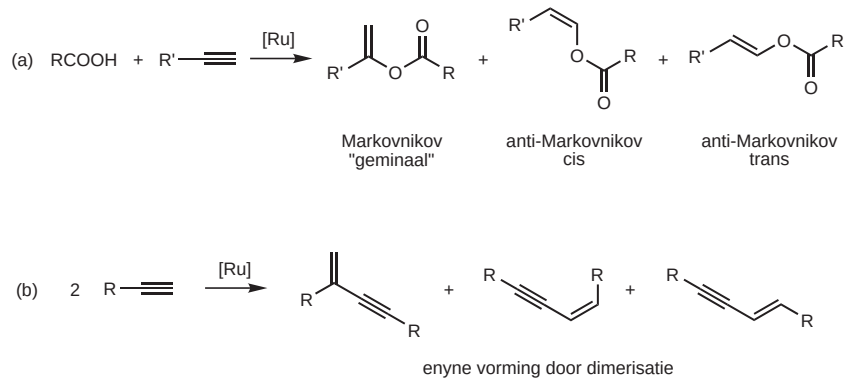


Figuur 8.9: Ruthenium katalysatoren voor enol ester synthese.

Ook andere transitiemetalen zijn in staat deze reactie te katalyseren. De eerste katalysatoren waren op basis van kwik, zoals bvb $Hg(OAc)_2$, maar door de toxiciteit van dit metaal raakten ze in onbruik. Daarnaast worden ook palladium, zilver, rhodium, molybdeen, iridium en renium complexen gebruikt.

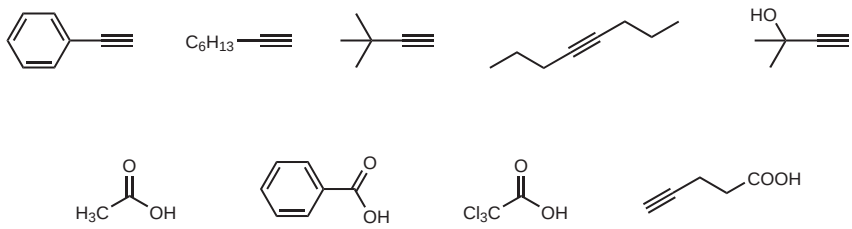
8.2.2 Ruthenium katalysatoren voor enol ester synthese

Bij de ruthenium gekatalyseerde synthese van enol esters kunnen er drie reactieproducten gevormd worden. Markovnikov additie geeft het geminale enol ester, terwijl anti-Markovnikov additie resulteert in cis en/of trans enol esters (Figuur 8.10). Dimerisatie van alkynes is een veel voorkomende nevenreactie.



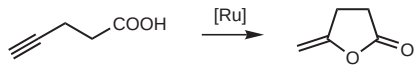
Figuur 8.10: (a) Algemene reactie van ruthenium gekatalyseerde enol ester synthese. (b) Dimerisatie als mogelijke nevenreactie.

In dit werk werd een nieuwe reeks ruthenium katalysatoren met Schiffse base liganden gesynthetiseerd (zie vorige paragraaf) en getest voor de koppelingsreactie tussen alkynes en carbonzuren. De reactie tussen fenylacetyleen en azijnzuur werd gekozen als modelreactie en volgende trends tussen de verschillende Schiffse base katalysatoren konden worden afgeleid. Complexen met een nitro groep op de Schiffse base presteerden duidelijk minder goed dan complexen zonder nitro groep. Daarnaast bleek ook de aard van de groep op de stikstof van de Schiffse base belangrijk te zijn: complexen met alfatische groepen presteerden veel beter dan de complexen met een aromatische groep. Een vergelijking met commercieel verkrijgbare katalysatoren leert dat complexen **4a** en **5a** competitief zijn met bestaande katalysatoren.
Uit de conversiecurven blijkt dat er initieel dimerisatie optreedt, en dat pas later in de reactie enol esters gevormd worden. Tijdens de reactie blijft de relatieve verhouding tussen de drie enol ester isomeren constant. Er treedt dus geen isomerisatie op tijdens de reactie. Terwijl complexen met fosfor liganden over het algemeen aanleiding geven tot Markovnikov enol esters, resulteert de reactie met Schiffse base complexen voornamelijk in anti-Markovnikov producten.
Een tweede testreactie met 1-octyn en azijnzuur bevestigt deze resultaten. Er is echter een belangrijk verschil: de reactie met 1-octyn geeft geen enynes. Bijgevolg worden ook hogere opbrengsten aan enol esters bekomen.
Vervolgens werden Schiffse base complexen **4a** en **5a** gebruikt voor de koppeling van verschillende alkynes (fenylacetyleen, 1-octyn, 3,3-dimethyl-1-butyn, 4-octyn en 2-methyl-3-butyn-2-ol) met verschillende carbonzuren (azijnzuur, benzoëzuur, trichloorazijnzuur en 4-pentynezuur) (Figuur 8.11). Voor bijna alle combinaties



Figuur 8.11: Verschillende alkyn en carbonzuur substraten die onderworpen werden aan de koppelingsreactie.

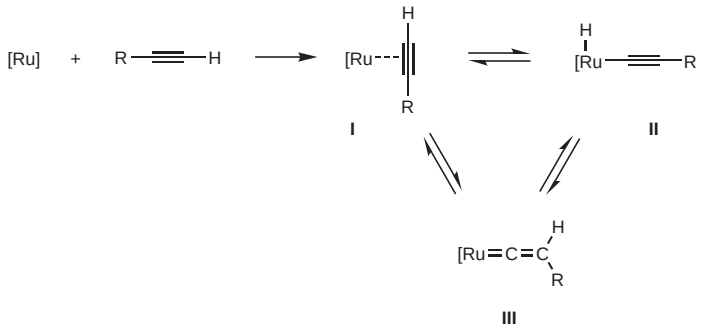
werden goede tot uitstekende opbrengsten van enol esters bekomen waarbij katalysator **4a** over het algemeen beter presteerde dan **5a** (hogere opbrengsten en kortere reactietijden). De reacties met azijnzuur en benzoëzuur resulteerden voornamelijk in anti-Markovnikov enol esters terwijl trichloorazijnzuur vooral Markovnikov additie gaf. Bovendien was de reactiesnelheid met trichloorazijnzuur veel hoger: volledige conversie van het alkyn werd reeds bekomen na 20 tot 40 minuten, in tegenstelling tot de andere zuren waar 3 tot 7 uur nodig was voor volledige omzetting. De reden voor dit snelheidsverschil kan gevonden worden in de zuursterkte. Sterkere zuren hebben een hogere dissociatiegraad, en dus een hogere concentratie van nucleofiele carboxylaat-anionen in oplossing, wat resulteert in een snellere reactie.
Het substraat 4-pentynezuur met een alkyn en carbonzure functie in dezelfde molecule geeft aanleiding tot een intramoleculaire reactie met de vorming van lactonen (Figuur 8.12). Quasi volledige omzetting tot het exocyclische lacton werd bekomen binnen het uur.



Figuur 8.12: Synthese van lactonen: cyclische enol esters.

Complexen **4a** en **5a** waren niet in staat om het interne alkyn 4-octyn en het gefunctionaliseerde alkyn 2-methyl-3-butyn-2-ol te koppelen met zuren.
De additie van N-heterocyclische carbeen (NHC) liganden resulteerde in hogere enol ester opbrengsten in de reacties van alkynes met azijnzuur. Bovendien werd de dimerisatie van fenylacetyleen in reactie met azijnzuur of benzoëzuur sterk afgeremd. De reacties met trichloorazijnzuur daarentegen, verliepen minder snel en minder efficiënt met de additie van NHC liganden. De toevoeging van basen had hetzelfde effect: dimerisatie van fenylacetyleen werd tegengegaan en hogere opbrengsten van enol esters werden bekomen. De stereochemie van de bekomen enol esters blijft ongewijzigd door toevoegen van NHC's of basen.
Het exacte reactiemechanisme is nog niet opgehelderd, maar volgende beschouwingen kunnen een globaal beeld van de reactie vormen. Het is algemeen bekend dat

alkynes kunnen coördineren aan transitiemetalen. Dit kan gebeuren op verschillende manieren zoals getoond in Figuur 8.13. De vorming van anti-Markovnikov enol



Figuur 8.13: Verschillende manieren voor alkyn coordinatie.

esters wordt dikwijls verklaard met een nucleofiele aanval van het carbonzuur op de elektrofiele α-koolstof van het vinylideen intermediair **III**. Markovnikov additie is mogelijk door een aanval op het alkyn ligand in intermediair **I**. Een belangrijke vraag die gesteld kan worden is of het carbonzuur zelf ook coördineert met het transitiemetaal. Sommige auteurs rapporteerden resultaten die in die richting wijzen, maar het is niet ondenkbaar dat dit afhankelijk is van het katalystische systeem.

8.2.3 Conclusies

Enol esters kunnen gesynthetiseerd worden in de ruthenium gekatalyseerde koppelingsreactie tussen alkynes en carbonzuren. Enkele nieuwe ruthenium Schiffse base complexen werden getest voor deze reactie en de resultaten tonen aan dat ze kunnen wedijveren met commercieel verkrijgbare katalysatoren. De aard van het Schiffse base ligand speelt een belangrijke rol.
De reactie werd uitgevoerd met verschillende alkynes en carbonzuren. De stereochemie van de bekomen enol esters was sterk afhankelijk van het gebruikte zuur. Reacties met azijnzuur of benzoëzuur produceerden vooral anti-Markovnikov enol esters, terwijl trichloorazijnzuur resulteerde in Markovnikov additie. De reacties met CCl_3COOH waren ook veel sneller. Dit kan toegeschreven worden aan de grotere zuursterkte wat resulteert in een hogere concentratie van nucleofiele carboxylaat anionen.
In de reacties met fenylacetyleen met azijnzuur en benzoëzuur werd steeds een aanzielijke hoeveelheid enynes gevormd door dimerizatie van het alkyn. Door de additie van NHC's of basen kon de dimerisatiereactie beperkt worden en werden hogere enol ester opbrengsten bekomen.

References

1. Saenz-Galindo, A.; Textle, H. M.; Jasso, A. R.; Torres-Lubian, J. R. *Journal of Polymer Science Part a-Polymer Chemistry* **2006,** *44,* 676-680.
2. Richel, A.; Delfosse, S.; Cremasco, C.; Delaude, L.; Demonceau, A.; Noels, A. F. *Tetrahedron Letters* **2003,** *44,* 6011-6015.
3. Noyori, R.; Hashiguchi, S. *Accounts of Chemical Research* **1997,** *30,* 97-102.
4. Klein, D. P.; Ellern, A.; Angelici, R. J. *Organometallics* **2004,** *23,* 5662-5670.
5. Bruneau, C.; Dixneuf, P. H. *Chemical Communications* **1997,** 507-512.
6. Grubbs, R. H. *Handbook of Metathesis;* volume 1-3 Wiley-VCH: Weinheim, 2003.
7. Chang, S.; Jones, L.; Wang, C. M.; Henling, L. M.; Grubbs, R. H. *Organometallics* **1998,** *17,* 3460-3465.
8. Drozdzak, R.; Allaert, B.; Ledoux, N.; Dragutan, I.; Dragutan, V.; Verpoort, F. *Coordination Chemistry Reviews* **2005,** *249,* 3055-3074.
9. Cho, C. S.; Kim, B. T.; Kim, T. J.; Shim, S. C. *Chemical Communications* **2001,** 2576-2577.
10. Venkatachalam, G.; Ramesh, R. *Inorganic Chemistry Communications* **2005,** *8,* 1009-1013.
11. Melis, K.; Verpoort, F. *Journal of Molecular Catalysis a-Chemical* **2003,** *194,* 39-47.
12. De Clercq, B.; Verpoort, F. *Catalysis Letters* **2002,** *83,* 9-13.
13. Jones, G. *The Chemistry of Heterocyclic Compounds;* John Wiley and Sons: London, 1977.
14. Runge, F. *Poggendorff's Annalen der Physik und Chemie* **1834,** *31,* 68.
15. Collin, G. *Ullmann's Encyclopedia of Industrial Chemistry (Vol. A22);* Wiley-VCH: Deerfield Beach, 5th ed.; 1993.
16. Lednicer, D.; Mitscher, L. *The Organic Chemistry of Drug Synthesis;* Wiley-Interscience: New York, 1977.
17. Jones, G. *Comprehensive heterocyclic chemistry;* Pergamon: New York, 5th ed.; 1984.
18. Gildchrist, T. *Heterocyclic Chemistry;* Pitman Publishing LTD: London, 1st ed.; 1985.
19. Ziegler, J.; Linck, R.; Wright, D. W. *Current Medicinal Chemistry* **2001,** *8,* 171-189.
20. Go, M. L.; Ngiam, T. L.; Tan, A. L. C.; Kuaha, K.; Wilairat, P. *European Journal of Pharmaceutical Sciences* **1998,** *6,* 19-26.
21. Portela, C.; Afonso, C. M. M.; Pinta, M. M. M.; Ramos, M. J. *Bioorganic and Medicinal Chemistry* **2004,** *12,* 3313-3321.
22. Roma, G.; Di Braccio, M.; Grossi, G.; Mattioli, F.; Ghia, M. *European*

Journal of Medicinal Chemistry **2000,** *35,* 1021-1035.
23. Savini, L.; Chiasserini, L.; Pellerano, C.; Filippelli, W.; Falcone, G. *Farmaco* **2001,** *56,* 939-945.
24. Heitsch, H. *Current Medicinal Chemistry* **2002,** *9,* 913-928.
25. Dube, D.; Blouin, M.; Brideau, C.; Chan, C. C.; Desmarais, S.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Girard, M.; Girard, Y.; Guay, J.; Riendeau, D.; Tagari, P.; Young, R. N. *Bioorganic and Medicinal Chemistry Letters* **1998,** *8,* 1255-1260.
26. Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *Journal of Medicinal Chemistry* **2001,** *44,* 2374-2377.
27. Sadana, A. K.; Mirza, Y.; Aneja, K. R.; Prakash, O. *European Journal of Medicinal Chemistry* **2003,** *38,* 533-536.
28. Kidwai, M.; Bhushan, K. R.; Sapra, P.; Saxena, R. K.; Gupta, R. *Bioorganic and Medicinal Chemistry* **2000,** *8,* 69-72.
29. Kayirere, M. G.; Mahamoud, A.; Chevalier, J.; Soyfer, J. C.; Cremieux, A.; Barbe, J. *European Journal of Medicinal Chemistry* **1998,** *33,* 55-63.
30. Ebisu, H.; Nishikawa, M.; Tanaka, M.; Okazoe, T.; Morizawa, Y.; Shinyama, H.; Nakamura, N. *Journal of Cardiovascular Pharmacology* **1999,** *34,* 526-532.
31. Muruganantham, N.; Sivakumar, R.; Anbalagan, N.; Gunasekaran, V.; Leonard, J. T. *Biological and Pharmaceutical Bulletin* **2004,** *27,* 1683-1687.
32. Perzyna, A.; Klupsch, F.; Houssin, R.; Pommery, N.; Lemoine, A.; Henichart, J. P. *Bioorganic and Medicinal Chemistry Letters* **2004,** *14,* 2363-2365.
33. Lamazzi, C.; Leonce, S.; Pfeiffer, B.; Renard, P.; Guillaumet, G.; Rees, C. W.; Besson, T. *Bioorganic and Medicinal Chemistry Letters* **2000,** *10,* 2183-2185.
34. Kaczmarek, L.; Peczynska-Czoch, W.; Osiadacz, J.; Mordarski, M.; Sokalski, W. A.; Boratynski, J.; Marcinkowska, E.; Glazman-Kusnierczyk, H.; Radzikowski, C. *Bioorganic and Medicinal Chemistry* **1999,** *7,* 2457-2464.
35. Martirosyan, A. R.; Rahim-Bata, R.; Freeman, A. B.; Clarke, C. D.; Howard, R. L.; Strobl, J. S. *Biochemical Pharmacology* **2004,** *68,* 1729-1738.
36. Maguire, M. P.; Sheets, K. R.; McVety, K.; Spada, A. P.; Zilberstein, A. *Journal of Medicinal Chemistry* **1994,** *37,* 2129-2137.
37. Nalwa, H. S.; Suzuki, M.; Takahashi, A.; Kageyama, A. *Applied Physics Letters* **1998,** *72,* 1311-1313.
38. Zhang, X. J.; Shetty, A. S.; Jenekhe, S. A. *Macromolecules* **1999,** *32,* 7422-7429.
39. Kim, J. L.; Kim, J. K.; Cho, H. N.; Kim, D. Y.; Hong, S. I. *Synthetic Metals* **2000,** *114,* 97-100.
40. Kim, J. L.; Kim, J. K.; Cho, H. N.; Kim, D. Y.; Kim, C. Y.; Hong, S. I. *Macromolecules* **2000,** *33,* 5880-5885.
41. Lee, T. S.; Yang, C.; Kim, J. L.; Lee, J. K.; Park, W. H.; Won, Y. *Journal of Polymer Science Part a-Polymer Chemistry* **2002,** *40,* 1831-1837.
42. Tonzola, C. J.; Alam, M. M.; Jenekhe, S. A. *Macromolecules* **2005,** *38,* 9539-9547.

43. Economopoulos, S. P.; Andreopoulou, A. K.; Gregoriou, V. G.; Kallitsis, J. K. *Journal of Macromolecular Science Part a-Pure and Applied Chemistry* **2006,** *43,* 977-988.
44. Huang, B.; Li, J.; Jiang, Z. Q.; Qin, J. G.; Yu, G.; Liu, Y. Q. *Macromolecules* **2005,** *38,* 6915-6922.
45. Kulkarni, A. P.; Gifford, A. P.; Tonzola, C. J.; Jenekhe, S. A. *Applied Physics Letters* **2005,** *86,*.
46. Wang, S.; Liu, Y. Q.; Zhan, X. W.; Yu, G.; Zhu, D. B. *Synthetic Metals* **2003,** *137,* 1153-1154.
47. Skraup, Z. H. *Monatshefte Fur Chemie* **1880,** *1,* 316-318.
48. Skraup, Z. H. *Monatshefte Fur Chemie* **1881,** *2,* 139-170.
49. Skraup, Z. H. *Chemische Berichte* **1882,** *15,* 893-898.
50. Doebner, O.; W.v., M. *Chemische Berichte* **1881,** *14,* 2812-2817.
51. Ranu, B. C.; Hajra, A.; Jana, U. *Tetrahedron Letters* **2000,** *41,* 531-533.
52. Ranu, B. C.; Hajra, A.; Dey, S. S.; Jana, U. *Tetrahedron* **2003,** *59,* 813-819.
53. Combes, A. *Bulletin de la Societe Chimique de France* **1988,** *49,* 89.
54. Friedlander, P. *Chemische Berichte* **1882,** *15,* 2572-2575.
55. Friedlander, P.; Gohring, C. F. *Chemische Berichte* **1883,** *16,* 2572-2575.
56. Muchowski, J. M.; Maddox, M. L. *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **2004,** *82,* 461-478.
57. Cheung, C. C.; Yan, S. *Organic Reactions* **1982,** *28,* 37.
58. Armit, J. W.; Robinson, R. J. *Journal of the Chemical Society, Transactions* **1922,** *121,* 827-838.
59. Edward, A. F.; James, A. D.; Mayer, B. D. *Journal of Organic Chemistry* **1958,** *23,* 1996-2001.
60. Bu, X. Y.; Deady, L. W. *Synthetic Communications* **1999,** *29,* 4223-4233.
61. Fernandez, M.; Lopez, F.; Tapia, R.; Valderrama, J. A. *Synthetic Communications* **1989,** *19,* 3087-3095.
62. von Niementowski, S. *Chemische Berichte* **1894,** *27,* 1394-1403.
63. Pfitzinger, W. *Journal fur praktische Chemie* **1886,** *33,* 100.
64. Manske, R. F. *Chemical Reviews* **1942,** *30,* 113-144.
65. Jia, C. S.; Zhang, Z.; Tu, S. J.; Wang, G. W. *Organic and Biomolecular Chemistry* **2006,** *4,* 104-110.
66. Muscia, G. C.; Bollini, M.; Carnevale, J. P.; Bruno, A. M.; Asis, S. E. *Tetrahedron Letters* **2006,** *47,* 8811-8815.
67. Zolfigol, M. A.; Salehi, P.; Ghaderi, A.; Shiri, M. *Catalysis Communications* **2007,** *8,* 1214-1218.
68. Zolfigol, M. A.; Salehi, P.; Ghaderi, A.; Shiri, M.; Tanbakouchian, Z. *Journal of Molecular Catalysis a-Chemical* **2006,** *259,* 253-258.
69. Palimkar, S. S.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Journal of Organic Chemistry* **2003,** *68,* 9371-9378.
70. Zhang, X. Y.; Fan, X. S.; Wang, J. J.; Li, Y. Z. *Journal of the Chinese Chemical Society* **2004,** *51,* 1339-1342.
71. Wang, J.; Fan, X.; Zhang, X.; Han, L. *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **2004,** *82,* 1192-1196.
72. Shaabani, A.; Soleimani, E.; Badri, Z. *Synthetic Communications* **2007,** *37,* 629-635.

73. Dabiri, M.; Baghbanzadeh, M.; Nikcheh, M. S. *Monatshefte Fur Chemie* **2007,** *138,* 1249-1252.
74. Yadav, J. S.; Rao, P. P.; Sreenu, D.; Rao, R. S.; Kumar, V. N.; Nagaiah, K.; Prasad, A. R. *Tetrahedron Letters* **2005,** *46,* 7249-7253.
75. Das, B.; Damodar, K.; Chowdhury, N.; Kumar, R. A. *Journal of Molecular Catalysis a-Chemical* **2007,** *274,* 148-152.
76. Dabiri, M.; Azimi, S. C.; Bazgir, A. *Monatshefte Fur Chemie* **2007,** *138,* 659-661.
77. Camps, R. *Chemische Berichte* **1899,** *33,* 3228-3234.
78. Camps, R. *Archiv der Pharmazie* **1899,** *237,* 659-691.
79. Knorr, L. *Liebigs Annalen* **1886,** *236,* 69-115.
80. Knorr, L. *Liebigs Annalen* **1888,** *245,* 357-382.
81. Conrad, M.; Limpach, L. *Chemische Berichte* **1987,** *20,* 944-948.
82. Conrad, M.; Limpach, L. *Chemische Berichte* **1991,** *24,* 2990-2992.
83. Li, J. J. *Name Reactions in Heterocyclic Chemistry;* John Wiley and Sons: Hoboken, 2004.
84. Povarov, L. S. *Russian Chemical Reviews* **1967,** *36,* 656-670.
85. Babu, G.; Perumal, P. T. *Tetrahedron* **1998,** *54,* 1627-1638.
86. Batey, R. A.; Simoncic, P. D.; Lin, D.; Smyj, R. P.; Lough, A. J. *Chemical Communications* **1999,** 651-652.
87. Babu, G.; Perumal, P. T. *Tetrahedron Letters* **1997,** *38,* 5025-5026.
88. Babu, G.; Perumal, P. T. *Tetrahedron Letters* **1998,** *39,* 3225-3228.
89. Babu, G.; Perumal, P. T. *Tetrahedron* **1999,** *55,* 4793-4802.
90. Babu, G.; Perumal, P. T. *Aldrichimica Acta* **2000,** *33,* 16-22.
91. Ranu, B. C. *European Journal of Organic Chemistry* **2000,** 2347-2356.
92. Yadav, J. S.; Reddy, B. V. S.; Rao, R. S.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron* **2002,** *58,* 7891-7896.
93. Elamparuthi, E.; Anniyappan, M.; Muralidharan, D.; Perumal, P. T. *Arkivoc* **2005,** 6-16.
94. Manian, R.; Jayashankaran, J.; Ramesh, R.; Raghunathan, R. *Tetrahedron Letters* **2006,** *47,* 7571-7574.
95. Kobayashi, S.; Komiyama, S.; Ishitani, H. *Biotechnology and Bioengineering* **1998,** *61,* 23-31.
96. Crousse, B.; Begue, J. P.; Bonnet-Delpon, D. *Tetrahedron Letters* **1998,** *39,* 5765-5768.
97. Jones, W.; Kiselyov, A. S. *Tetrahedron Letters* **2000,** *41,* 2309-2312.
98. Batey, R. A.; Powell, D. A.; Acton, A.; Lough, A. J. *Tetrahedron Letters* **2001,** *42,* 7935-7939.
99. Alves, M. J.; Azoia, N. G.; Fortes, A. G. *Tetrahedron* **2007,** *63,* 727-734.
100. Ishitani, H.; Kobayashi, S. *Tetrahedron Letters* **1996,** *37,* 7357-7360.
101. Xing, X. L.; Wu, J. L.; Dai, W. M. *Tetrahedron* **2006,** *62,* 11200-11206.
102. Collin, J.; Jaber, N.; Lannou, M. I. *Tetrahedron Letters* **2001,** *42,* 7405-7407.
103. Sabitha, G.; Reddy, E. V.; Yadav, J. S.; Krishna, K.; Sankar, A. R. *Tetrahedron Letters* **2002,** *43,* 4029-4032.
104. Maiti, G.; Kundu, P. *Tetrahedron Letters* **2006,** *47,* 5733-5736.
105. Sabitha, G.; Reddy, M. S. K.; Arundhathi, K.; Yadav, J. S. *Arkivoc* **2006,** 153-160.

106. Savitha, G.; Perumal, P. T. *Tetrahedron Letters* **2006,** *47,* 3589-3593.
107. Cho, C. S.; Ren, W. X.; Shim, S. C. *Tetrahedron Letters* **2006,** *47,* 6781-6785.
108. Cho, C. S.; Ren, W. X.; Shim, S. C. *Bulletin of the Korean Chemical Society* **2005,** *26,* 1286-1288.
109. Cho, C. S.; Ren, W. X. *Journal of Organometallic Chemistry* **2007,** *692,* 4182-4186.
110. Motokura, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Letters* **2004,** *45,* 6029-6032.
111. Taguchi, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Letters* **2005,** *46,* 4539-4542.
112. Cho, C. S.; Kim, B. T.; Choi, H. J.; Kim, T. J.; Shim, S. C. *Tetrahedron* **2003,** *59,* 7997-8002.
113. Martinez, R.; Brand, G. J.; Ramon, D. J.; Yus, M. *Tetrahedron Letters* **2005,** *46,* 3683-3686.
114. Martinez, R.; Ramon, D. J.; Yus, M. *Tetrahedron* **2006,** *62,* 8988-9001.
115. Martinez, R.; Ramon, D. J.; Yus, M. *Tetrahedron* **2006,** *62,* 8982-8987.
116. Martinez, R.; Ramon, D. J.; Yus, M. *European Journal of Organic Chemistry* **2007,** 1599-1605.
117. Watanabe, Y.; Tsuji, Y.; Ohsugi, Y. *Tetrahedron Letters* **1981,** *22,* 2667-2670.
118. Tsuji, Y.; Nishimura, H.; Huh, K. T.; Watanabe, Y. *Journal of Organometallic Chemistry* **1985,** *286,* C44-C46.
119. Tsuji, Y.; Huh, K. T.; Watanabe, Y. *Journal of Organic Chemistry* **1987,** *52,* 1673-1680.
120. Cho, C. S.; Oh, B. H.; Shim, S. C. *Tetrahedron Letters* **1999,** *40,* 1499-1500.
121. Cho, C. S.; Kim, D. T.; Kim, T. J.; Shim, S. C. *Bulletin of the Korean Chemical Society* **2003,** *24,* 1026-1028.
122. Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T. J.; Shim, S. C.; Yoon, N. S. *Tetrahedron* **2000,** *56,* 7747-7750.
123. Cho, C. S.; Oh, B. H.; Kim, J. S.; Kim, T. J.; Shim, S. C. *Chemical Communications* **2000,** 1885-1886.
124. Cho, C. S.; Kim, T. K.; Kim, B. T.; Kim, T. J.; Shim, S. C. *Journal of Organometallic Chemistry* **2002,** *650,* 65-68.
125. Cho, C. S.; Kim, T. K.; Choi, H. J.; Kim, T. J.; Shim, S. C. *Bulletin of the Korean Chemical Society* **2002,** *23,* 541-542.
126. Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M. *Tetrahedron Letters* **2001,** *42,* 8029-8033.
127. Theeraladanon, C.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron* **2004,** *60,* 3017-3035.
128. Arisawa, M.; Terada, Y.; Theeraladanon, C.; Takahashi, K.; Nakagawa, M.; Nishida, A. *Journal of Organometallic Chemistry* **2005,** *690,* 5398-5406.
129. Arisawa, M.; Nishida, A.; Nakagawa, M. *Journal of Organometallic Chemistry* **2006,** *691,* 5109-5121.
130. Theeraladanon, C.; Arisawa, M.; Nakagawa, M.; Nishida, A. *Tetrahedron-Asymmetry* **2005,** *16,* 827-831.
131. Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *Journal of the American Chemical Society* **1978,** *100,* 5800-5807.
132. Larock, R. C.; Babu, S. *Tetrahedron Letters* **1987,** *28,* 5291-5294.

133. Larock, R. C.; Kuo, M. Y. *Tetrahedron Letters* **1991,** *32,* 569-572.
134. Mahanty, J. S.; De, M.; Das, P.; Kundu, N. G. *Tetrahedron* **1997,** *53,* 13397-13418.
135. Cho, C. S. *Journal of Organometallic Chemistry* **2005,** *690,* 4094-4097.
136. Cortese, N. A.; Ziegler, C. B.; Hrnjez, B. J.; Heck, R. F. *Journal of Organic Chemistry* **1978,** *43,* 2952-2958.
137. Hatano, M.; Mikami, K. *Journal of the American Chemical Society* **2003,** *125,* 4704-4705.
138. Abbiati, G.; Arcadi, A.; Canevari, V.; Capezzuto, L.; Rossi, E. *Journal of Organic Chemistry* **2005,** *70,* 6454-6460.
139. Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Plastina, P. *Journal of Organic Chemistry* **2007,** *72,* 6873-6877.
140. Diamond, S. E.; Szalkiewicz, A.; Mares, F. *Journal of the American Chemical Society* **1979,** *101,* 490-491.
141. Beller, M.; Thiel, O. R.; Trauthwein, H.; Hartung, C. G. *Chemistry-a European Journal* **2000,** *6,* 2513-2522.
142. Vieira, T. O.; Alper, H. *Chemical Communications* **2007,** 2710-2711.
143. Jacob, J.; Cavalier, C. M.; Jones, W. D.; Godleski, S. A.; Valente, R. R. *Journal of Molecular Catalysis a-Chemical* **2002,** *182,* 565-570.
144. Jacob, J.; Jones, W. D. *Journal of Organic Chemistry* **2003,** *68,* 3563-3568.
145. Korivi, R. P.; Cheng, C. H. *Journal of Organic Chemistry* **2006,** *71,* 7079-7082.
146. Igarashi, T.; Inada, T.; Sekioka, T.; Nakajima, T.; Shimizu, I. *Chemistry Letters* **2005,** *34,* 106-107.
147. Atechian, S.; Nock, N.; Norcross, R. D.; Ratni, H.; Thomas, A. W.; Verron, J.; Masciadri, R. *Tetrahedron* **2007,** *63,* 2811-2823.
148. Oppenauer, R. V. *Recueil des Travaux Chimiques des Pays-Bas* **1937,** *56,* 137-144.
149. Meerwein, H.; Schmidt, R. *Annalen* **1925,** *444,* 221.
150. Ponndorf, W. *Angewandte Chemie* **1926,** *39,* 138.
151. Verley, M. *Bulletin de la Societe Chimique de France* **1925,** *37,* 537.
152. Moulton, W. N.; Ruch, R. R.; Vanatta, R. E. *Journal of Organic Chemistry* **1961,** *26,* 290-292.
153. Backvall, J. E. *Journal of Organometallic Chemistry* **2002,** *652,* 105-111.
154. Johnstone, R. A. W.; Wilby, A. H.; Entwistle, I. D. *Chemical Reviews* **1985,** *85,* 129-170.
155. Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chemical Reviews* **1992,** *92,* 1051-1069.
156. Imai, H.; Nishiguchi, T.; Fukuzumi, K. *Journal of Organic Chemistry* **1976,** *41,* 665-671.
157. Chowdhury, R. L.; Backvall, J. E. *Journal of the Chemical Society-Chemical Communications* **1991,** 1063-1064.
158. Karlsson, U.; Wang, G. Z.; Backvall, J. E. *Journal of Organic Chemistry* **1994,** *59,* 1196-1198.
159. Murahashi, S. I.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. *Journal of Organic Chemistry* **1987,** *52,* 4319-4327.
160. Fernandez, M. J.; Esteruelas, M. A.; Covarrubias, M.; Oro, L. A. *Journal*

of Organometallic Chemistry **1986,** *316,* 343-349.
161. Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *Journal of Organic Chemistry* **1986,** *51,* 2034-2039.
162. Blum, Y.; Czarkie, D.; Rahamim, Y.; Shvo, Y. *Organometallics* **1985,** *4,* 1459-1461.
163. Smith, T. A.; Maitlis, P. M. *Journal of Organometallic Chemistry* **1985,** *289,* 385-395.
164. Farnetti, E.; Vinzi, F.; Mestroni, G. *Journal of Molecular Catalysis* **1984,** *24,* 147-163.
165. Descotes, G.; Sinou, D. *Tetrahedron Letters* **1976,** 4083-4086.
166. Ohkubo, K.; Hirata, K.; Yoshinaga, K.; Okada, M. *Chemistry Letters* **1976,** 183-184.
167. Sasson, Y.; Blum, J. *Journal of Organic Chemistry* **1975,** *40,* 1887-1896.
168. Blum, J.; Sasson, Y.; Iflah, S. *Tetrahedron Letters* **1972,** 1015-1018.
169. Sasson, Y.; Blum, J. *Tetrahedron Letters* **1971,** 2167-2170.
170. Trocha-Grimshaw, J.; Henbest, H. B. *Chemical Communications* **1967,** 544.
171. Haddad, Y. M. Y.; Husbands, J.; Henbest, H. B.; Mitchell, T. R. *Proceedings of the Chemical Society of London* **1964,** 361.
172. Yamakawa, M.; Ito, H.; Noyori, R. *Journal of the American Chemical Society* **2000,** *122,* 1466-1478.
173. Palmer, M. J.; Wills, M. *Tetrahedron-Asymmetry* **1999,** *10,* 2045-2061.
174. Rautenstrauch, V.; Hoang-Cong, X.; Churlaud, R.; Abdur-Rashid, K.; Morris, R. H. *Chemistry-a European Journal* **2003,** *9,* 4954-4967.
175. Miecznikowski, J. R.; Crabtree, R. H. *Polyhedron* **2004,** *23,* 2857-2872.
176. Vastila, P.; Zaitsev, A. B.; Wettergren, J.; Privalov, T.; Adolfsson, H. *Chemistry-a European Journal* **2006,** *12,* 3218-3225.
177. Cheung, F. K.; Hayes, A. M.; Hannedouche, J.; Yim, A. S. Y.; Wills, M. *Journal of Organic Chemistry* **2005,** *70,* 3188-3197.
178. Noyori, R.; Yamakawa, M.; Hashiguchi, S. *Journal of Organic Chemistry* **2001,** *66,* 7931-7944.
179. Wu, X. F.; Xiao, J. L. *Chemical Communications* **2007,** 2449-2466.
180. Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *Journal of the American Chemical Society* **1995,** *117,* 7562-7563.
181. Chen, J. S.; Li, Y. Y.; Dong, Z. R.; Li, B. Z.; Gao, J. X. *Tetrahedron Letters* **2004,** *45,* 8415-8418.
182. Gamez, P.; Fache, F.; Lemaire, M. *Tetrahedron-Asymmetry* **1995,** *6,* 705-718.
183. Albrecht, M.; Miecznikowski, J. R.; Samuel, A.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2002,** *21,* 3596-3604.
184. Murata, K.; Ikariya, T. *Journal of Organic Chemistry* **1999,** *64,* 2186-2187.
185. Wu, X. F.; Liu, J. K.; Li, X. H.; Zanotti-Gerosa, A.; Hancock, F.; Vinci, D.; Ruan, J. W.; Xiao, J. L. *Angewandte Chemie-International Edition* **2006,** *45,* 6718-6722.
186. Himeda, Y.; Onozawa-Komatsuzaki, N.; Sugihara, H.; Arakawa, H.; Kasuga, K. *Journal of Molecular Catalysis a-Chemical* **2003,** *195,* 95-100.
187. Kriis, K.; Kanger, T.; Muurisepp, A. M.; Lopp, M. *Tetrahedron-Asymmetry* **2003,** *14,* 2271-2275.

188. Guiral, V.; Delbecq, F.; Sautet, P. *Organometallics* **2001,** *20,* 2207-2214.
189. Leitner, W.; Brown, J. M.; Brunner, H. *Journal of the American Chemical Society* **1993,** *115,* 152-159.
190. Albrecht, M.; Crabtree, R. H.; Mata, J.; Peris, E. *Chemical Communications* **2002,** 32-33.
191. Bernard, M.; Delbecq, F.; Sautet, P.; Fache, F.; Lemaire, M. *Organometallics* **2000,** *19,* 5715-5722.
192. Wu, X. F.; Vinci, D.; Ikariya, T.; Xiao, J. L. *Chemical Communications* **2005,** 4447-4449.
193. Alonso, F.; Riente, P.; Yus, M. *Tetrahedron* **2008,** *64,* 1847-1852.
194. Kuhl, S.; Schneider, R.; Fort, Y. *Organometallics* **2003,** *22,* 4184-4186.
195. Basu, B.; Bhuiyan, M. H.; Das, P.; Hossain, I. *Tetrahedron Letters* **2003,** *44,* 8931-8934.
196. Yu, J. Q.; Wu, H. C.; Ramarao, C.; Spencer, J. B.; Ley, S. V. *Chemical Communications* **2003,** 678-679.
197. Evans, D. A.; Nelson, S. G.; Gagne, M. R.; Muci, A. R. *Journal of the American Chemical Society* **1993,** *115,* 9800-9801.
198. Gao, J. X.; Ikariya, T.; Noyori, R. *Organometallics* **1996,** *15,* 1087-1089.
199. Samec, J. S. M.; Backvall, J. E. *Chemistry-a European Journal* **2002,** *8,* 2955-2961.
200. Blum, Y.; Czarkie, D.; Rahamim, Y.; Shvo, Y. *Organometallics* **1985,** *4,* 1459-1461.
201. Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *Journal of the American Chemical Society* **1996,** *118,* 2521-2522.
202. Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.; Ikariya, T.; Noyori, R. *Chemical Communications* **1996,** 233-234.
203. Puntener, K.; Schwink, L.; Knochel, P. *Tetrahedron Letters* **1996,** *37,* 8165-8168.
204. Palmer, M.; Walsgrove, T.; Wills, M. *Journal of Organic Chemistry* **1997,** *62,* 5226-5228.
205. Brunner, H.; Henning, F.; Weber, M. *Tetrahedron-Asymmetry* **2002,** *13,* 37-42.
206. Rhyoo, H. Y.; Yoon, Y. A.; Park, H. J.; Chung, Y. K. *Tetrahedron Letters* **2001,** *42,* 5045-5048.
207. Cho, C. S.; Kim, B. T.; Kim, T. J.; Shim, S. C. *Journal of Organic Chemistry* **2001,** *66,* 9020-9022.
208. Nishiguci, T.; Fukuzumi, K. *Journal of the American Chemical Society* **1974,** *96,* 1893-1897.
209. Nishiguci, T.; Tachi, K.; Fukuzumi, K. *Journal of the American Chemical Society* **1972,** *94,* 8916-8917.
210. Cho, C. S.; Kim, B. T.; Kim, T. J.; Shim, S. C. *Tetrahedron Letters* **2002,** *43,* 7987-7989.
211. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *Journal of the American Chemical Society* **1996,** *118,* 100-110.
212. Allaert, B.; Dieltiens, N.; Ledoux, N.; Vercaemst, C.; Van der Voort, P.; Stevens, C. V.; Linden, A.; Verpoort, F. *Journal of Molecular Catalysis a-Chemical* **2006,** *260,* 221-226.

213. Ledoux, N.; Allaert, B.; Pattyn, S.; Vander Mierde, H.; Vercaemst, C.; Verpoort, F. *Chemistry-a European Journal* **2006,** *12,* 4654-4661.
214. Monsaert, S.; Drozdzak, R.; Dragutan, V.; Dragutan, I.; Verpoort, F. *European Journal of Inorganic Chemistry* **2008,** 432-440.
215. Ledoux, N.; Linden, A.; Allaerta, B.; Mierde, H. V.; Verpoort, F. *Advanced Synthesis and Catalysis* **2007,** *349,* 1692-1700.
216. Ledoux, N.; Drozdzak, R.; Allaert, B.; Linden, A.; Van Der Voort, P.; Verpoort, F. *Dalton Transactions* **2007,** 5201-5210.
217. Ledoux, N.; Allaert, B.; Verpoort, F. *European Journal of Inorganic Chemistry* **2007,** 5578-5583.
218. Ledoux, N.; Allaert, B.; Schaubroeck, D.; Monsaert, S.; Drozdzak, R.; Van Der Voort, P.; Verpoort, F. *Journal of Organometallic Chemistry* **2006,** *691,* 5482-5486.
219. Ledoux, N.; Allaert, B.; Linden, A.; Van der Voort, P.; Verpoort, F. *Organometallics* **2007,** *26,* 1052-1056.
220. Rath, R. K.; Nethaji, M.; Chakravarty, A. R. *Polyhedron* **2001,** *20,* 2735-2739.
221. Rath, R. K.; Nethaji, M.; Chakravarty, A. R. *Journal of Organometallic Chemistry* **2001,** *633,* 79-84.
222. Kwong, H. L.; Lee, W. S.; Lai, T. S.; Wong, W. T. *Inorganic Chemistry Communications* **1999,** *2,* 66-69.
223. Ghebreyessus, K. Y.; Nelson, J. H. *Journal of Organometallic Chemistry* **2003,** *669,* 48-56.
224. Diez, J.; Gamasa, M. P.; Lastra, E.; Garcia-Fernandez, A.; Tarazona, M. P. *European Journal of Inorganic Chemistry* **2006,** 2855-2864.
225. Krasik, P.; Alper, H. *Tetrahedron* **1994,** *50,* 4347-4354.
226. Bhowon, M. G.; Wah, H. L. K.; Narain, R. *Polyhedron* **1999,** *18,* 341-345.
227. Elhendawy, A. M.; Elkourashy, A. E.; Shanab, M. M. *Polyhedron* **1992,** *11,* 523-530.
228. Elhendawy, A. M.; Alkubaisi, A. H.; Elkourashy, A. E.; Shanab, M. M. *Polyhedron* **1993,** *12,* 2343-2350.
229. Bennett, M. A.; Huang, T. N.; Matheson, T. W.; Smith, A. K. *Inorganic Syntheses* **1982,** *21,* 74-78.
230. De Clercq, B.; Verpoort, F. *Journal of Molecular Catalysis a-Chemical* **2002,** *180,* 67-76.
231. Rath, R. K.; Nethaji, M.; Chakravarty, A. R. *Polyhedron* **2002,** *21,* 1929-1934.
232. Zelonka, R. A.; Baird, M. C. *Canadian Journal of Chemistry* **1972,** *50,* 3063-3072.
233. Bennett, M. A.; Smith, A. K. *Journal of the Chemical Society-Dalton Transactions* **1974,** 233-241.
234. Herrmann, W. A. *Angewandte Chemie-International Edition* **2002,** *41,* 1291-1309.
235. Dragutan, I.; Dragutan, V.; Delaude, L.; Demonceau, A. *Arkivoc* **2005,** 206-253.
236. Jafarpour, L.; Nolan, S. P. *Advances in Organometallic Chemistry* **2001,** *46,* 181-222.

237. Delaude, L.; Demonceau, A.; Noels, A. F. *Chemical Communications* **2001,** 986-987.
238. Delaude, L.; Szypa, M.; Demonceau, A.; Noels, A. F. *Advanced Synthesis and Catalysis* **2002,** *344,* 749-756.
239. Jafarpour, L.; Huang, J. K.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999,** *18,* 3760-3763.
240. Arduengo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999,** *55,* 14523-14534.
241. Tudose, A.; Demonceau, A.; Delaude, L. *Journal of Organometallic Chemistry* **2006,** *691,* 5356-5365.
242. Waltman, A. W.; Grubbs, R. H. *Organometallics* **2004,** *23,* 3105-3107.
243. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Organic Letters* **1999,** *1,* 953-956.
244. Sanford, M. S.; Love, J. A.; Grubbs, R. H. *Organometallics* **2001,** *20,* 5314-5318.
245. Furstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chemistry-a European Journal* **2001,** *7,* 4811-4820.
246. Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *Journal of the American Chemical Society* **1999,** *121,* 791-799.
247. Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Letters* **2000,** *41,* 9973-9976.
248. Sanford, M. S.; Henling, L. M.; Day, M. W.; Grubbs, R. H. *Angewandte Chemie-International Edition* **2000,** *39,* 3451-3453.
249. Vander Mierde, H.; Van Der Voort, P.; De Vos, D.; Verpoort, F. *European Journal of Organic Chemistry* **2008,** 1625-1631.
250. Tanaka, T.; Kawabata, H.; Hayashi, M. *Tetrahedron Letters* **2005,** *46,* 4989-4991.
251. Dinger, M. B.; Mol, J. C. *Organometallics* **2003,** *22,* 1089-1095.
252. Banti, D.; Mol, J. C. *Journal of Organometallic Chemistry* **2004,** *689,* 3113-3116.
253. Dinger, M. B.; Mol, J. C. *European Journal of Inorganic Chemistry* **2003,** 2827-2833.
254. Cho, C. S.; Ren, W. X.; Shim, S. C. *Bulletin of the Korean Chemical Society* **2005,** *26,* 2038-2040.
255. Fulop, F.; Pihlaja, K.; Mattinen, J.; Bernath, G. *Journal of Organic Chemistry* **1987,** *52,* 3821-3825.
256. Szakonyi, Z.; Fulop, F.; Bernath, G.; Evanics, F.; Riddell, F. G. *Tetrahedron* **1998,** *54,* 1013-1020.
257. Martinek, T.; Lazar, L.; Fulop, F.; Riddell, F. G. *Tetrahedron* **1998,** *54,* 12887-12896.
258. Neuvonen, K.; Fulop, F.; Neuvonen, H.; Koch, A.; Kleinpeter, E.; Pihlaja, K. *Journal of Organic Chemistry* **2001,** *66,* 4132-4140.
259. Szatmari, I.; Martinek, T. A.; Lazar, L.; Fulop, F. *Tetrahedron* **2003,** *59,* 2877-2884.
260. Perez, S.; Lopez, C.; Caubet, A.; Roig, A.; Molins, E. *Journal of Organic Chemistry* **2005,** *70,* 4857-4860.
261. Toth, D.; Szatmari, I.; Fulop, F. *European Journal of Organic Chemistry* **2006,** 4664-4669.

262. Ouberai, M.; Asche, C.; Carrez, D.; Croisy, A.; Dumy, P.; Demeunynck, M. *Bioorganic and Medicinal Chemistry Letters* **2006,** *16,* 4641-4643.
263. Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B. K. *European Journal of Organic Chemistry* **2004,** 1254-1260.
264. Walling, C.; Bollyky, L. *Journal of the American Chemical Society* **1961,** *83,* 2968-2969.
265. Walling, C.; Bollyky, L. *Journal of the American Chemical Society* **1964,** *86,* 3750-3752.
266. Berkessel, A.; Schubert, T. J. S.; Muller, T. N. *Journal of the American Chemical Society* **2002,** *124,* 8693-8698.
267. Hagemeyer, H. J.; Hull, D. C. *Industrial And Engineering Chemistry* **1949,** *41,* 2920-2924.
268. Wasserman, H. H.; Wharton, P. S. *Journal of the American Chemical Society* **1960,** *82,* 661-665.
269. Lobell, M.; Schneider, M. P. *Tetrahedron-Asymmetry* **1993,** *4,* 1027-1030.
270. Neveux, M.; Bruneau, C.; Lecolier, S.; Dixneuf, P. H. *Tetrahedron* **1993,** *49,* 2629-2640.
271. Muir, W. M.; Ritchie, P. D.; Lyman, D. J. *Journal of Organic Chemistry* **1966,** *31,* 3790-3793.
272. Kabouche, Z.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron Letters* **1991,** *32,* 5359-5362.
273. Ema, T.; Maeno, S.; Takaya, Y.; Sakai, T.; Utaka, M. *Journal of Organic Chemistry* **1996,** *61,* 8610-8616.
274. Kawasaki, M.; Goto, M.; Kawabata, S.; Kometani, T. *Tetrahedron-Asymmetry* **2001,** *12,* 585-596.
275. Rozen, S.; Lerman, O. *Journal of the American Chemical Society* **1979,** *101,* 2782-2784.
276. Torii, S.; Inokuchi, T.; Misima, S.; Kobayashi, T. *Journal of Organic Chemistry* **1980,** *45,* 2731-2735.
277. Stavber, S.; Sket, B.; Zajc, B.; Zupan, M. *Tetrahedron* **1989,** *45,* 6003-6010.
278. Cort, A. D. *Journal of Organic Chemistry* **1991,** *56,* 6708-6709.
279. Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Letters* **1983,** *24,* 5639-5640.
280. Masuyama, Y.; Sakai, T.; Kurusu, Y. *Tetrahedron Letters* **1993,** *34,* 653-656.
281. Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chemical Communications* **1997,** 1201-1202.
282. Picquet, M.; Fernandez, A.; Bruneau, C.; Dixneuf, P. H. *European Journal of Organic Chemistry* **2000,** 2361-2366.
283. House, H. O.; Trost, B. M. *Journal of Organic Chemistry* **1965,** *30,* 2502-2512.
284. Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Journal of the Chemical Society-Chemical Communications* **1983,** 344-345.
285. Ito, H.; Ueda, M. *Macromolecules* **1990,** *23,* 2885-2894.
286. Jong, T. T.; Williard, P. G.; Porwoll, J. P. *Journal of Organic Chemistry* **1984,** *49,* 735-736.
287. Niwa, M.; Iguchi, M.; Yamamura, S. *Tetrahedron Letters* **1975,** 1539-1542.
288. Niwa, M.; Iguchi, M.; Yamamura, S. *Tetrahedron Letters* **1975,** 4395-4398.
289. Martinez, J. C.; Yoshida, M.; Gottlieb, O. R. *Tetrahedron Letters* **1979,**

1021-1024.
290. Pettus, J. A.; Wing, R. M.; Sims, J. J. *Tetrahedron Letters* **1977,** 41-44.
291. Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. *Tetrahedron Letters* **1977,** 37-40.
292. Dembitsky, V. M.; Tostikov, G. A. *Chemistry for Sustainable Development* **2003,** 697-703.
293. Han, Y. F.; Kumar, D.; Sivadinarayana, C.; W., G. D. *Journal of Catalysis* **2004,** *224,* 60-68.
294. Chen, F.; Cheng, Z.; Zhu, J.; Zhang, W.; Zhu, X. *European Polymer Journal* **2008,** *44,* 1789-1795.
295. Gustin, J. L.; Laganier, F. *Organic Process Research and Development* **2005,** *9,* 962-975.
296. Trost, B. M. *Angewandte Chemie-International Edition in English* **1995,** *34,* 259-281.
297. Trost, B. M. *Accounts of Chemical Research* **2002,** *35,* 695-705.
298. Lemaire, H.; Lucas, H. J. *Journal of the American Chemical Society* **1955,** *77,* 939-945.
299. Amos, R. A.; Katzenellenbogen, J. A. *Journal of Organic Chemistry* **1978,** *43,* 560-564.
300. Krafft, G. A.; Katzenellenbogen, J. A. *Journal of the American Chemical Society* **1981,** *103,* 5459-5466.
301. Yamamoto, M. *Journal of the Chemical Society-Perkin Transactions 1* **1981,** 582-587.
302. Jellal, A.; Grimaldi, J.; Santelli, M. *Tetrahedron Letters* **1984,** *25,* 3179-3182.
303. Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *Journal of the American Chemical Society* **1981,** *103,* 4114-4125.
304. Sofia, M. J.; Katzenellenbogen, J. A. *Journal of Organic Chemistry* **1985,** *50,* 2331-2336.
305. Spencer, R. W.; Tam, T. F.; Thomas, E.; Robinson, V. J.; Krantz, A. *Journal of the American Chemical Society* **1986,** *108,* 5589-5597.
306. Bach, R. D.; Woodard, R. A.; Anderson, T. J.; Glick, M. D. *Journal of Organic Chemistry* **1982,** *47,* 3707-3712.
307. Foster, D. J.; Tobler, E. *Journal of Organic Chemistry* **1962,** *27,* 661-665.
308. Larock, R. C.; Oertle, K.; Beatty, K. M. *Journal of the American Chemical Society* **1980,** *102,* 1966-1974.
309. Fukuda, W.; Sato, H.; Kakiuchi, H. *Bulletin of the Chemical Society of Japan* **1986,** *59,* 751-756.
310. Hudrlik, P. F.; Hudrlik, A. M. *Journal of Organic Chemistry* **1973,** *38,* 4254-4258.
311. Rotem, M.; Shvo, Y. *Organometallics* **1983,** *2,* 1689-1691.
312. Mitsudo, T.; Hori, Y.; Watanabe, Y. *Journal of Organic Chemistry* **1985,** *50,* 1566-1568.
313. Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *Tetrahedron Letters* **1986,** *27,* 2125-2126.
314. Hori, Y.; Mitsudo, T. A.; Watanabe, Y. *Journal of Organometallic Chemistry* **1987,** *321,* 397-407.
315. Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *Journal of Organic*

Chemistry **1987,** *52,* 2230-2239.
316. Ruppin, C.; Dixneuf, P. H. *Tetrahedron Letters* **1986,** *27,* 6323-6324.
317. Philippot, K.; Devanne, D.; Dixneuf, P. H. *Journal of the Chemical Society-Chemical Communications* **1990,** 1199-1200.
318. Neveux, M.; Bruneau, C.; Dixneuf, P. H. *Journal of the Chemical Society-Perkin Transactions 1* **1991,** 1197-1199.
319. Ruppin, C.; Dixneuf, P. H.; Lecolier, S. *Tetrahedron Letters* **1988,** *29,* 5365-5368.
320. Doucet, H.; Hofer, J.; Bruneau, C.; Dixneuf, P. H. *Journal of the Chemical Society-Chemical Communications* **1993,** 850-851.
321. Doucet, H.; Martinvaca, B.; Bruneau, C.; Dixneuf, P. H. *Journal of Organic Chemistry* **1995,** *60,* 7247-7255.
322. Doucet, H.; Derrien, N.; Kabouche, Z.; Bruneau, C.; Dixneuf, P. H. *Journal of Organometallic Chemistry* **1998,** *551,* 151-157.
323. Seiller, B.; Heins, D.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995,** *51,* 10901-10912.
324. Lavastre, O.; Bebin, P.; Marchaland, O.; Dixneuf, P. H. *Journal of Molecular Catalysis a-Chemical* **1996,** *108,* 29-34.
325. Kabouche, A.; Kabouche, Z.; Bruneau, C.; Dixneuf, P. H. *Journal of Chemical Research-S* **1999,** 249.
326. Kabouche, A.; Kabouche, Z.; Bruneau, C.; Dixneuf, P. H. *Journal of Chemical Research-M* **1999,** 1247-1256.
327. Lavastre, O.; Dixneuf, P. H. *Journal of Organometallic Chemistry* **1995,** *488,* C9-C10.
328. Sasaki, Y.; Dixneuf, P. H. *Journal of the Chemical Society-Chemical Communications* **1986,** 790-791.
329. Mahe, R.; Sasaki, Y.; Bruneau, C.; Dixneuf, P. H. *Journal of Organic Chemistry* **1989,** *54,* 1518-1523.
330. Hofer, J.; Doucet, H.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron Letters* **1991,** *32,* 7409-7410.
331. Kita, Y.; Maeda, H.; Omori, K.; Okuno, T.; Tamura, Y. *Journal of the Chemical Society-Perkin Transactions 1* **1993,** 2999-3005.
332. Leadbeater, N. E.; Scott, K. A.; Scott, L. J. *Journal of Organic Chemistry* **2000,** *65,* 3231-3232.
333. Goossen, L. J.; Paetzold, J.; Koley, D. *Chemical Communications* **2003,** 706-707.
334. Le Paih, J.; Monnier, F.; Derien, S.; Dixneuf, P. H.; Clot, E.; Eisenstein, O. *Journal of the American Chemical Society* **2003,** *125,* 11964-11975.
335. Derien, S.; Dixneuf, P. H. *Journal of Organometallic Chemistry* **2004,** *689,* 1382-1392.
336. Doherty, S.; Knight, J. G.; Rath, R. K.; Clegg, W.; Harrington, R. W.; Newman, C. R.; Campbell, R.; Amin, H. *Organometallics* **2005,** *24,* 2633-2644.
337. Ye, S. M.; Leong, W. K. *Journal of Organometallic Chemistry* **2006,** *691,* 1117-1120.
338. Pelagatti, P.; Bacchi, A.; Balordi, M.; Bolano, S.; Calbiani, F.; Elviri, L.; Gonsalvi, L.; Pelizzi, C.; Peruzzini, M.; Rogolino, D. *European Journal of*

Inorganic Chemistry **2006,** 2422-2436.
339. Melis, K.; Opstal, T.; Verpoort, F. *European Journal of Organic Chemistry* **2002,** 3779-3784.
340. Melis, K.; Samulkiewicz, P.; Rynkowski, J.; Verpoort, F. *Tetrahedron Letters* **2002,** *43,* 2713-2716.
341. Melis, K.; De Vos, D.; Jacobs, P.; Verpoort, F. *Journal of Organometallic Chemistry* **2003,** *671,* 131-136.
342. Le Gendre, P.; Comte, V.; Michelot, A.; Moise, C. *Inorganica Chimica Acta* **2003,** *350,* 289-292.
343. Ye, S. M.; Leong, W. K. *Journal of Organometallic Chemistry* **2006,** *691,* 1216-1222.
344. Bianchini, C.; Peruzzini, M.; Zanobini, F.; Frediani, P.; Albinati, A. *Journal of the American Chemical Society* **1991,** *113,* 5453-5454.
345. Echavarren, A. M.; Lopez, J.; Santos, A.; Montoya, J. *Journal of Organometallic Chemistry* **1991,** *414,* 393-400.
346. Bianchini, C.; Frediani, P.; Masi, D.; Peruzzini, M.; Zanobini, F. *Organometallics* **1994,** *13,* 4616-4632.
347. Yi, C. S.; Liu, N. H. *Organometallics* **1996,** *15,* 3968-3971.
348. Slugovc, C.; Mereiter, K.; Zobetz, E.; Schmid, R.; Kirchner, K. *Organometallics* **1996,** *15,* 5275-5277.
349. Baratta, W.; Herrmann, W. A.; Rigo, P.; Schwarz, J. *Journal of Organometallic Chemistry* **2000,** *594,* 489-493.
350. Tenorio, M. A. J.; Tenorio, M. J.; Puerta, M. C.; Valerga, P. *Organometallics* **2000,** *19,* 1333-1342.
351. Bassetti, M.; Marini, S.; Tortorella, F.; Cadierno, V.; Diez, J.; Gamasa, M. P.; Gimeno, J. *Journal of Organometallic Chemistry* **2000,** *594,* 292-298.
352. Lu, X. Y.; Zhu, G. X.; Ma, S. M. *Tetrahedron Letters* **1992,** *33,* 7205-7206.
353. El Ali, B.; Vasapollo, G.; Alper, H. *Journal of Organic Chemistry* **1993,** *58,* 4739-4741.
354. Yanagihara, N.; Lambert, C.; Iritani, K.; Utimoto, K.; Nozaki, H. *Journal of the American Chemical Society* **1986,** *108,* 2753-2754.
355. Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Letters* **1984,** *25,* 5323-5326.
356. Tsuda, T.; Ohashi, Y.; Nagahama, N.; Sumiya, R.; Saegusa, T. *Journal of Organic Chemistry* **1988,** *53,* 2650-2653.
357. Bouyssi, D.; Gore, J.; Balme, G. *Tetrahedron Letters* **1992,** *33,* 2811-2814.
358. Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *Journal of Organic Chemistry* **1992,** *57,* 976-982.
359. Kundu, N. G.; Pal, M. *Journal of the Chemical Society-Chemical Communications* **1993,** 86-88.
360. Pale, P.; Chuche, J. *Tetrahedron Letters* **1987,** *28,* 6447-6448.
361. Dalla, V.; Pale, P. *Tetrahedron Letters* **1994,** *35,* 3525-3528.
362. Marder, T. B.; Chan, D. M. T.; Fultz, W. C.; Calabrese, J. C.; Milstein, D. *Journal of the Chemical Society-Chemical Communications* **1987,** 1885-1887.
363. Chan, D. M. T.; Marder, T. B.; Milstein, D.; Taylor, N. J. *Journal of the American Chemical Society* **1987,** *109,* 6385-6388.

364. Wakabayashi, T.; Ishii, Y.; Murata, T.; Mizobe, Y.; Hidai, M. *Tetrahedron Letters* **1995,** *36,* 5585-5588.
365. Wakabayashi, T.; Ishii, Y.; Ishikawa, K.; Hidai, M. *Angewandte Chemie-International Edition in English* **1996,** *35,* 2123-2124.
366. Takei, I.; Wakebe, Y.; Suzuki, K.; Enta, Y.; Suzuki, T.; Mizobe, Y.; Hidai, M. *Organometallics* **2003,** *22,* 4639-4641.
367. Nakagawa, H.; Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Letters* **2003,** *44,* 103-106.
368. Hua, R. M.; Tian, X. *Journal of Organic Chemistry* **2004,** *69,* 5782-5784.
369. Yoshida, K.; Yamashita, Y. *Tetrahedron Letters* **1966,** *7,* 693-696.
370. Cahiez, G.; Figadere, B.; Clery, P. *Tetrahedron Letters* **1994,** *35,* 6295-6298.
371. Gong, L. Y.; Leungtoung, R.; Tidwell, T. T. *Journal of Organic Chemistry* **1990,** *55,* 3634-3639.
372. House, H. O.; Kramar, V. *Journal of Organic Chemistry* **1963,** *28,* 3362-3379.
373. House, H. O.; Auerbach, R. A.; Gall, M.; Peet, N. P. *Journal of Organic Chemistry* **1973,** *38,* 514-522.
374. Mitsudo, T.; Watanabe, Y.; Sasaki, T.; Nakanishi, H.; Yamashita, M.; Takegami, Y. *Tetrahedron Letters* **1975,** 3163-3164.
375. Kowalski, C. J.; Haque, M. S. *Journal of the American Chemical Society* **1986,** *108,* 1325-1327.
376. Schaefer, C.; Fu, G. C. *Angewandte Chemie-International Edition* **2005,** *44,* 4606-4608.
377. Tidwell, T. T. *Angewandte Chemie-International Edition* **2005,** *44,* 6812-6814.
378. Kitching, W.; Rappoport, Z.; Winstein, S.; Young, W. *Journal of the American Chemical Society* **1966,** *88,* 2054-2055.
379. Hudrlik, P. F.; Hudrlik, A. M.; Rona, R. J.; Misra, R. N.; Withers, G. P. *Journal of the American Chemical Society* **1977,** *99,* 1993-1996.
380. Chemla, F.; Normant, J. F. *Tetrahedron* **1997,** *53,* 17265-17274.
381. Melis, K.; De Vos, D.; Jacobs, P.; Verpoort, F. *Journal of Organometallic Chemistry* **2002,** *659,* 159-164.
382. Herrmann, W. A.; Kocher, C. *Angewandte Chemie-International Edition in English* **1997,** *36,* 2163-2187.
383. Alder, R. W.; Allen, P. R.; Williams, S. J. *Journal of the Chemical Society-Chemical Communications* **1995,** 1267-1268.
384. Bruneau, C.; Dixneuf, P. H. *Accounts of Chemical Research* **1999,** *32,* 311-323.
385. Nesmeyanov, A. N.; Aleksandrov, G. G.; Antonova, A. B.; Anisimov, K. N.; Kolobova, N. E.; Struchkov, Y. T. *Journal of Organometallic Chemistry* **1976,** *110,* C36-C38.
386. Bruce, M. I.; Swincer, A. G. *Advances in Organometallic Chemistry* **1983,** *22,* 59-128.
387. Bruce, M. I. *Chemical Reviews* **1991,** *91,* 197-257.
388. Wakatsuki, Y.; Koga, N.; Yamazaki, H.; Morokuma, K. *Journal of the American Chemical Society* **1994,** *116,* 8105-8111.
389. Esteruelas, M. A.; Lahoz, F. J.; Lopez, A. M.; Onate, E.; Oro, L. A. *Organometallics* **1994,** *13,* 1669-1678.

390. Kawano, H.; Masaki, Y.; Matsunaga, T.; Hiraki, K.; Onishi, M.; Tsubomura, T. *Journal of Organometallic Chemistry* **2000,** *601,* 69-77.
391. Bruneau, C.; Dixneuf, P. H. *Angewandte Chemie-International Edition* **2006,** *45,* 2176-2203.
392. Clavier, H.; Coutable, L.; Guillemin, J. C.; Mauduit, M. *Tetrahedron-Asymmetry* **2005,** *16,* 921-924.
393. Waltman, A. W.; Grubbs, R. H. *Organometallics* **2004,** *23,* 3105-3107.
394. Allaert, B. *Development and Exploration of Schiff base Ruthenium Carbene Catalysts for Olefin Metathesis,* Thesis, Ghent University, 2008.

Scientific publications

N,N'-dialkyl- and N-alkyl-N-mesityl-substituted N-heterocyclic carbenes as ligands in Grubbs catalysts. Ledoux, N.; Allaert, B.; Pattyn, S.; Vander Mierde, H.; Vercaemst, C.; Verpoort, F. *Chemistry-a European Journal* **2006**, *12*, 4654-4661.

Comparative investigation of Hoveyda-Grubbs catalysts bearing modified N-heterocyclic carbene ligands. Ledoux, N.; Linden, A.; Allaert, B.; Vander Mierde, H.; Verpoort, F. *Advanced Synthesis & Catalysis* **2007**, *349*, 1692-1700.

Improved ruthenium catalysts for the modified Friedlaender quinoline synthesis. Vander Mierde, H.; Ledoux, N.; Allaert, B.; Van Der Voort, P.; Drozdzak, R.; De Vos, D.; Verpoort, F. *New Journal of Chemistry* **2007**, *31*, 1572-1574.

Secondary metathesis with Grubbs catalysts in the 1,4 polybutadiene system. Allaert, B.; Ledoux, N.; Dieltiens, N.; Vander Mierde, H.; Stevens, C.; Verpoort, F. *Catalysis Communications* **2008**, *9*, 1054-1059.

A ruthenium-catalyzed approach to the Friedlander quinoline synthesis. Vander Mierde, H.; Van Der Voort, P.; De Vos, D.; Verpoort, F.; *European Journal of Organic Chemistry* **2008**, 1625-1631.

Base-mediated synthesis of quinolines: an unexpected cyclization reaction between 2-aminobenzylalcohol and ketones. Vander Mierde, H.; Van Der Voort, P.; Verpoort, F.; *Tetrahedron Letters* **2008**, accepted.

Fast and convenient base-mediated synthesis of 3-substituted quinolines. Vander Mierde, H.; Van Der Voort, P.; Verpoort, F.; *Tetrahedron Letters* **2008**, accepted.

Ruthenium Schiff base catalysts for the synthesis of enol esters. Vander Mierde, H.; Van Der Voort, P.; Verpoort, F.; *Journal of Organometallic Chemistry*, in preparation.