Ru / PNNP Catalyzed Asymmetric Diels-Alder and Ficini Reactions on Alkylidene $\beta$-Ketoesters
Ru / PNNP-Catalyzed Asymmetric Diels-Alder and
Ficini Reactions on Alkylidene \( \beta \)-Ketoesters

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Überzeugungen sind gefährlichere Feinde der Wahrheit als Lügen. - Friedrich Nietzsche
(1844 - 1900)

If you don’t get what you want, try to want what you get. - source unknown
Dedicated to
Deborah and my parents.
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The work described in this thesis is part of the following publications:


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Abstract

Upon double chloride abstraction with (Et$_3$O)PF$_6$, complex [RuCl$_2$(PNNP)] (1) forms the elusive dicationic complex [Ru(OEt)$_2$(PNNP)](PF$_6$)$_2$ (2), which contains a highly Lewis acidic Ru / PNNP fragment and reacts with β-ketoesters like 2-tert-butoxycarbonylcyclopentanone (3a) to form [Ru(3a)(PNNP)](PF$_6$)$_2$ (4a), a rare example of a transition metal complex with a non-deprotonated β-ketoester. The α-methine proton in 4a is acidified by at least 6 orders of magnitude as compared to 3a, and deprotonation by amines forms the stable monocationic enolato complex [Ru(3a–H)(PNNP)](PF$_6$) (5a). This species undergoes a hydride abstraction reaction upon treatment with Ph$_3$C(PF$_6$) to give the dicationic complex [Ru(6a)(PNNP)](PF$_6$)$_2$ (7a), which contains the alkylidene β-ketoester 6a.

The enone moiety of the unsaturated β-ketoester 6a is activated by coordination to the dicationic Ru / PNNP fragment, thus catalytic amounts of 2 readily promote Diels-Alder reactions with dienes 8, 9, and 10 to form the bicyclic products 11, 12, and 13 in high yields and up to 93% ee.
With Dane’s diene (14), enantiomerically pure estrone derivatives (15) were obtained with an ester-\textit{exo:endo} ratio of up to 145:1 (after recrystallization). These products are interesting in view of applications in medicinal chemistry, e.g., for prostate and breast cancer treatment. Complex 7a also catalyzes the first example of an enantioselective Ficini reaction, which, in its original form, is the [2+2] cycloaddition between an ynamine and an enone. Ynamides 16 react with unsaturated $\beta$-ketoesters of type 6 in the presence of catalyst 2 to give the corresponding cyclobuteneamides 17 with excellent yield and enantioselectivity (16 examples, up to 99.5% ee after recrystallization). Selected examples of 17 have been transformed into chiral ligands for Rh(I) and Pd(II) catalysis. Both the Diels-Alder and the Ficini cycloaddition reactions make use of alkylidene $\beta$-ketoesters, which have been scarcely explored in cycloaddition reactions, to form all-carbon quaternary stereocenters with high enantioselectivity.

\[
\text{[RuCl}_2\text{(PNNP)}] \text{ (10 mol\%)} \quad \text{(Et}_3\text{O)}\text{PF}_6 \text{ (20 mol\%)} \quad \text{CH}_2\text{Cl}_2, 55^\circ\text{C} \quad \text{sealed tube, 24 h}
\]

\[
\text{up to 99\% yield} \quad \text{up to 92\% ee}
\]

\(R^2\text{ is c-C}_6\text{H}_{11}, \text{ Ph, n-C}_6\text{H}_{13}, \text{ CH}_2\text{OBn, or (CH}_2\text{)}_2\text{OSiMe}_2\text{tBu,}
\)

\(R^3\text{ is Bn or Me, } R^4\text{ is Ts, Ms, or Mbs}

The absolute configuration of three representative cycloaddition products and the structure of the catalyst/substrate adduct 7a were determined by X-ray diffraction. In 7a a phenyl ring of the PNNP ligand efficiently shields the lower face of the enone 6a, which is in agreement with the absolute configuration of the products and accounts for the high enantioselectivity. The large tert-butyl ester moiety of 6a points away from the bulky diphenylphosphine groups of the ligand, thus ensuring complete diastereoselectivity in the formation of 7a.

On the other hand, the smaller methyl ester analogue 6c forms two diastereomeric complexes (7b and 7c), which were prepared in pure form by separating a mixture of the corresponding enolato complexes 5b and 5c via column chromatography, followed by hydride abstraction. Complexes 7b and 7c do not interconvert in solution and expose opposite enantiomeric faces of the coordinated alkylidene $\beta$-ketoester 6c. Addition of a stoichiometric amount of Dane’s diene (14) to 7b gives the major enantiomer 15b with 87% ee, whereas 7c gives the minor enantiomer \textit{ent}-15b with 97% ee.
This confirms our stereochemical model and provides a rationale for the decreased enantioselectivity of cycloaddition reactions with 6b and 6c as compared to the tert-butyl analogue 6a. We further used the extraordinary characterizability of complexes 7 to study the relative rates of cycloaddition reaction and product release from the catalyst.
Zusammenfassung

Die Abstraktion zweier Chlorid Liganden von Komplex \([\text{RuCl}_2(\text{PNNP})]\) (1) durch \((\text{Et}_3\text{O})\text{PF}_6\) führt zur Bildung des dikationischen Komplexes \([\text{Ru}(\text{OEt}_2)_2(\text{PNNP})]((\text{PF}_6)_2\) (2), welcher ein stark Lewis-azides Ru / PNNP Fragment enthält und mit \(\beta\)-Ketoestern wie \(2\text{-}t\text{ert}-\text{butoxycarbonylcyclopentanon}\) (3a) zu \([\text{Ru}(3a)(\text{PNNP})]((\text{PF}_6)_2\) (4a) reagiert, einem seltenen Beispiel eines Übergangsmetallkomplexes mit einem nicht deprotonierten \(\beta\)-Ketoester.

Die Azidität des \(\alpha\)-Methinprotons in 4a wird, im Vergleich zu 3a, um mindestens 6 Größenordnungen erhöht, und eine Deprotonierung durch Amine bildet den stabilen monokationischen Komplex \([\text{Ru}(3a\text{-H})(\text{PNNP})]((\text{PF}_6)_2\) (5a). Versetzt man diese Spezies mit \(\text{Ph}_3\text{C}(\text{PF}_6)\) vollzieht sich eine Hydridabstraktion und es formt sich der dikationische Komplex \([\text{Ru}(6a)(\text{PNNP})]((\text{PF}_6)_2\) (7a), welchen den Alkyliden-\(\beta\)-Ketoester 6a als Liganden trägt.

Der Enon Teil des ungesättigten \(\beta\)-Ketoesters 6a wird durch die Koordination zum dikationischen Ru / PNNP Fragment aktiviert, und katalytische Mengen von 2 ermöglichen Diels-Alder Reaktionen mit den Dienen 8, 9 und 10, welche die bizyklischen Produkte 11, 12 und 13 mit hohen Ausbeuten und bis zu 93% ee bilden.

Die absolute Konfiguration von drei repräsentativen Zykloadditionsprodukten und die Struktur des Katalysator/Substrat Adduktes 7a wurden per Röntgenstrukturanalyse bestimmt. In 7a schirmt ein Phenylring des PNNP Liganden die untere Seite des Enons 6a effizient ab. Dies stimmt mit der absoluten Konfiguration der Katalyseprodukte überein und erklärt die hohe Enantioselektivität der Reaktion. Die stichisch anspruchsvolle tert-Butylestergruppe von 6a wendet sich von den grossen Diphenylphosphingruppen des Ligan-
den ab.

Der kleinere, analoge Methylester 6c bildet zwei diastereomere Komplexe (7b und 7c), die sich in reiner Form, durch Trennung einer Mischung der entsprechenden Enolatkomplexes (5b und 5c) mittels Säulenchromatographie und anschliessender Hydridabstraktion, darstellen lassen. Die Komplexe 7b und 7c wandeln sich in Lösung nicht ineinander um und schirmen entgegengesetzte Seiten des gebundenen Alkylidin-β-Ketoesters 6c ab. Die Zugabe einer stöchiometrischen Menge von Danes Dien (14) zum Komplex 7b bildet das Hauptenantiomer 15b mit 87% ee, während 7c das Nebenenantiomer ent-15b mit 97% ee erzeugt.
Dies bestätigt unser stereochemisches Modell und gibt eine Erklärung für die geringere Enantioselektivität von Zykloadditionsreaktionen mit 6b und 6c, im Vergleich zum analogen tert-Butylester 6a. Weiterhin haben wir die außergewöhnliche Charakterisierbarkeit der Komplexe vom Typ 7 genutzt, um die relativen Geschwindigkeiten der Zykloadditionsreaktion und der Freisetzung des Produktes vom Kataysator zu untersuchen.
1 Ruthenium PNNP $\beta$-Ketoester Complexes and Unsaturated $\beta$-Ketoesters

At the core of this thesis stand ruthenium complexes bearing a chiral tetradentate PNNP ligand. This introductory chapter describes the development of Ru / PNNP catalysts containing $\beta$-ketoesters and a consecutive proton-hydride abstraction reaction leading to complexes containing the corresponding alkylidene $\beta$-ketoesters. The second part of the chapter gives a short survey of the synthesis and catalytic applications of unsaturated $\beta$-ketoesters, except for Diels-Alder reactions, which are discussed in chapter 2.

1.1 Ruthenium PNNP $\beta$-Ketoester Complexes

The starting point for all Ru / PNNP $\beta$-ketoester complexes is the diimine based Ru / PNNP dichloro complex $[\text{RuCl}_2(\text{PNNP})]$ (1), first reported by Gao and Noyori.\textsuperscript{1} It was originally designed for the transfer hydrogenation reaction of 2-propanol and acetophenone. However, in contrast to its reduced diamine analogue, it performed poorly in terms of yield and enantioselectivity. Discoveries made in the Mezzetti group showed that it is possible to abstract one or both chloro ligands from 1 to obtain mono- or dicationic complexes, which act as catalysts in a variety of reactions.\textsuperscript{2}

Complex $[\text{RuCl}_2(\text{PNNP})]$ is a stable 18 electron complex with an octahedral $d^6$ electron configuration. Therefore, it is kinetically inert under all but the harshest conditions and has to be activated by chloride scavengers to form catalytically active cationic complexes.\textsuperscript{2,3} When no coordinating molecules are present, very reactive 14 or 16 electron species are generated, which readily form more stable 18 electron complexes upon addition of oxygen donors like diethyl ether or water. However, the neutral oxygen donors are bound more weakly than chloride. Thus, these complexes still act as catalyst in atom transfer reactions.\textsuperscript{2}

The monocationic complexes are prepared by adding 1 equiv of TlPF$_6$, AgX (X = PF$_6$, SbF$_6$, BF$_4$), or (Et$_3$O)PF$_6$ to a CH$_2$Cl$_2$ solution of $[\text{RuCl}_2(\text{PNNP})]$ (1). The resulting complexes are reactive in cyclopropanation,\textsuperscript{4-6} aziridination,\textsuperscript{7} and epoxidation\textsuperscript{3,8} reactions (see also section 6). The silver and Meerwein salts are very powerful chloride scavengers, thus 2 equiv of these reagents remove both chloride ligands from 1, and dicationic species are generated. In case of (Et$_3$O)PF$_6$, the chloride abstraction leads to the formation of ethyl chloride and diethyl ether. The latter acts as a weakly bound ligand to form the elusive dicationic complex $[\text{Ru(OEt}_2]_2(\text{PNNP})](\text{PF}_6)_2$ (2) (Scheme 1).
Scheme 1: Double chloride abstraction from complex 1 to form dicationic 2.

The highly Lewis-acidic dicationic Ru / PNNP fragment binds bidentate oxygen donors, in particular β-ketoesters, to form adduct complexes such as [Ru(3a)(PNNP)](PF$_6$)$_2$ (4a). Investigations performed in our group by Francesco Santoro and Martin Althaus indicated that the 1,3-dicarbonyl compound in 4a is coordinated in its neutral, non-enolized form. Only a few cases of such complexes have been reported,\textsuperscript{9,10} because ruthenium, as a late transition metal, does not generally form strong bonds to bidentate oxygen ligands due to its low oxophilicity. Therefore, the complexes are usually only stable after deprotonation and formation of the enolato complexes.\textsuperscript{11–14}

Scheme 2: Electrophilic fluorination and Michael Addition reactions on 3a catalyzed by 2.

In general, the affinity for oxygen-containing ligands (oxophilicity) is a key property of early transition metals, which progressively declines on going towards the late transition elements.\textsuperscript{15} Oxophilicity is a manifestation of the hard nature of these metal ions as expressed by the HSAB principle.\textsuperscript{16} However, according to the principle of symbiosis, the ligands influence the hard/soft character of the metal in a complex.\textsuperscript{17} Therefore, the whole coordination sphere must be considered when discussing the affinity of a metal for a particular class of ligands. In case of complex 4a, the coordination of the two hard nitrogen moi-
eties render complex 2 extraordinarily oxophilic, so that neutral oxygen donor species are much more strongly coordinated, than it is the case in the softer ruthenium-phosphine complexes.2 A further stabilizing factor is the double positive charge of 4a. By analogy to the electroneutrality principle (see page 6), one can infer that the increase of the overall charge on going from the monocationic complexes [RuCl(OR₂)(PNNP)]⁺ to the dicationic β-ketoester complex 4a similarly contributes to the inert nature of the latter species.

Complex 4a is stable in solution as long as proton accepting molecules are absent. The acidity of the α-methine proton was found to be increased by at least 6 orders of magnitude, which activates the substrate towards Michael addition, hydroxylation, and electrophilic fluorination (Scheme 2). Also, the coordination of 3a greatly facilitates its deprotonation by amine bases like triethylamine to form the corresponding enolato derivative 5a (Scheme 3).

Scheme 3: Deprotonation of 4a by triethylamine to form 5a.

This monocationic enolato complex is considerably more stable than dicationic 4a and can even be purified by filtering over silica without protective gas atmosphere. A similar strategy was utilized with dicationic palladium(II) complexes [Pd(OH₂)₂(P-P)](OTf)₂ (PP = chiral diphosphine), which also acidify 1,3-dicarbonyl compounds and form stable enolato complexes. The enolato complexes are inactive as nucleophiles in Michael addition reactions, and conversion was only observed after activation with triflic acid. In the case of palladium, the activation is believed to take place via protonation of the carbonyl group of the Michael acceptor enone and not via protonation of the catalyst bound enolate. In contrast, treatment of the Ru / PNNP enolato complex 5a with HBF₄·OEt₂ (1 equiv) results in its quantitative protonation and formation of the dicationic β-ketoester complex 4a, which is, unlike 5a, active in Michael addition reactions. However, complex 5a is not intrinsically unreactive and gives extraordinarily good results in stoichiometric electrophilic fluorination reactions with NFSI, which is a much stronger electrophile than the Michael acceptor methyl vinyl ketone. Nevertheless, enolato complex 5a is inefficient in catalytic
electrophilic fluorination reactions, because of the gradual formation and coordination of NSI$^-\ ((\text{PhSO}_2)_2\text{N})$, hence impeding turn-over.$^{21}$

### 1.1.1 β-Hydride Abstraction from Complex 5a

During the study of the electrophilic fluorination of β-ketoester 3a, Martin Althaus observed that the enantioselectivity increased at higher conversions. As a possible explanation, it was proposed that a more enantioselective ruthenium(III) species may be formed during the catalytic reaction.$^{21}$ In an attempt to prepare such a species from enolato complex 5a with tritylium hexafluorophosphate as an oxidizing reagent, an unexpected hydride abstraction reaction took place at the β-position of the coordinated β-ketoester 3a. The dicationic complex [Ru(6a)(PNNP)](PF$_6$)$_2$ (7a), in which the unsaturated β-ketoester 6a is coordinated to the ruthenium center (Scheme 4), was cleanly formed.

![Scheme 4: Unexpected hydride abstraction from 5a by tritylium hexafluorophosphate.](image)

The key experimental data leading to the assignment of complex 7a were the characteristic $^1$H NMR signals of the tertiary C-H hydrogen in Ph$_3$CH (δ 5.59), and of the vinylic proton of coordinated 6a (δ 8.38), as well as the $^{13}$C NMR signals of the sp$^2$ carbons of 6a at δ 131.9 and 188.3 (see also Figure 25). Furthermore, the absence of Gomberg’s dimer in the reaction mixture indicated that the desired single electron oxidation had not occurred.$^{25,28}$ Eventually, it was concluded that the most plausible explanation for the increase in enantioselectivity over reaction time is that the fluorinated β-ketoester product, accumulating during the catalytic reaction, deprotonates the β-ketoester complex 4a to furnish the enolato analogue 5a. Accordingly, complex 5a is fluorinated with higher enantioselectivity than 4a, as proven by independent stoichiometric reactions.$^{21}$

The hydride-abstracting properties of tritylium salts have been used in organic reactions for instance for the conversion of secondary alcohols to ketones.$^{29}$ The trityl cation is known to abstract a hydride from silyl enol ethers to give the corresponding enones,$^{30}$ but its reaction
with an enolato complex (and β-ketoesters in general) is, to the best of our knowledge, unprecedented. The closest literature analogue is the oxidative cleavage of titanium bound enediolates by triphosgene to form cyclopentane-1,2-diones, a reaction whose mechanism has not been investigated (Scheme 5, left).\textsuperscript{31} Apart from this, clean hydride abstraction reactions by the trityl cation are known in transition metal chemistry from the transformation of metal-alkyl to carbene complexes (Scheme 5, right).\textsuperscript{32–35}

**Scheme 5:** Left: oxidative cleavage of titanium bound enediolates;\textsuperscript{31} right: recent example of carbene formation by hydride abstraction with Ph\textsubscript{3}CPF\textsubscript{6}.\textsuperscript{32}

Complex 7a contains the alkylidene β-ketoester 6a as a neutral ligand, which makes it considerably less stable than 5a, in analogy to complex 4a. Not surprisingly, fully characterized complexes of transition metals with these neutral unsaturated β-ketoester ligands are not reported in literature. The closest analogues are α-unsaturated malonate complexes, which have been reported with iridium(III),\textsuperscript{36,37} copper(II)\textsuperscript{38,39} and titanium(IV) (Figure 1).\textsuperscript{40}

**Figure 1:** Unsaturated malonate complexes reported in literature.

Whereas the complex formation with the highly oxophilic titanium(IV) center is hardly surprising (see above), the oxophilicity of copper(II) is considerably smaller, yet still larger than in ruthenium(II). The stability of the unsaturated malonate copper complex is probably
enhanced by the same factors that act in complex 4a, that is, the double positive charge and the coordination of the hard nitrogen donors. The iridium(III) complex surely has the lowest oxophilicity and is most similar to the ruthenium(II) complexes 4a and 7a. The soft diphosphine ligand will not favor the coordination of the unsaturated malonate, but the complex is stabilized by its double positive charge and by the strongly π-accepting carbonyl ligand, which decreases the electron density at the iridium center and "makes it harder".\(^\text{17}\) Also, the high oxidation state (+3) will have a stabilizing effect as, according to the electroneutrality principle,\(^\text{19}\) the covalent character of a metal-ligand bond increases with the oxidation state of the metal, hence decreasing the lability of the ligand.

In case of Ru / PNNP, crystal structures were obtained both for the stable enolato complex \((\text{rac})-5a\) and for the highly reactive dicaticonic complex \((\text{rac})-7a\). The analysis of the complexes with the \((S,S)\)-enantiomer of the PNNP ligand (as used in all catalytic reactions) revealed that the lower (\(si\)) face of the substrate is shielded by one of the phenyl rings of the ligand (Figure 2). When coordinated to the Ru / PNNP fragment, the enolate of 3a can only be attacked by an electrophilic reagent from the open top (\(re\)) face, which explains the high enantioselectivity observed in the catalytic fluorination and Michael addition reactions (Scheme 2). These reactions are promoted by the acidification of the α-methylene proton (see above).

**Figure 2:** ORTEP plots of \([\text{Ru}(3a-\text{H})(\text{PNNP})](\text{PF}_6)\) (5a) and \([\text{Ru}(6a)(\text{PNNP})](\text{PF}_6)_2\) (7a).
In case of 7a, the coordination of the alkylidene $\beta$-ketoester 6a to the Ru / PNNP fragment should lower the LUMO of the enone, and thus promote reactions targeting the activated double bond, and in particular cycloaddition reactions, which are at the core of this thesis. Indications that corroborate this hypothesis can be found in crystallographic and $^{13}$C NMR spectroscopic data and will be discussed together with the structural aspects of 7a in section 4.1. The cycloaddition reactions onto alkylidene $\beta$-ketoesters such as 6a would give products containing highly desired quaternary all-carbon stereocenters.

1.2 Enantioselective Formation of All-Carbon Stereocenters

The enantioselective formation of stereocenters is a very important goal in organic synthesis, as two different enantiomers of the same molecule can have a very different effect in biological systems. The use of catalytic methods to achieve this goal is preferential to the use of chiral auxiliaries, because small amounts of chiral catalyst can produce large amounts of chiral product and no additional steps are required for the removal of the chiral auxiliary. This makes a catalytic reaction more atom and time efficient. Moreover, both enantiomers of a product are commonly available by using the two different enantiomeric forms of the catalyst. This can usually not be achieved using chiral auxiliaries or enzyme chemistry, as they tend to be derived from nature and thus are only available in one enantiomeric form. These advantages have made catalytic enantioselective reactions one of the most dynamic aspects of chemistry today.

All-carbon quaternary centers are particularly challenging targets for enantioselective catalytic reactions, because of the steric repulsion between the carbon substituents. However, all-carbon quaternary centers are present in numerous natural products, which created broad interest in the study of their generation and led to numerous reviews on this topic. Saturated $\beta$-ketoesters, applied as nucleophiles, are among the most exploited substrates to achieve the asymmetric formation of quaternary stereocenters. Their unsaturated analogues have the potential to form up to two quaternary all-carbon stereocenters enantioselectively (depending on their substitution pattern) in one step, which makes them an interesting substrate class to investigate.

1.3 Synthesis and Properties of Unsaturated $\beta$-Ketoesters

$\beta$-Ketoesters are versatile synthetic building blocks in organic chemistry, due to the possibility of separately addressing four different functionalities within the $\beta$-ketoester moiety (Figure 3). The most exhaustive review concerning their chemistry was published by Benetti.
While a large number of different reactions illustrate the diverse and thoroughly explored applications of $\beta$-ketoesters, unsaturated $\beta$-ketoesters are virtually absent in this publication and have not been subject to any review articles since. This may be surprising, as unsaturated $\beta$-ketoesters are promising dienophiles in Diels-Alder chemistry as alternatives to the widely used $\alpha,\beta$-unsaturated imides and $\alpha,\beta$-unsaturated aldehydes. However, their use is restricted to a few specialized research fields (see section 1.4), because bulky alkylidene $\beta$-ketoesters are poor dienophiles, tend to polymerize, and undergo significant keto-enol tautomerism.

The strong polymerization tendency under acidic, basic, or high temperature conditions derives from the polarization of the enone moiety. This is reflected by the large deshielding of the vinyl proton, which generally appears at ca. $\delta$ 8.0 in the $^1$H NMR spectrum. The polymerization tendency renders the isolation of these compounds difficult. In fact, they are usually not stable to column chromatography and partially decompose at the elevated temperatures necessary for their distillation. In order to maximize the product yield, independently of the preparation pathway, certain precautions should be taken, which are elucidated in section 7.2.1 on page 118.

The problem of keto-enol tautomerism has been avoided for a long time by using $\gamma$-gem-dialkyl substituted alkylidene $\beta$-ketoesters, which can no longer undergo this rearrangement (Scheme 6). However, this approach limits the synthetic applicability of the reaction products, as it is usually not possible to remove the geminal alkyl groups at a later point of the synthesis.

The first preparation of an unsaturated $\beta$-ketoester was reported in 1909 by Koetz via a hydrogen bromide elimination reaction from an $\alpha$-bromo $\beta$-ketoester. Another early example is the oxidation of saturated $\beta$-ketoesters with selenium dioxide. Due to the strong tendency towards polymerization, a pure sample of unsaturated $\beta$-ketoester 6c was

![Figure 3: Addressable sites within the $\beta$-ketoester moiety.](image-url)
1.3 Synthesis and Properties of Unsaturated $\beta$-Ketoesters

Scheme 6: Enolization in unsaturated $\beta$-ketoesters.

only obtained by trapping with cyclopentadiene and subsequent pyrolysis of the Diels-Alder product, during which 6c was isolated by condensation (Scheme 7).

Scheme 7: Preparation of unsaturated $\beta$-ketoester 6c by pyrolysis of its cyclopentadiene adduct.

Since then, the most widely applied method has become the selenide oxidation-elimination reaction, whose first step is a derivatization of the saturated $\beta$-ketoester in the $\alpha$-position by phenyl selenyl chloride in the presence of a base. Thus, the $\beta$-ketoester is deprotonated with sodium hydride$^{62}$ or LDA$^{63}$ and the resulting enolate is quenched by the selenide reagent (Scheme 8, a). Alternatively, pyridine is added directly together with phenyl selenyl chloride to give an activated, more electrophilic intermediate that readily reacts with the non-deprotonated form of the $\beta$-ketoester.$^{64}$ The second step is the oxidation of the phenyl selenyl group with hydrogen peroxide and in situ syn-elimination of benzeneselenenic acid. Direct oxidation of a saturated $\beta$-ketoester can be achieved by use of either Pb(OAc)$_4$ with catalytic amounts of Cu(OAc)$_2$ or with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).$^{66}$ However, the reported yields are usually moderate at best.

A more popular method is the Brønsted$^{67}$ or Lewis$^{68}$ acid-catalyzed aldol condensation of a $\beta$-ketoester with an aldehyde (Scheme 8, b). The aldehyde can be introduced as an acetal group and deprotected in situ under the reaction conditions. Less explored methods are the rhodium-catalyzed cyclization of diazo $\beta$-ketoesters by C-H activation$^{69}$ and the palladium(II)-catalyzed coupling of 2-bromo-cyclopent-2-en-1-one with carbon monoxide and methanol (Scheme 9).$^{70}$
The chemistry of unsaturated \( \beta \)-ketoesters is profoundly different from the structurally related alkoxycarbonyl benzoquinones (Figure 4). The latter are easier to handle and have an additional carbonyl group conjugated to the reactive double bond, which drastically increases their reactivity.

Accordingly, a large number of transformations like Michael additions,\(^{71-73}\) Diels-Alder reactions (see 2.1.3), epoxidations,\(^{74}\) \([3+2]\) cycloadditions,\(^{75}\) and Nenitzescu reactions\(^{76}\) on alkoxycarbonyl benzoquinones have been reported. In general, benzoquinones are central building blocks in organic synthesis\(^ {77}\) and they are known to be readily available.\(^ {78}\) They also show excellent reactivity as well as defined and predictable stereochemistry in Diels-Alder reactions. Interestingly, enantioselective variants of these transformations have only started to appear rather late in the development of quinone chemistry.\(^ {79}\)
1.4 Transformations on Unsaturated $\beta$-Ketoesters

Due to the problems described in section 1.3, unsaturated $\beta$-ketoesters have rarely been used as synthetic building blocks. Apart from some early attempts in Diels-Alder reactions, which are discussed in chapter 2, non-alkoxycarbonylquinone-type unsaturated $\beta$-ketoesters have only recently started to gain attention as Michael acceptors in asymmetric transformations. One of the first applications is found in the enantioselective Mukaiyama-Michael addition to 2-methoxycarbonyl-2-cyclopenten-1-one ($6c$) catalyzed by copper(II)-BOX ligand systems.$^{80}$ Although different copper(II) sources, BOX ligands and solvents were screened, only moderate yields (up to 63%) and enantioselectivities (up to 66% ee) were obtained (Scheme 10, a). A similar system was used more recently by Snapper to perform enantioselective Hosomi-Sakurai conjugate allylation reactions on cyclic unsaturated $\beta$-ketoesters with excellent enantioselectivity (Scheme 10, b).$^{51}$

![Scheme 10: Cu(II)-BOX-catalyzed Michael addition reactions on unsaturated $\beta$-ketoesters.$^{51,80}$]

A third Michael-type addition reaction was reported by Bella in 2010 using nitroalkanes as nucleophiles and chinchona alkaloid derivatives as catalysts (Scheme 11, a).$^{81}$ Optimized conditions gave the desired products in excellent diastereo- and enantioselectivities. Chinchona alkaloids were also used as the backbone of a thiourea catalyst in a first example of an asymmetric oxo-conjugate addition to unsaturated $\beta$-ketoesters by Scheidt.$^{82}$ This enantioselective ring closing reaction yields flavanones and chromanones in moderate to high enantioslectivity after acid-catalyzed decarboxylation (Scheme 11, b).
Scheme 11: Michael addition reactions catalyzed by chinchona alkaloid derivatives.\textsuperscript{81,82}

Further cyclization reactions on unsaturated $\beta$-ketoesters are the diastereoselective double Michael addition reaction in the synthesis of the biologically valuable cardenolide backbone reported by Deslongchamps\textsuperscript{83} (Scheme 12, a) and the formal synthesis of (±)-clavukerin A in an amine induced Michael/Conia-ene cascade reaction (Scheme 12, b).\textsuperscript{84}

Scheme 12: Michael addition reactions leading to cyclization of unsaturated $\beta$-ketoesters.\textsuperscript{83,84}

Unsaturated $\beta$-ketoesters have also been applied as cross-conjugated dienones in the Nazarov cyclization. This process is a $4\pi$ electrocyclization of a cross-conjugated diene.\textsuperscript{85,86}
which can be catalyzed by Bronsted or Lewis acids and leads to the formation of cyclopentenones. The reaction can be performed in a stereoselective way either by pre-introducing a chiral center to the dieneone or by using a chiral Lewis acid as catalyst (Scheme 13). The priorly reported asymmetric [2+2] cycloaddition of thioacetylene derivatives to unsaturated $\beta$-ketoesters will be discussed in section 5.1.

![Scheme 13: Enantioselective Nazarov cyclization by a Ni(II)-Pigiphos catalyst system.](image)

1.5 Goal of this Thesis

The goal of this thesis is to take advantage of the well defined Ru / PNNP-alkylidene $\beta$-ketoester adducts such as 7a, and thus develop a catalytic system for the enantioselective functionalization of the coordinated unsaturated $\beta$-ketoesters such as 6a. The most appealing transformations for this scarcely explored substrate class are cycloaddition reactions, as they lead to the formation of quaternary all-carbon stereocenters (see above). In chapter 2, Diels-Alder reactions will be discussed as a first application of the protocol, and chapter 3 describes the enantioselective [2+2] Ficini cycloaddition of ynamides to alkylidene $\beta$-ketoesters 6.

The well defined character of complexes 7 allows for detailed investigations by stoichiometric reactions, and the obtained mechanistic insights will be discussed in chapter 4. Chapter 5 describes the study of copper triflate as a possible alternative to the Ru / PNNP system, whereas in chapter 6 the characteristics of the dicationic complexes of type 7 are compared to their more labile monocationic analogues.
2 Diels-Alder Reactions

This chapter describes the use of Ru / PNNP complexes as catalysts in the enantioselective Diels-Alder reaction of alkylidene $\beta$-ketoesters. The introductory section gives a brief review on the history of the Diels-Alder reaction and illustrates the state of the art, focusing on catalyst systems that show broad applicability. It further highlights the main parameters that influence the transition state structure and thus the stereochemical outcome of the reaction. The few reported examples of [4+2] cycloaddition reactions on alkylidene $\beta$-ketoesters and alkoxy carbonylquinones, as well as the remaining challenges in the field of Diels-Alder reactions, will be discussed in detail. The second part of the chapter reports the development of the Ru / PNNP catalyzed Diels-Alder reaction and the application of the protocol to the synthesis of estrone derivatives. Finally, the key stereochemical aspects of enantio- and endo/exo selectivity are discussed.

2.1 Introduction

2.1.1 Development of the Diels-Alder Reaction

Since its discovery by Kurt Alder and Otto Diels, the Diels-Alder reaction has developed to one of the most important tools in organic synthesis, as it greatly facilitates the rapid development of molecular complexity. The key to this achievement, which is vital in natural product synthesis, is the controlled simultaneous formation of multiple stereocenters, a task uniquely fulfilled by the Diels-Alder reaction. Several milestones made the broad applicability of the reaction possible. Among them are Lewis acid accelerated, intramolecular, pressure-accelerated, hetero-, and stereoselective Diels-Alder reactions by use of chiral auxiliaries or chiral catalysts.

The acceleration of Diels-Alder reactions by Lewis acids was discovered by Yates and Eaton, who observed a rate acceleration of $10^5$ in the reaction of maleic anhydride with anthracene in the presence of stoichiometric amounts of aluminum chloride, thus reducing the reaction time from months to minutes. The positive effect is caused by a lowering of the activation energy, which was later explained on the basis of frontier molecular orbital theory by Houk and Strozier (Figure 5). Coordination of the electron-poor dienophile to the Lewis (or Brønsted) acid lowers its LUMO and allows for a better interaction with the HOMO of the electron-rich diene (normal electron demand). In inverse electron demand reactions, the roles are reversed and coordination of the electron-poor diene occurs, facilitating the attack
to the electron-rich dienophile. The lowering of the activation barrier of Diels-Alder reactions by Lewis acids was determined to be commonly around 10 kcal/mol.\(^96\)

![Frontier orbitals for a Lewis acid-catalyzed normal electron demand Diels-Alder reaction.\(^41\)](image)

**Figure 5:** Frontier orbitals for a Lewis acid-catalyzed normal electron demand Diels-Alder reaction.\(^41\)

A second effect of the coordination was an improved *endo* diastereoselectivity (Figure 6), attributed to stronger secondary orbital interactions in the "tighter" transition state with Lewis acids. Later, more refined studies suggested that this transition state has partial zwitterionic character, and that the *endo* transition state is favored, because it allows for the smallest possible induced charge separation.\(^97\)

![Endo and exo transition states of Diels-Alder reactions.](image)

**Figure 6:** *Endo* and *exo* transition states of Diels-Alder reactions.

With cyclopentadiene, the most common diene in organic synthesis, a general trend shows the splitting of the most common dienophiles into two groups of which the first (acrolein derivatives) usually gives the *exo* products, whereas the second one (acrylate derivatives) reacts via the *endo* transition state.\(^98\) However, an effective stereochemical environment defined by a catalyst can overrule the natural trends.\(^99\) As a final aspect, Diels-Alder reactions in the presence of Lewis acids usually show less concerted bond formation than their non-activated analogues.\(^100\)
It was soon realized that the Lewis acid could be added in substoichiometric amounts. In 1969, Corey was the first to apply a Lewis acid-catalyzed Diels-Alder reaction in the synthesis of a complex natural product with the help of a chiral auxiliary.\textsuperscript{101} The synthesis is a prime example of the next important development, namely highly stereoselective Diels-Alder reactions. This first protocol applied 8-phenylmenthol functionalized acrylate to achieve the Diels-Alder reaction to a cyclopentadiene derivative in a highly diastereoselective fashion (Scheme 14). The main organizing elements in the proposed transition state are the steric repulsion between the double bond and AlCl\textsubscript{3} (leading to the $s$-trans conformation) and a $\pi - \pi$ interaction between the aromatic ring and the carbonyl group.\textsuperscript{43,102}

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme14.png}
\end{center}

**Scheme 14:** 8-Phenylmenthol as a chiral auxiliary in a diastereoselective Diels-Alder reaction.

While stereoselective reactions based on chiral auxiliaries are still important today, the concept of using the chiral component in a catalytic amount is more efficient and increasingly replacing the older methods.\textsuperscript{103} In spite of the many advantages of catalytic enantioselective Diels-Alder reactions (see section 1.2), the challenges connected to them are equally great. For a highly enantioselective process, the reaction should occur via a defined transition state that is substantially lower in energy than all other possible diastereomeric transition states. This calls for a high degree of organization and rigidity in the transition state in order to minimize the degrees of freedom of the coordinated dienophile. For the by far most common substrates in Diels-Alder reactions (acrolein and acryloyl/crotonyl imide derivatives), this organization concerns the mode of complexation (single point or chelate binding) and the regiochemistry of the substrate binding (only for single point binding), as the coordination of the Lewis acid can happen either cis or trans to the conjugated double bond. A further parameter is the conformation of the dienophile which can be either $s$-cis or $s$-trans (Figure 7) in the transition state.\textsuperscript{104}

Especially this last point has proven to be a major challenge in studies aiming at the exploration of the transition state, as the $s$-cis and $s$-trans conformer can still exist in an equi-
2.1 Introduction

Figure 7: Organizational parameters in Lewis acid-catalyzed enantioselective Diels-Alder reactions of acroleins and unsaturated imides.

librium after coordination with a rotational barrier of about 8-12 kcal/mol, a value similar to the activation energy of a Lewis acid-catalyzed Diels-Alder reaction. This immensely complicates any deductions made from the absolute configuration of the catalysis product, as the two conformers form opposite enantiomers in any proposed transition state. While NMR experiments and crystallographic data led to the deduction of certain trends for different classes of dienophiles (acroleins: s-trans, unsaturated amides: s-cis, acrylates: either of both), the predictions derived from models describing catalyst-substrate adducts are often at difference with the real stereochemical outcome. When such models predict the wrong stereochemical outcome, the usual explanation is that the reaction does not involve the catalyst-bound dienophile in the ground-state conformation, but rather a more reactive rotamer with the opposite conformation, hence giving the opposite enantiomer under Curtin-Hammett conditions. Ideally, these assumptions are backed up by calculations predicting a lower activation barrier for the reaction from the higher energy conformation or by double stereodifferentiating experiments.

2.1.1.1 Catalysis by Single Point Binding. The first enantioselective Diels-Alder reactions by single point binding were catalyzed by aluminum-based Lewis acids, which were used with acrolein derivatives, but also with acyl oxazolidinones (classical chelating substrates). Today, the field is dominated by boron based Lewis acids mostly using acrolein derivatives. In contrast to chelate binding (see below), single point binding has to cope with the issue of regioselectivity of catalyst coordination to either side of the carbonyl moiety (Figure 7). Whereas it has been reasonably established that the coordination can be predicted for acrolein derivatives (syn to the formyl hydrogen) and for acrylic acid derivatives (anti to the alkoxy moiety), this ambivalence posed a big problem in the application of unsaturated ketones as dienophiles. Ten years ago, the only way to achieve highly enantioselective Diels-Alder reactions on unsaturated ketones was to assure a defined coordination by chelate binding to a second Lewis basic moiety (see section 2.1.1.2). Accordingly, the first generally applicable systems, like Yamamoto’s CAB based catalyst (Figure 8, left), only showed broad substrate scope within the dienophile class of unsaturated aldehydes.
Chiral, cationic oxazaborolidines derived from L-proline were introduced by Corey in 2002\textsuperscript{117} and represent the first catalytic systems that were widely applicable to different classes of dienophiles, among them the demanding unsaturated ketones. Even today, the breadth of employable single point binding dienophiles of this catalyst class seems unmatched. (Figure 9).\textsuperscript{118–121}

The catalyst-substrate adducts are believed to be stabilized by a hydrogen bond between the oxazaborolidine oxygen and the formyl proton (acrolein derivatives) or the olefinic proton in $\alpha$-position (acrylates, enones,...) (Figure 8, right).\textsuperscript{112,122} Additionally, $\pi - \pi$-interactions

**Figure 8:** Proposed transition states for CAB and cationic oxazaborolidine catalysts, explaining the shielding of the lower face of the substrate.

**Figure 9:** Non exhaustive overview of the dienophile scope of Corey’s cationic oxazaborolidine catalysts.\textsuperscript{118}
between \(\pi\)-donating aromatic groups of the catalyst and the \(\pi\)-accepting enone moieties of the dienophile are assumed to play an important directing role in the substrate coordination. However, the stability of the catalyst-substrate adducts is still rather low, and substrate coordination is rapidly reversible on the NMR timescale, even at \(-63^\circ\text{C}\). Accordingly, the effect of \(\pi - \pi\)-interactions was never visualized by X-ray crystallography. Based on the insights obtained through the study of this system, Yamamoto and co-workers reported a related \(L\)-valine-derived Lewis acid activated oxazaborolidine that is insensitive to moisture and has a relatively broad dienophile scope. High levels of enantioselectivity were achieved in the reaction of cyclopentadiene with \(\alpha,\beta\)-unsaturated aldehydes, enones, esters, and quinones.

An elegant example of the challenging Diels-Alder reactions on \(\alpha,\beta\)-unsaturated ketones was reported by Kündig. A monocationic ruthenium(II) complex acted as catalyst in the reaction of cyclic or acyclic dienes with several ketone dienophiles (Scheme 15). High yields and enantioselectivities were achieved, which was explained based on a crystal structure of the catalyst-substrate adduct with methyl vinyl ketone.

![Scheme 15: Ruthenium based Lewis acid-catalyzed Diels-Alder reaction of unsaturated ketones.](image)

**2.1.1.2 Catalysis by Chelate Binding.** The by far most investigated and broadest catalytic systems relying on chelate binding are copper(II)-bis(oxazoline) (= BOX) complexes designed by Evans and the titanium(IV) TADDOL system (TADDOL is tetraaryl-1,3-dioxolane-4,5-dimethanol) introduced by Narasaka. Both systems mostly use \(\alpha,\beta\)-unsaturated imides (acyl oxazolidinones) as dienophiles. Naturally, the chelate ring formation directs the complexation of the carbonyl group and circumvents the regioselectivity problem that affects single point binding substrates like acrolein. A \(\text{t}er\text{t}\)-leucine-derived BOX ligand in combination with copper(II) salts catalyzes the reaction of cyclopentadiene with a number of differently substituted acyl oxazolidinones to form the favored endo products in high yields and enantioselectivities (Scheme 16).
**Scheme 16**: Enantioselective Diels-Alder reaction catalyzed by a copper(II)-BOX system.

A stereochemical model for the catalyst-substrate adduct was developed based on the structural data of the corresponding diaqua complex. Calculations based on this model suggest that the substrate is coordinated in the s-cis conformation and that the attack occurs from the lower face (si) of the substrate (Figure 10). Credit was given to this assumption by double stereodifferentiating experiments, observing the matched/mismatched situations, carried out with enantiomerically pure substrates that are benzyl substituted α to nitrogen. The results show that the expected shielding of the upper face of the substrate was enhanced when the benzyl group was also pointing upwards (matched), whereas a downwards pointing benzyl group decreased the enantioselectivity (mismatched).

![Figure 10: Proposed transition state of copper(II)-BOX catalyst.](image)

In recent years, the scope of the copper(II)-BOX catalyst system has been considerably expanded to less explored chelating dienophiles like α'-hydroxy enones, 2-alkenoyl pyridine N-oxides, acyl pyrazolidinones, α'-arylsulfonylenones, and α-thioacrylates (Figure 11).

Titanium TADDOL complexes have been extensively studied in enantioselective Diels-Alder reactions. Their generality in terms of reaction partners is exceptionally large and includes unsaturated imides, acrylates, and quinones as dienophiles and numerous differently substituted dienes and furans as cycloaddition reagents (Scheme 17).
Figure 11: Examples of dienophiles recently employed in Cu(II)-BOX-catalyzed Diels-Alder reactions.

Scheme 17: Titanium TADDOL-catalyzed Diels-Alder reactions with different dienophiles.

Unfortunately, the octahedral transition state leads to a larger number of possible configurations for the catalyst-substrate adduct than in the case of the tetrahedral copper complexes (see Figure 10). The crystal structure of the major species shows a coordination of the unsaturated imide in the equatorial plane with no reasonable explanation for stereoinduction, although high enantioselectivity is achieved in the Diels-Alder reaction with cyclopentadiene (Figure 12). Therefore, it was proposed that the actual reactive complex is either of two envisioned minor cis complexes, in which the unsaturated imide shows the expected shielding of the si face of the substrate. A third possibility is an aggregated transition state, as suggested by Seebach, who discovered positive non-linear effects in Ti(IV)-TADDOL-catalyzed Diels-Alder reactions. Despite the uncertainty in terms of coordination chemistry, the titanium TADDOL system had great applicational success, like the first highly enantioselective Diels-Alder reaction on an α,β-unsaturated ketone with the help of a sulfonyl group in α’ position as chelating partner.
2.1.1.3 Challenges in Enantioselective Diels-Alder Reactions. In spite of the tremendous advances made in the field of catalytic enantioselective Diels-Alder reactions, certain challenges still remain. They were eloquently expressed 12 years ago in the chapter "Diels-Alder Reactions" written by Evans and Johnson as part of the series "Comprehensive Asymmetric Catalysis". According to the authors’ opinion, the two greatest remaining challenges were the restricted scope of dienophiles and the limited mechanistic understanding and lack of reliable stereochemical models accurately describing catalyst-substrate interactions.

The breadth of the substrate scope in enantioselective Diels-Alder reactions has increased considerably during the last ten years, most notably driven by Corey’s chiral, cationic oxazaborolidine catalysts (for single point binding dienophiles) and Evans’ Cu(II)-BOX system (for chelating dienophiles). However, acrolein derivatives and unsaturated imides still remain the most commonly used substrates. In particular, poorly reactive dienophiles like unsaturated β-ketoesters are rarely studied, probably because, as remarked by Corey, most of the chiral Lewis acids used in enantioselective Diels-Alder reactions are generally not powerful enough to function successfully in cases for which the intrinsic reactivity (that is, for the uncatalyzed reaction) is marginal or low.

Evans’ and Johnson’s concern for detailed mechanistic studies led them to the sharp statement:

[...] a brief survey of the literature reveals that structural characterization of catalysts and catalyst-substrate complexes does not appear to be a prerequisite for the formulation of transition structures. It is not coincidence that the mostly broadly useful Diels-Alder catalysts are those which are best understood mechanistically.
The reason why researchers often shy away from the task of gathering structural information concerning the catalyst-substrate adduct in order to understand the mechanism of stereoselection and rationally modify the catalyst is the inherently low stability of these species. Lewis acidic catalysts are mostly based on hard, but labile Lewis acids, such as early transition metals, lanthanides, Cu(II), and boron compounds. Accordingly, observing the catalytically active species is not a trivial task with these systems because of fast exchange reactions in solution and/or the possibility that many different complexes coexist in equilibrium. For instance, enal complexation to boron-based Lewis acids is rapidly reversible on the NMR timescale, and the selectivity depends only on the energy difference between the two diastereoisomeric transition states. Such problems are often intractable experimentally and their solution must be sought by calculation.

A further example is the highly enantioselective Diels-Alder reaction of 3-cinnamoyloxazolidin-2-one and cyclopentadiene catalyzed by the \([\text{TiCl}_2(\text{TADDOL})]\) system, whose catalyst-substrate adduct has been subject of debate as for its structure, configuration, and even nuclearity (see page 21). Such uncertainties led Evans to state that "our understanding pertaining to substrate-catalyst interactions [in Diels-Alder reactions] is still in its infancy." A rare example of a crystal structure of a well defined catalyst-substrate adduct explaining the facial selectivity was published by Kündig (see section 4.4). As in case of 7a, the crystallized species is a relatively stable ruthenium d^6 low-spin complex. The exceptional stability of these complexes is discussed in section 4.4.

A commonly used option to model the catalytically active species with very reactive systems is to use structurally characterized complexes with strongly coordinating but inactive ancillary ligands as a basis for the substrate/catalyst adduct model. Then, the structure of the hypothetical catalyst-substrate adduct is calculated, as seen in the stereochemical model of Cu-BOX (page 20 and Figure 10). Further examples of this strategy have been reported with many transition metals like Cu(II), Ni(II), Zn(II), Rh(III), and Fe(II). This method, albeit useful, is intrinsically less reliable than X-ray structure determination of the catalyst-substrate adducts. For example, in the case of Evans’ Cu(II)-tert-butyl-BOX-catalyzed enantioselective Michael addition to alkyldiene malonates the calculated structure of the catalyst-substrate adduct did not show a reasonable explanation for the observed enantioselectivity (Figure 13, left). Finally, the obtained crystal structure of the complex revealed that the substrate is coordinated in the reversed fashion compared to the calculated model (Figure 13, right).
Figure 13: Calculated model and crystal structure of a Cu-BOX alkylidene malonate complex.\textsuperscript{39}

Also, the phenyl ring of the alkylidene malonate is significantly distorted out of planarity, which diminishes the conjugation of the system. In this revised stereochemical model, the re face of the substrate is shielded, which explains the high enantioselectivity obtained in the Michael addition reactions.\textsuperscript{39} In the crystal structure of the corresponding Ph-BOX complex, the substrate coordination is reversed again, that is, as originally predicted for the tert-butyl-BOX complex. This observation is accompanied by the formation of the opposite enantiomer in the catalysis reaction. This study underlines the immense importance of gathering reliable structural information on the catalyst-substrate adduct before formulating a stereochemical model. Therefore, a desirable requirement for a Lewis acidic catalyst is to form stable adducts with the substrate according to a well-defined stoichiometry, in order to make structural characterization possible.

Despite considerable efforts, the problem remains that the more reactive a system, the more difficult is the characterization of the active species involved. However, high reactivity is pivotal for a synthetically useful system, as it bears the promise of low catalyst loadings and conversion of poorly reactive reagents. As we will see later, dicationic ruthenium complexes provide an elegant balance between high reactivity (activation of poorly reactive unsaturated \(\beta\)-ketoesters) and characterizable reactive species (crystal structure of catalytically active complex 7a).

2.1.2 Diels-Alder Reactions on Unsaturated \(\beta\)-Ketoesters

The use of unsaturated \(\beta\)-ketoesters in enantioselective Diels-Alder reactions avoids many of the problems associated with the standard dienophiles (acrolein derivatives and unsaturated imides). Unsaturated \(\beta\)-ketoesters are ideally suited for catalysis by chelate binding and thus eliminate the problem of the regioselectivity of complexation, which is especially dire with \(\alpha,\beta\)-unsaturated ketones (see section 2.1.1.1). Moreover, the enone conformation is constrained to \(s\)-trans, which greatly simplifies mechanistic considerations counting on a
defined organization of the dienophile in the transition state. Furthermore, the absence of s-cis and s-trans conformers avoids the sometimes elusive assumption of Curtin-Hammett conditions that is required when the stereochemical outcome does not match the expectations derived from the model of the catalyst-substrate adduct (see 2.1.1).

In spite of these advantages, unsaturated β-ketoesters have been rarely used in Diels-Alder reactions. Apart from the difficulties of alkylidene β-ketoester chemistry discussed in section 1.4, they are especially challenging substrates because of their low intrinsic reactivity towards Diels-Alder reactions. This property renders enantioselective catalytic Diels-Alder reactions difficult to perform (see above). The first example of a Diels-Alder reaction on unsaturated β-ketoesters was reported by Marx with substrate 6c, which was generated in situ from 3c with SeO₂, by stirring the mixture together with an excess of cyclopentadiene (see Scheme 7, page 9). The product was obtained in low yield in this procedure, which was actually aimed at the isolation of 6c by pyrolysis of the bicyclic cycloaddition product.

The Diels-Alder chemistry of unsaturated β-ketoesters was thoroughly explored by Browne, who screened a broad variety of non-chiral Lewis acids and found that high catalyst loadings of SnCl₄ usually gave the best yields (Scheme 18, a). However, the reactions on unsaturated β-ketoesters that were not disubstituted in the γ-position were complicated by keto-enol tautomerization, and only moderate yields were obtained. Moreover, the strong Lewis acid SnCl₄ was reported to decompose unsaturated β-ketoesters, which may also account for the moderate yields observed. Browne, who usually focused on six-membered ring unsaturated β-ketoesters, discovered that the ester-endo product was generally favored in Diels-Alder reactions on these dienophiles (Scheme 18, b). Reactions on the five-membered ring analogues were only performed with γ-gem-dimethylated derivatives. Interestingly, no exo-endo selectivity was found in the reaction of this dienophile with (E)- tert-butyl((4-ethoxy-3-methylbuta-1,3-dien-2-yl)oxy)dimethylsilane, though one would expect a destabilizing effect between the two methyl groups of the cyclopentenone ring and the large silyloxy group of the diene in the ester-exo transition state (Scheme 18, b).

The low reactivity of unsaturated β-ketoesters was addressed by Welker with an extremely elaborate approach, based on stoichiometric diene-activation. The highly electron-rich 2-cobaloxime-substituted 1-methylbuta-1,3-diene reacted with 2-ethoxycarbonyl-2-cyclohexen-1-one (6d, 4 equiv) in boiling THF during 3 days to give the cycloaddition product in high yield and high ester-endo selectivity (Scheme 19). As expected, the ester exo-endo selectivity changed towards the ester-exo product when the more bulky tert-butyl-ester analogue (6e) of the dienophile was used. This selectivity is explained by the highly unfavorable interaction.
**Scheme 18:** Diels-Alder reaction on unsaturated \(\beta\)-ketoesters by Browne and *exo-endo* transition states for five- and six-membered ring \(\beta\)-ketoesters.

of the large *tert*-butyl group pointing towards the forming pericyclic ring in the *ester-endo* transition state. As both transition states are high in energy in this reaction, the reactivity was further reduced and the yield dropped from 89\% (for the ethyl ester analogue) to 60\%.

Besides the lack in atom economy, a general problem of this approach is the necessity to remove the cobaloxim group from the Diels-Alder product using AlMe\(_3\), which gave only moderate yields and thus further diminished the overall yield of the protocol.

**Scheme 19:** Diene activation approach for the *exo-endo* selective Diels-Alder reaction on unsaturated \(\beta\)-ketoesters.

After describing a highly diastereoselective Diels-Alder reaction of an unsaturated \(\beta\)-ketoester\(^{150}\) using the same chiral auxiliary as previously applied by Corey\(^{102}\) (Scheme 14, page 16), Yamauchi realized the first enantioselective Diels-Alder reaction of an alkylidene \(\beta\)-ketoester.\(^{55}\) The catalytic system contained magnesium salts in combination with bisoxa-
zoline or mono(oxazoline) ligands and employed ethyl 2-benzoylacrylate (6f) as dienophile, which is sterically less demanding than cyclic unsaturated β-ketoesters. Good yields and enantioselectivities, as well as excellent selectivity in favor of the ester-endo product, were achieved in the reaction with cyclopentadiene (Scheme 20).

Scheme 20: First enantioselective Diels-Alder reaction on unsaturated β-ketoesters.

The drawbacks of the protocol are the high catalyst loadings of 20 to 40 mol% (based on the ligands as they are the most expensive component) and the necessity for extremely low temperatures (−90 °C) in order to achieve high enantioselectivities. Moreover, the fact that it was not possible to isolate a catalyst-substrate adduct for X-ray crystallography hinders the investigation of possible transition states, although calculations have been performed in a more extensive report on the system.\(^{56}\) This report also contained a comparison to a titanium TADDOL catalyst, one of the most utilized systems for Diels-Alder reactions on chelating dienophiles (see 2.1.1.2). However, this benchmark system does not seem to be suitable for the transformation of unsaturated β-ketoesters, as only moderate yields, low enantio-, and poor exo-endo selectivities were observed. To the best of our knowledge, no further reports on enantioselective Diels-Alder reactions on unsaturated β-ketoesters have been published prior to the results of this PhD thesis.

2.1.3 Enantioselective Diels-Alder Reactions on Alkoxycarbonylquinones

Alkoxycarbonylquinones have been used more often as dienophiles in enantioselective Diels-Alder reactions than their unsaturated β-ketoester analogues. Their uncatalyzed reactions with cyclopentadiene\(^{151}\) and 1,3-dimethoxybuta-1,3-diene\(^{152}\) have been observed, which indicates that they have a higher intrinsic reactivity, and is a promising starting point for catalytic, enantioselective Diels-Alder reactions.\(^{119}\) The first enantioselective Diels-Alder reaction of an alkoxycarbonylquinone was achieved using a titanium BINOL system (see 2.1.1.2). The cycloaddition product was obtained in 51% yield and 36% ee. An outstanding
system for enantioselective Diels-Alder reactions of alkoxy carbonylquinones was published by Evans in 2003 (Scheme 21).\textsuperscript{153}

![Scheme 21: Highly enantioselective catalytic Diels-Alder reactions on alkoxy carbonylquinones.](image)

The described protocol uses tricationic samarium and gadolinium PyBOX complexes (PyBOX is pyridyl-bis(oxazoline)) to achieve enantioselective Diels-Alder reactions of 2-(methylcarboxylato)benzoquinones with various dienes with excellent yields and enantioselectivities. Perfect diastereoselectivity for the ester-\textit{exo} products was observed, however, regioisomers were encountered at times.

### 2.2 Ru / PNNP-catalyzed Diels-Alder Reactions with Symmetric Dienes

The catalyst precursor used for the Ru / PNNP-catalyzed Diels-Alder reaction is the putative dicationic complex [Ru(OEt\textsubscript{2})\textsubscript{2}(PNNP)]\textsubscript{2}(PF\textsubscript{6})\textsubscript{2} (2), which is formed by double chloride abstraction from the dichloro complex 1 with (Et\textsubscript{3}O)PF\textsubscript{6} (2 equiv) in dry CH\textsubscript{2}Cl\textsubscript{2} (Scheme 22). The activation of 1 was run overnight in a closed Schlenk tube fitted with a Young valve under an argon atmosphere. A color change from red to brown indicated the formation of the diether complex 2.

![Scheme 22: Activation of dichloro complex 1 with (Et\textsubscript{3}O)PF\textsubscript{6} (2 equiv).](image)
2.2 Ru / PNNP-catalyzed Diels-Alder Reactions with Symmetric Dienes

The formation of 2 can be monitored by $^{31}$P NMR spectroscopy. After addition of (Et$_3$O)PF$_6$, the signal of complex 1 (singlet at $\delta$ 47.5) disappears, and broad, ill defined signals become visible, which finally transform into the AX spin system of the cis-$\beta$ complex 2 ($\delta$ 40.5 and 59.2). It has to be noted that the chloride abstraction reaction is not well behaved and that the formation of the sharp AX spin system cannot always be observed. However, effects on catalytic reactions were never detected. In fact, irrespective of the formation of the AX pattern, the addition of the alkylidene $\beta$-ketoester substrates, such as 2-tert-butoxycarbonyl-2-cyclopenten-1-one (6a), immediately leads to the formation of well-defined adduct complexes like [Ru(6a)(PNNP)]$^{2+}$ (Scheme 23). The latter is identical to 7a obtained via the hydride abstraction pathway described in section 1.1.1 (see chapter 4 for a more detailed discussion).

Scheme 23: Coordination of alkylidene $\beta$-ketoester 6a to complex 2.

The coordination of 6a to the Ru / PNNP fragment lowers the energy of its LUMO and activates the double bond towards cycloadditions with electron-rich dienes. Such metal-catalyzed activations of alkylidene $\beta$-ketoesters involving fully characterized substrate/catalyst adducts are unprecedented. The closest analogues are the copper-catalyzed Michael reactions of alkylidene malonates$^{38,39}$ and the iridium-promoted Nazarov cyclization of divinyl ketones,$^{36,37}$ whose catalyst-substrate adducts have been discussed previously (see page 5).

2.2.1 Preliminary Experiments

Preliminary experiments performed by Martin Althaus revealed that the dicationic complex 2 is catalytically active in the Diels-Alder reaction of 2-ethoxycarbonyl-2-cyclohexen-1-one (6d) with an excess of cyclopentadiene (Scheme 24). Cyclopentadiene is the most frequently used diene in Diels-Alder reactions, as its ring structure fixes the two conjugated double bonds in the s-cis conformation, which is necessary for a Diels-Alder reaction to take place.
This makes cyclopentadiene extraordinarily reactive towards a large variety of dienophiles. In our case, the bicyclic product was obtained in 19% yield with moderate diastereoselectivity (5:1 for the ester-*endo* product) and 70% ee. However, more extensive investigations revealed that the reaction shows poor reproducibility in terms of diastereo- and enantioselection, whereas the yield of the reaction was always around 20%. The five-membered ring ethyl (6b) and *tert*-butyl (6a) analogues were also tested in the reaction and found to give drastically increased yields. Unfortunately, both diastereoisomers of the respective cycloaddition products were racemic and were formed with low diastereoselectivity.

![Scheme 24: Preliminary results of Diels-Alder reactions using cyclopentadiene.](image)

The crude Diels-Alder products were obtained together with in a large amount of a rubbery substance, which can only originate from the large excess of cyclopentadiene. The $^1$H NMR spectra of all summarily purified products showed a characteristic broad signal at $\delta$ 5.67. Thus, it is reasonable to assume that the rubbery substance is polycyclopentadiene from the ring opening metathesis polymerization of dicyclopentadiene, formed by the Diels-Alder reaction of two cyclopentadiene molecules in the reaction mixture at room temperature. The polymerization is most probably catalyzed by the dicationic complex 2. This would explain for the poor and unreproducible catalysis results with cyclopentadiene, as the overwhelming side reaction probably deactivates the species that catalyzes the Diels-Alder reaction.

In order to avoid these complications, two heteroanalogues of cyclopentadiene (2,5-dimethylfuran and 1,2,5-trimethylpyrrole) were used instead, as they do not form the dimeric compounds necessary for the ring opening metathesis polymerization. However, the analysis of the $^1$H NMR spectra revealed that the resulting products were not bicyclic Diels-Alder
products. Instead, the heteroaromatic compounds had acted as nucleophiles in a Michael addition reaction, forming the respective monocyclic products in good yields (Scheme 25).

**Scheme 25:** Attempted Diels-Alder reactions using 2,5-dimethylfuran and 1,2,5-trimethylpyrrole.

As the α-methine proton of β-ketoesters generally takes part in keto-enol tautomery, there is no persistent stereoinformation in the α-position of the Michael addition products, and no diastereoisomers are detected in the $^1$H NMR spectra and GC chromatograms. Unfortunately, no enantioselectivity was observed in either of these reactions. The Michael addition of heteroaromatic nucleophiles is further discussed in chapter 5.

Another possibility to exclude ring opening polymerization reactions is the use of acyclic dienes, which unfortunately also eliminates the favorable fixed $s$-cis conformation of the diene. Nevertheless, the reaction of 2-methoxycarbonyl-2-cyclohexen-1-one (6c) with 2,3-dimethylbutadiene (8) proceeded with a so far unprecedented combination of yield (78%) and enantioselectivity (43%) (Scheme 26).

**Scheme 26:** Diels-Alder reactions using acyclic 2,3-dimethylbutadiene (8).
Thus the use of 2,3-dimethylbutadiene (8) represented a breakthrough in the investigations of the Ru / PNNP-catalyzed Diels-Alder reaction. The results using the corresponding five membered ring analogue 6c proved to be superior in terms of yield (88%) and enantioselectivity (69%). Therefore, in the ensuing optimization of the catalytic system, we focused on cyclic alkylidene \( \beta \)-ketoesters with a five-membered ring (6a-c).

### 2.2.2 Optimized Reaction Conditions

The application of \([\text{Ru(OEt}_2\text{)}_2\text{(PNNP)}](\text{PF}_6)_2\) (2) with the unsaturated \( \beta \)-ketoesters 6 and 2,3-dimethylbutadiene (8) gives access to the enantiomerically enriched bicyclic products 11 (Scheme 27). However, the inexpensive and moderately reactive 2,3-dimethylbutadiene (8) has to be added in large excess (10 equiv) in order to achieve full conversion of the unsaturated \( \beta \)-ketoester within 24 h (Table 1, entries 1-3, values in parenthesis). On the other hand, the reactions are run at room temperature, which renders them more convenient than Yamauchi’s Mg-BOX system, which requires extraordinarily low temperatures of \(-90^\circ\text{C}\) (see page 27).\(^{55,56}\) In order to reduce the excess of diene, we investigated the use of more electron-rich, and thus more reactive dienes, such as 2,3-dimethoxybutadiene (9). Indeed, 4.5 equivalents (added in three portions of 1.5 equiv) were sufficient to achieve high yields. Also, the enantioselectivity increased up to 84% ee for product 12b (entry 5). However, the reaction yields suffered from poor reproducibility and were often considerably lower than the values reported in Table 1 (entries 4 - 6).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{+} & \quad \text{Et}_2\text{O} \\
10 \text{ mol}\% & \quad \text{Ru} \quad \text{N} \quad \text{P} \quad \text{N} \quad \text{P} \\
(\text{2}) & \quad \text{CH}_2\text{Cl}_2 (8) \\
(1.5-10 \text{ equiv}) & \quad \text{CH}_2\text{Cl}_2:\text{Et}_2\text{O} (1:1) (9, 10) \\
\text{room temperature} & \quad \text{Me} \ (6\text{b}) \quad \text{Me} \ (6\text{c}) \\
\end{align*}
\]

**Scheme 27:** Enantioselective Diels-Alder reaction with symmetrical dienes 8-10.

Similar inconsistencies were encountered during the investigation of electrophilic fluorination\(^{21}\) and Michael addition\(^{22}\) by Martin Althaus and Francesco Santoro. In these cases,
the problems were overcome by using a 1:1 solvent mixture of dichloromethane and diethyl ether. It is believed that the ether acts as a proton shuttle in these catalytic systems and thus facilitates the reaction. This rationale does not apply for Diels-Alder reactions, which do not feature any proton transfers and thus do not benefit from the proton shuttle role of diethyl ether. Nevertheless, performing the reaction in the 1:1 solvent mixture does solve the reproducibility problem in Diels-Alder reactions with 2,3-dimethoxybutadiene (9) (as well as dienes 10 and 14, see below) and thus was used in all reactions with electron-rich dienes. On the other hand, non activated 2,3-dimethylbutadiene (8) gives the highest yields in pure CH₂Cl₂ (Table 1, entries 1-3), a fact that is discussed in detail in section 4.3.

<table>
<thead>
<tr>
<th>entry</th>
<th>dienophile</th>
<th>diene</th>
<th>produt</th>
<th>R¹</th>
<th>R²</th>
<th>yield (%) b</th>
<th>ee (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a</td>
<td>8</td>
<td>11a</td>
<td>¹Bu</td>
<td>Me</td>
<td>52 (82)</td>
<td>84 (67)</td>
</tr>
<tr>
<td>2</td>
<td>6b</td>
<td>8</td>
<td>11b</td>
<td>Et</td>
<td>Me</td>
<td>59 (87)</td>
<td>60 (60)</td>
</tr>
<tr>
<td>3</td>
<td>6c</td>
<td>8</td>
<td>11c</td>
<td>Me</td>
<td>Me</td>
<td>67 (88)</td>
<td>67 (69)</td>
</tr>
<tr>
<td>4</td>
<td>6a</td>
<td>9</td>
<td>12a</td>
<td>¹Bu</td>
<td>OMe</td>
<td>86</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>6b</td>
<td>9</td>
<td>12b</td>
<td>Et</td>
<td>OMe</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>6c</td>
<td>9</td>
<td>12c</td>
<td>Me</td>
<td>OMe</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>6a</td>
<td>10</td>
<td>13a</td>
<td>¹Bu</td>
<td>OBn</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>6b</td>
<td>10</td>
<td>13b</td>
<td>Et</td>
<td>OBn</td>
<td>99</td>
<td>77</td>
</tr>
<tr>
<td>9</td>
<td>6c</td>
<td>10</td>
<td>13c</td>
<td>Me</td>
<td>OBn</td>
<td>90</td>
<td>76</td>
</tr>
</tbody>
</table>

a Standard run in CH₂Cl₂/Et₂O 1:1, further reaction conditions: see experimental part. b Results in parenthesis from reaction in pure CH₂Cl₂.

In spite of the improved reaction conditions in the 1:1 solvent mixture, diene 9 still has to be added in three subsequent portions in order to achieve high conversion. After the first addition of 1.5 equivalents, TLC analysis shows that the reaction stops after about 3 - 4 h and continues after addition of the second batch of diene. The same is observed after about 8 h, after which the third batch is added and the mixture is stirred overnight, giving high yields of the cycloaddition products 12. This protocol is probably necessary due to partial polymerization of 9 in the presence of complex 2.

The more bulky 2,3-(dibenzyl oxy)butadiene 10 should be less prone to interact with 2 and thus allow for the use of a lower diene excess. Indeed, a nearly stoichiometric amount (1.5 equiv) of 10, added in one batch, is sufficient to give full conversion of the dienophiles 6. The
Diels-Alder products are obtained in high yield and with up to 93% ee for product 13a (Table 1, entry 7). Another advantage of diene 10 is that the benzyl groups in the corresponding Diels-Alder products 13 should be more easily deprotectable than the dimethoxy groups in compounds 12. This may prove to be useful for further functionalization when 13 is used as a building block.

It should be noted that only one product (11c) of the alkoxy carbonyltetrahydro-1-indanone class has been previously prepared as racemate, with low yield, and under harsh conditions (see 2.1.2). Therefore, the Ru / PNNP-catalyzed reaction is the first enantioselective synthesis of compounds 11-13, which are versatile intermediates as they contain multiple, separately addressable reaction sites apart from the still intact β-ketoester functionality (Figure 3). In contrast to the harsh reaction conditions for Diels-Alder reactions of unsaturated β-ketoesters reported in the previous sections, the coordination of the unsaturated β-ketoesters 6 to the dicationic Ru / PNNP fragment enhances their reactivity without promoting polymerization at a detectable level, which is notable for these rather sensitive dienophiles (for tips concerning their proper isolation and handling see page 118). Thus, Ru / PNNP complexes seem specially suited for catalyzing Diels-Alder reactions of alkylidene β-ketoesters. The high yield and enantioselectivity with this catalytic system are remarkable, bearing in mind that alkylidene β-ketoesters are poor dienophiles and that their Diels-Alder reactions should thus, according to Corey, be difficult to perform in an enantioselective way (see section 2.1.1.3, page 22). Furthermore, these reactions are examples of smooth enantioselective formation of a quaternary all-carbon stereocenters, which is also considered to be a challenging task.

2.3 Synthesis of Estrone Derivatives with Dane’s Diene

Together with estriol and estradiol, estrone is one of the three naturally occurring estrogens that were identified to support the growth and development of hormone dependent tumors. Estrone derivatives are of biomedical interest because of their potential application in antiestrogen therapy, applied for prostate and breast cancer treatment. The various derivatives follow different mechanisms of action to exert their anticancer activity, like stopping cell mitosis by acting as an antimicrotubule agent, or reduction of estrone production by inhibition of aromatase and sulfatase enzymes (estrone antagonist). In order to achieve the desired effect, it is imperative that the employed estrogen derivative shows minimal estrogenic activity itself (low agonist activity).
In order to find potential drug candidates, a large array of differently substituted estrone derivatives has been reported (Scheme 28, a), but functionalization is not equally accessible throughout the estrone skeleton. For example, the C(18) position has been reported to be especially challenging to modify, therefore only a few derivatives of this class are synthetically available as compared to the large number of differently substituted estrones. Accordingly, studies of the special properties of C(18) functionalized estrone derivatives have been scarce (Scheme 28, b).

**Scheme 28:** Estrone derivatives as targets for breast cancer treatment.

We realized that application of Dane’s diene (14) in combination with unsaturated β-ketoesters 6 would give estrone derivatives that bear an ester group as a synthetic handle at C(18). In fact, 14 (1.1 equiv) reacted with the unsaturated β-ketoester 6a according to the protocol described above to give crude 15a as a single regioisomer of the ester-exo diastereoisomer in excellent yield, an ester-exo:endo ratio of 27:1, and 86% ee. Recrystallization from 2-propanol gave enantiomerically pure 15a with an ester-exo:endo ratio of 145:1 (Scheme 29).

The structure of 15a has been ascertained by X-ray diffraction. Figure 14 shows an ORTEP view of 15a and the structure of a rare example of a related compound by Kuhl et al.\(^{165}\) that features an ester moiety at the same position as in 15a. The comparison of the bond length and angles involving the five-membered ring reveals that the two compounds
Scheme 29: Enantioselective Diels-Alder reaction with Dane’s diene 14.

are structurally very similar, apart from an obvious distortion of the C(18)–C(2)–C(3) angle (15a: 106.4(1)°, Kuhl’s compound: 118.0(3)°), which is caused by the fact that in the structure by Kuhl C(2) and C(3) are part of an additional lactone ring.

Figure 14: ORTEP plot of estrone derivative 15a and structure of a C(2)–C(3) bridged analogue.

The Ru / PNNP protocol gives access to both the nat- and ent- estrone derivatives, which is interesting, since ent- steroids usually show different biological activity than their nat-analogues and are often devoid of its hormonal activity (no agonist activity, see above). When the less bulky methyl ester 6c is used as dienophile, the enantio- and diastereoselectivity drops considerably (60% ee, d.r. = 3:1). The enantioselectivity is one of the subjects of chapter 4, whereas the diastereoselectivity will be discussed in section 2.4.2.

It should be noted that Corey has recently reported the synthesis of an enantiomerically enriched estrone methyl ether whose key step is an enantioselective Diels-Alder reaction of 2-methylcyclopent-2-enone and Dane’s diene (14) (Scheme 30). This procedure, if applied to Diels-Alder products 15a and 15b, should give access to enantiomerically enriched estrone derivatives that are fully functionalizable at the C(18) position by virtue of the attached ester group.
Scheme 30: Corey’s synthesis of an estrone methyl ether using Dane’s diene (14).

2.4 Stereochemical Analysis

Like their saturated analogues 3, the unsaturated β-ketoesters 6 coordinate to the rigid dicationic Ru / PNNP framework to form [Ru(6)(PNNP)]^{2+} complexes. The crystal structure of [Ru(6a)(PNNP)](PF_{6})_{2} (7a) shows close similarity to that of enolato complex 5a, including the protection of the lower face of the coordinated substrate by one of the phenyl rings of the ligand (see section 4.1.2 and Figure 2, page 6). In the electrophilic transformations performed with the saturated β-ketoesters 3 (Scheme 2, page 2), the reagent attacks from the top face of the substrate. Analogously, the enantioface selectivity in the Diels-Alder reaction with dienes 8, 9, 10, and 14 should originate from the shielding of the lower face of the coordinated alkylidene β-ketoesters 6 in complexes 7. This enantioface selection defines the absolute configuration of the bridgehead centers of the bicyclic products. The following studies are directed to prove this hypothesis.

2.4.1 Enantioface Selectivity

The absolute configuration of the Diels-Alder product 11c was determined by reduction of the ketone moiety with sodium borohydride to form its 9-hydroxy analogue 18a, followed by esterification with (1S,4R)-(−)-camphanic acid chloride (Scheme 31).

Due to the moderate enantiomeric purity of 11c, the camphanic ester derivative was obtained as a mixture of the (1S,4R,1’S,6’S,9’S)-19a (major) and (1S,4R,1’R,6’R,9’R)-19a’ (minor) diastereoisomers, which were separated via preparative HPLC. However, only the minor diastereoisomer 19a’ crystallized by slow evaporation of diethylether. The crystal structure indicates that the absolute configuration at the bridgehead positions is (2R,7R), which means that it is (2S,7S) in the major diastereoisomer. Thus, the attack occurs from
the unprotected upper (re) face of the substrate, as proposed by our stereochemical model based on the structure of 7a (Scheme 32). Dienes 8, 9, and 10 are not substituted at their terminal positions. Therefore, the determination of the absolute configuration of the catalysis products can only give insights into the enantioface selection. It can not be stated whether the attack of the diene happens preferentially over the cyclopentenone ring (ester-exo transition state) or over the ester moiety (ester-endo transition state), since both transition states lead to the formation of the same isomer of the product.

### 2.4.2 Ester-endo/exo Selectivity

In contrast to the symmetrical dienes 8-10, the unsymmetrical Dane’s diene (14) is substituted on one terminal position, thus allowing for the formation of ester-exo and the ester-endo diastereoisomers that differ in the configuration at the C(8) carbon center. In order to gain insight into the ester-endo/exo selectivity of the catalytic system, as well as a second verification of the re face attack, the reduction/esterification protocol was applied to the enantiomerically pure estrone derivative 15a. The corresponding camphanic acid derivative readily crystallized by slow evaporation of diethyl ether and the crystal structure shows that its configuration is \((1S,4R,8'R,13'S,14'S,17'S)\). Thus, the absolute configuration at the bridgehead positions (C(13) and C(14)) is again \((S,S)\) (Scheme 33).
Scheme 32: Ester-\textit{exo} and ester-\textit{endo} approach of 2,3-dimethylbutadiene, illustrated on the ORTEP plot of 7a.

Scheme 33: Determination of the absolute configuration of compound 15a via the camphanic acid derivative 19b.

Both 6a and 6c favor the ester-\textit{exo} product, in which the configuration at C(8) is \textit{R}. However, the diastereomeric ratio is highly dependent on the ester moiety and drops from 27:1 for the \textit{tert}-butyl ester to 3:1 for the methyl ester. In order to understand these results, both steric and electronic factors have to be taken into account. Deciding which of the two
influences is dominating is not a trivial task, as alkylidene $\beta$-ketoesters are rarely used in Diels-Alder reactions, and thus little information can be derived from the literature.

### 2.4.2.1 Steric Influences

The observed diastereoselectivity is a direct result of the stereoselective approach of the diene to the catalyst-bound substrate (Scheme 34). If the diene approaches from the cyclopentenone ring, the favored ester-exo product is formed ($8R$), while an approach over the ester moiety results in the formation of the unfavored ester-endo product ($8S$). Clearly, the approach over the bulky tert-butyl ester moiety of $6a$ is very hindered, so this residue is likely to point away from the forming ring in the pericyclic transition state. This is in agreement with the observed high ester-exo selectivity.

In the sterically less demanding methyl ester derivative $6c$, the approach over the ester group is less disfavored than in $6a$, which results in lower endo/exo selectivity. As the absolute configuration of compounds $15$ is $8R,13S,14S$, the diene approach over the cyclopentenone ring is in agreement with the observed sense of induction.

![Scheme 34: Ester-exo and ester-endo approach of Dane’s diene (14), illustrated on the ORTEP plot of 7a. The methoxybenzene ring is omitted for clarity.](image)

#### 2.4.2.2 Secondary Orbital Overlaps

Electronic factors influence the diastereoselectivity of Diels-Alder reactions via secondary orbital overlaps (SOO). In addition to the bond-forming primary orbital overlaps (bold lines), secondary orbital overlaps (dashed lines)
can be present in both transition states (Figure 15). In the ester-\textit{exo} transition state, there is a secondary overlap of the diene HOMO with the LUMO component located at the ketone moiety of the cyclopentenone ring. In the case of the unfavored ester-\textit{endo} transition state, this interaction involves the carbonyl group of the ester moiety instead. As \(\beta\)-ketoesters are rarely used in Diels-Alder reactions, it is hitherto unknown - to the best of our knowledge - whether interactions with ketones or esters result in a more effective overlap. However, it has been shown that secondary orbital overlaps are only crucial if the HOMO\textit{diene}-LUMO\textit{dienophile} gap is small, which results in a very close transition state (Scheme 35, a).

![Figure 15: Secondary orbital overlaps in the ester-\textit{exo} and ester-\textit{endo} transition state.](image)

In systems featuring large HOMO-LUMO gaps (Scheme 35, b), steric factors can dominate the stereoselectivity even at the expense of having no SOOs at all. Therefore, as in the case of the unsaturated \(\beta\)-ketoesters 6 there is merely a competition between two slightly different secondary orbital overlaps, we suggest that steric effects are pivotal. Similarly, Welker has shown that steric influences entirely dominate the diastereoselectivity of Diels-Alder reactions with \(\beta\)-ketoesters when a large substituent is present on the diene (Figure 16).

Finally, it should be noted that the related alkoxy carbonylquinone derivatives (Figure 4, page 10)\(^{153}\) are not directly comparable to standard unsaturated \(\beta\)-ketoesters as their LUMO energy is lowered due to the conjugation with an additional carbonyl group. As a result, their HOMO-LUMO gap is considerably smaller (in agreement with their higher reactivity), and secondary orbital overlaps play a major role. A strong ester-\textit{exo} selectivity is often observed for these substrates (see Scheme 21, page 28).
2 Diels-Alder Reactions

Scheme 35: Influence of SOOs in Diels-Alder reactions with high or low HOMO-LUMO gap.\textsuperscript{168}

Figure 16: Dominating steric influences in the Diels-Alder reaction of alkylidene $\beta$-ketoesters by Welker.\textsuperscript{149}

2.5 Conclusion and Outlook

The ruthenium / PNNP catalyst \textsuperscript{2} promotes asymmetric Diels-Alder reactions on unsaturated $\beta$-ketoesters very efficiently in spite of the low intrinsic reactivity of these substrates, which has been a challenge in this field of chemistry. Most of the resulting multifunctional tetrahydro-1-indanone derivatives have not been reported before. Mild reaction conditions and high regio-, diastereo-, and enantioselectivity are key features of this reaction. Together with Yamauchi’s Mg-BOX system,\textsuperscript{55,56} complexes of type 7 are so far the only highly enantioselective catalysts for Diels-Alder reactions of alkylidene $\beta$-ketoesters.\textsuperscript{169} Therefore, the Ru / PNNP catalysts extend the scope of Diels-Alder reactions in the challenging task of enantio-
selective formation of all-carbon quaternary centers,\textsuperscript{42} which is an area of intense research. Also, the reaction with Dane’s diene (14) gives access to both \textit{nat}- and \textit{ent}-enantiomers of estrone derivatives bearing an ester functionality at the \(\alpha\)-carbonyl bridgehead position. The latter may act as a useful synthetic handle for further derivatization of these important biomolecules with potential applications in medicinal chemistry. An exceptional and rare feature of the catalytic system is its predictable stereochemistry based on the crystal structure of catalyst-substrate adduct 7a. In chapter 4 it will be shown that the extraordinary stability of the Ru / PNNP system provides means to obtain more detailed information on its structure, stereoselectivity, and reactivity.
3 Ficini [2+2] Cycloaddition of Ynamides

This chapter describes the first example of an enantioselective Ficini reaction and the first stereoselective Ficini cycloaddition with ynamides, which was achieved by employing the same Ru / PNNP / alkylidene β-ketoester system used in the Diels-Alder reactions (chapter 2). Heteroatom-substituted alkynes probably represent the most versatile subgroup within the vast field of alkyne chemistry. Ynamines, bearing a nitrogen atom directly at the triple bond, have found broad application after their discovery more than 50 years ago and have witnessed a revival in the form of the less electron rich ynamides in the last 20 years.\cite{170,171} The origins and advances of ynamine and ynamide chemistry, with a focus on enantioselective reactions and the Ficini [2+2] cycloadditions,\cite{172} are discussed in the introduction.

3.1 Introduction

3.1.1 Ynamines and the Ficini Reaction

By definition, ynamines feature a C-C triple bond directly attached to a nitrogen atom substituted with alkyl or aryl groups. After the first isolation of an ynamine by Zaugg,\cite{173} Viehe developed the first practical synthesis in 1963 (Scheme 36, a).\cite{174,175}

\begin{center}
\begin{align*}
\text{(a)} & \quad \text{Ph} \begin{array}{c}
\text{Cl} \\
\downarrow \\
\text{F}
\end{array} \xrightarrow{\text{LiNEt}_2 (2 \text{ equiv})} \text{Et}_2\text{O} \quad \text{Ph} \equiv \text{NET}_2 \\
\text{(b)} & \quad \text{TMS} \begin{array}{c}
\equiv \\
\downarrow \\
\text{Ph}
\end{array} \xrightarrow{\text{LiNPh}_2} \text{Et}_2\text{O} \quad \text{TMS} \equiv \text{NPh}_2
\end{align*}
\end{center}

Scheme 36: Ynamine preparation by Viehe\cite{174} and Stang\cite{176}

In the ensuing 20 years, the chemistry of ynamines was thoroughly explored and their exceptional versatility led to many inspired synthetic applications, many of which were extensively reviewed through the years.\cite{172,177–182} Their rather tedious preparation by halogen-elimination protocols\cite{181} can be circumvented using alkynyliodonium salts, as reported by Stang (Scheme 36, b).\cite{176} Preparation of relatively stable N-alkynylheteroarenes via copper-catalyzed coupling of alkynylibromides was reported in 2010 by Davies.\cite{183}

Some of the major advantages of ynamines, as opposed to other classes of alkynes, are their high reactivity, allowing the performance of otherwise unfeasible reactions, and the
predictable regiochemical outcome of a reaction, due to the strong electronic differentiation between the two \( sp \)-hybridized carbon centers of the triple bond (Scheme 37).\(^\text{171}\)

\[
\begin{array}{c}
\text{R}_2\text{N} \quad \text{R}^1 \\
\downarrow \quad \alpha \quad \beta \\
\text{R}_2\text{N} \quad \alpha \quad \beta \\
\end{array}
\]

\[
+ \quad \text{E}-\text{Nu} \\
\text{R}_2\text{N} \quad \text{Nu} \\
\text{R}^1
\]

**Scheme 37:** General reactivity of ynamines.\(^\text{171}\)

The predictable regioselectivity was exploited by Jacqueline Ficini to perform a \([2+2]\) cycloaddition on cyclic unsaturated ketones (enones) or quinones (Scheme 38).\(^\text{184-188}\) The resulting highly strained bicyclic products are thermally stable, as the energy required for the conrotatory ring opening of the cyclobutene is not available under the reaction conditions.\(^\text{172}\)

\[
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\]

**Scheme 38:** Thermal Ficini reactions of unsaturates ketones and naphtoquinone with ynamines.

Although formally a \([2+2]\) cycloaddition, the reaction between the ynamide and the enone is likely to occur stepwise via nucleophilic attack of the \( \beta \)-C atom of the ynamine onto the electrophilic position of the enone (Scheme 39).\(^\text{172}\) The resulting dipolar intermediate is likely to undergo rapid intramolecular ring closure by attack of the enolate to the iminium ion. A rationale for this assumption is provided by the fact that the HOMO frontier molecular orbital of the ynamide should have no, or very little, electron density in the \( \alpha \)-position to the nitrogen atom, and is thus not well suited for a concerted addition.\(^\text{189,190}\)

**Scheme 39:** Proposed reaction mechanism of the Ficini reaction.
Lewis acids can influence the Ficini reaction considerably. The presence of MgBr$_2$ increases the yield of the [2+2] cycloaddition reaction of cyclopentenone with N,N-diethylaminopropyne by allowing the use of milder reaction conditions.$^{191}$ With the six-membered analogue cyclohexenone, the addition of MgBr$_2$ leads to an attack at the carbonyl moiety, completely reversing the regioselectivity of the reaction (Scheme 40, above).

![Scheme 40](image)

Scheme 40: Left: effect of MgBr$_2$ as Lewis acid in Ficini reactions; right: trans-selectivity in the reaction with 5-methylcyclohex-2-en-1-one.

A high degree of cis/trans selectivity was observed in the Ficini reaction of N,N-diethylaminopropyne with 5-methylcyclohex-2-en-1-one (Scheme 40, below).$^{172}$ In this reaction, only the trans isomer was formed, which was explained by a better orbital overlap in the transition state when the forming bond is axial rather than equatorial.

A popular application of the cyclobutenamine products is their diastereoselective acidic hydrolysis as alternative to Michael addition chemistry.$^{185}$ This protocol was applied in the stereospecific synthesis of (±)-juvabione (Scheme 41).$^{192}$

![Scheme 41](image)

Scheme 41: Total synthesis of (±)-juvabione via hydrolysis of a Ficini reaction product.
3.1 Introduction

3.1.2 The Emergence of Ynamides

Despite the impressive versatility of ynamines, the exploration of their chemistry and their applications in synthesis has declined since the initial boost after their discovery. The reasons for this are their difficult preparation and handling, and their low stability, which comes along with their high reactivity.\textsuperscript{171} In contrast, the last ten years have seen a surge in the application of ynamides, in which the nitrogen moiety is substituted by an electron withdrawing substituent. Ynamides still feature a relatively strong polarization of the triple bond, but its electron density is reduced by the delocalization of the nitrogen lone pair into the electron withdrawing group. This renders ynamides more stable, usually even towards aqueous workup and chromatographic purification on silica gel.

A second important factor for the recent popularity of ynamides is the relatively new discovery of comfortable and inexpensive preparation methods, which has never been fully accomplished for ynamines. While earlier synthetic approaches largely relied on elimination protocols\textsuperscript{193,194} or on the use of alkynyliodonium salts\textsuperscript{195,196} similarly to ynamine synthesis (see above), a breakthrough in the synthetic access to ynamides was made in 2003 by Hsung.\textsuperscript{197} By using catalytic amounts of CuCN or CuI in combination with DMEDA (DMEDA = N,N'-dimethylethylenediamine), the first catalyzed amidation of alkynyl bro- mides was achieved, which provided direct and atom-economical access to several ynamides (Scheme 42, a).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{(a)} $\ce{R1-Br} + \ce{HN\text{EWG}} \rightarrow \ce{R1-N\text{EWG}}$};
\node (b) at (4,0) {\textbf{(b)} $\ce{R1-Br} + \ce{HN\text{EWG}} \rightarrow \ce{R1-N\text{EWG}}$};
\node (c) at (2,1) {CuCN (5 mol%)};
\node (d) at (2,0) {K\textsubscript{3}PO\textsubscript{4}, toluene};
\node (e) at (2,-1) {110 °C};
\node (f) at (2,-2) {22 examples};
\node (g) at (2,-2.5) {10 - 85\% yield};
\node (h) at (2,-3) {CuI (1 equiv)};
\node (i) at (2,-3.5) {KHMDS (1 equiv)};
\node (j) at (2,-4) {pyridine/THF, 25 °C};
\node (k) at (2,-4.5) {19 examples};
\node (l) at (2,-5) {40 - 82\% yield};
\end{tikzpicture}
\end{center}

\textbf{Scheme 42:} First metal-catalyzed synthesis of ynamides by Hsung\textsuperscript{197} and an alternative protocol by Danheiser.\textsuperscript{198,199}
The limitations of this catalytic system, like high reaction temperatures and low substrate scope (e.g. sulfonamides did not react at all), were first tackled by Danheiser\textsuperscript{198,199} (Scheme 42, b) and again by Hsung (Scheme 43).\textsuperscript{200} This most recent protocol gives access to a broad range of differently substituted ynamides under mild conditions using inexpensive copper(II) sulfate and 1,10-phenanthroline.

![Scheme 43: Mild copper-catalyzed amidation of alkynes with broad substrate scope.\textsuperscript{200}](image)

The major drawback of these coupling reactions is the necessity to prepare the alkynyl bromides as starting materials. However, they are usually obtained from terminal alkynes via bromination in good yields. Terminal alkynes can be directly used in the copper-catalyzed oxidative coupling by Stahl.\textsuperscript{201} In this elegant approach, oxygen is used as a terminal oxidant to prepare the respective ynamides in good to excellent yields (Scheme 44). Unfortunately, in order to limit the amount of Glaser-Hay dimerized dialkynes, an excess of the amide has to be used. Furthermore, acyclic amides, carbamates and ureas are not supported by the protocol.

![Scheme 44: Ynamide synthesis starting from terminal alkynes.](image)

The above catalytic amidation reactions for ynamide synthesis start from terminal alkynes, which are usually prepared from the corresponding aldehydes applying Corey-Fuchs reaction conditions with geminal dibromides as intermediate products. In 2009, Evano’s
group developed a modified protocol allowing for the direct reaction of these dibromides with sulfonamides, oxazolidinones, and pyrrolidinones, thus saving two reaction steps as compared to starting from alkynyl bromides (Scheme 45). Very recently, alkynyl carboxylic acids and alkynyltrifluoroborates have been applied as alkyne source in amide coupling reactions. This protocol features very mild reaction conditions (room temperature) without the need for a base.

\[
\begin{align*}
\text{R}_1^\text{Br} + \text{HN}^\text{EWG} & \xrightarrow{\text{CuI (12 mol%)}} \text{R}_1^\text{N}^\text{EWG} \\
\text{R}_2^\text{Br} + \text{HN}^\text{EWG} & \xrightarrow{\text{Cs}_2\text{CO}_3 (4 \text{ equiv})} \text{R}_1^\text{N}^\text{EWG} \\
\end{align*}
\]

\text{Scheme 45: Ynamide synthesis starting from geminal dibromides.}

### 3.1.3 Enantioselective Reactions and [2+2] Cycloadditions of Ynamides

With the available manifold of easy and cost efficient methods for ynamide synthesis described above, a large number of new and elegant transformations of ynamides, including additions at the \(\alpha\)- or \(\beta\)-positions, oxidative or reductive coupling, oxidation, ring-closing metathesis, cycloisomerization, and cycloaddition reactions have been reported in the last 5 - 10 years. In spite of the attention paid to ynamides by the synthetic community, enantioselective reactions using ynamides are very rare. To the best of our knowledge, there are only two examples of enantioselective reactions with ynamides.

The rhodium-catalyzed enantioselective [2+2+2] cyloaddition of 1,6-diynes was first reported by Tanaka. The reaction forms atropisomeric anilides in moderate yields and excellent enantioselectivities when (S)-xyllyl-BINAP is used as ligand (Scheme 46). The protocol was later used by Hsung in the synthesis of \(N,O\)-biaryls, generating two sources of axial chirality at once with high enantioselectivity but modest diastereoselectivity.

In 2009, Rovis reported the use of ynamides (and numerous other alkynes) in enantioselective rhodium-catalyzed cycloaddition reactions with alkenyl isocyanates. The reaction was chemoselective towards the formation of vinylogous amides when ynamides were used. In one case, high yield and enantioselectivity were achieved (Scheme 47).

49
Scheme 46: Enantioselective [2+2+2] cycloaddition reactions generating axial chirality.

Scheme 47: Enantioselective cycloaddition reaction with ynamides and alkenyl isocyanates.

Ynamides were also used as a starting point for the enantioselective synthesis of β-hydroxy enamines by Walsh and co-workers. In this protocol, the ynamide is subjected to hydroboration and transmetallation to zinc, forming a β-amido alkenylzinc reagent. After addition of morphilino isoborneol as chiral ligand, the reagent takes part in enantioselective nucleophilic additions to various aldehydes. However, since the ynamide is not involved in the enantioselective reaction step, the protocol does not feature enantioselective reactions of ynamides in the narrower sense.

Although [2+2] cycloaddition reactions of N-substituted alkynes were among the first reactions to be discovered, reports on this straightforward application of ynamides are scarce. In 2005, Tam used a monocationic ruthenium(II) catalyst in the reaction of norbornene with differently substituted ynamides. When chiral auxiliaries were attached to the nitrogen moiety, moderate levels of diastereoselectivity were achieved. To the best of our knowledge, this is the first and only example of a stereoselective [2+2] cycloaddition using ynamides so far (Scheme 48). The drawbacks of the reaction are long reaction times (68 to 168 h),
elevated temperatures, low substrate scope, and the requirement of an excess of norbornene (2.5 - 5 equiv).

Scheme 48: [2+2] Cycloaddition of ynamides to norbornene.

Danheiser reported elegant examples of [2+2] cycloadditions with various classes of ketenes. These highly reactive cycloaddition reagents are generated in situ, and high yields of the cyclobutenamide products are obtained (Scheme 49).

Scheme 49: [2+2] Cycloaddition of ketenes with ynamides reported by Danheiser.

Recently, the Ficini [2+2] cycloaddition was extended to ynamides by the group of Hsung. After 13 years of development, their reaction of cyclohexenone with sulfonyl substituted ynamides was realized using high catalyst loadings of CuCl$_2$ (20 mol%) and AgSbF$_6$ (60 mol%) to produce the corresponding cyclobutenamides in 21 - 77% yield. The substitution pattern on the ynamide is relatively general, as various combinations of alkyl and sulfonyl substituents on the nitrogen moiety were shown to be reactive. However, only cyclohexenone was tested as reaction partner for the ynamides. No diastereoselection was observed when a chiral sultam group was attached to the alkyne moiety of the ynamide (Scheme 50). This may be due to the fact that the chiral information is relatively remote from the reactive center.
3 Ficini [2+2] Cycloaddition of Ynamides

![Scheme 50](image)

Scheme 50: First Ficini [2+2] cycloaddition of ynamides.

### 3.2 Ru / PNNP-Catalyzed Asymmetric Ficini Reaction

#### 3.2.1 Preliminary Experiments

When developing a new catalytic reaction, it is crucial to choose reagents that give an adequate balance of sufficient reactivity, while avoiding too reactive conditions that enforce fast background reaction. As alkylidene β-ketoesters 6 show a general trend towards low reactivity in Diels-Alder reactions (see chapter 2), we envisioned the use of highly reactive ynamines as a compensating factor. In order to investigate the reactivity of ynamines towards unsaturated β-ketoesters, we added N,N-diethyl-2-phenylethynamine (1.2 equiv) to a CDCl\textsubscript{3} solution of substrate 6a (Scheme 51).

![Scheme 51](image)

Scheme 51: Preliminary reactivity study of substrate 6a with a representative ynamine.

After 30 minutes, the signal of the enone proton (δ 8.29) of 6a had disappeared from the \textsuperscript{1}H NMR spectrum of the reaction solution, thus indicating full conversion of the substrate. At the same time, the NCH\textsubscript{2} protons of the ynamine had split into a complicated pattern (δ 3.0 - 3.35). This is a clear sign of the formation of the chiral bicycle, which renders the NCH\textsubscript{2} protons diastereotopic. Besides the expected problems in purifying the highly reactive enamine product, we deemed this uncatalyzed reaction to be too fast to be a good starting point for the Ru / PNNP-catalyzed Ficini reaction. Therefore, we turned our attention to the related reagent class of ynamides.
Besides the higher stability and ease of handling, an important advantage of ynamides over ynamines is the decreased reactivity of the triple bond, which potentially inhibits the thermal reaction and allows for a catalytic approach. Indeed, ynamide 16c (Scheme 52) does not react with 6a under the same conditions as applied for N,N-diethyl-2-phenylethynamine above.

### 3.2.2 Enantioselective [2+2] Cycloaddition of Ynamides

The reduced reactivity of ynamides makes them attractive for enantioselective cycloaddition reactions. However, to the best of our knowledge, no enantioselective [2+2] cycloaddition of ynamides had been reported so far. In order to test the Ru / PNNP system in the Ficini reaction, we added alkylidene β-ketoester 6a to a CH₂Cl₂ solution of complex 2, prepared in situ from dichloro complex 1 as previously described. Ynamide 16c (1.1 equiv) was added, and the mixture was stirred at room temperature overnight. As TLC analysis revealed that substrate 6a had been only partially converted, the mixture was heated to 55 °C and stirred overnight once again, after which full conversion of 6a was observed. The corresponding cycloaddition product 17c was isolated by column chromatography on silica.

![Scheme 52: Enantioselective Ficini [2+2] cycloaddition of ynamide 16c to 6a.](image)

In a new experiment, the reaction mixture was heated to 55 °C directly after addition of ynamide 16c. TLC analysis after 24 h showed full conversion of unsaturated β-ketoester 6a, and the corresponding amidocyclobutene 17c was isolated in 72% yield. The enantioselectivity of the reaction was determined to be 90% ee by chiral HPLC analysis (Table 2, entry 3).
Table 2: Catalysis results for enantioselective Ficini Reactions on 6a.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>R(^3)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17a</td>
<td>c-C(<em>6)H(</em>{11})</td>
<td>Bn</td>
<td>Ts</td>
<td>97 (75)</td>
<td>90 (&gt;99.5)(^b)</td>
</tr>
<tr>
<td>2</td>
<td>17b</td>
<td>c-C(<em>6)H(</em>{11})</td>
<td>Me</td>
<td>Ts</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>17c</td>
<td>Ph</td>
<td>Bn</td>
<td>Ts</td>
<td>72</td>
<td>90</td>
</tr>
<tr>
<td>4(^c)</td>
<td>17c</td>
<td>Ph</td>
<td>Bn</td>
<td>Ts</td>
<td>66</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>17d</td>
<td>Ph</td>
<td>Me</td>
<td>Ts</td>
<td>64</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>17e</td>
<td>Ph</td>
<td>Me</td>
<td>Ms</td>
<td>69</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>17f</td>
<td>Ph</td>
<td>Me</td>
<td>Mbs</td>
<td>75</td>
<td>61</td>
</tr>
<tr>
<td>8</td>
<td>17g</td>
<td>n-C(<em>6)H(</em>{13})</td>
<td>Bn</td>
<td>Ts</td>
<td>99</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>17h</td>
<td>n-C(<em>6)H(</em>{13})</td>
<td>Me</td>
<td>Ms</td>
<td>94</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>17i</td>
<td>n-C(<em>6)H(</em>{13})</td>
<td>Me</td>
<td>Mbs</td>
<td>99</td>
<td>78</td>
</tr>
<tr>
<td>11</td>
<td>17j</td>
<td>CH(_2)OBn</td>
<td>Me</td>
<td>Mbs</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>12</td>
<td>17k</td>
<td>(CH(_2))(_2)OSiMe(_2)Bu</td>
<td>Bn</td>
<td>Ts</td>
<td>86</td>
<td>76</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: See experimental section. \(^b\) After a single recrystallization from hexane. \(^c\) At room temperature.

In order to investigate the effect of the elevated temperature, the reaction of 6a with 16c was run at room temperature for 5 days. A slight increase in enantioselectivity to 92% ee was observed (entry 4). Even after the long reaction time, the yield was still slightly reduced as opposed to the experiment at 55 °C over 24 h (66% instead of 72%). Thus, we decided to keep the elevated temperature conditions during our investigations on the scope of the reaction,\(^{189,190}\) although these conditions are at difference with the Diels-Alder reactions, which were run at room temperature and mostly in a 1:1 dichloromethane/diethyl ether mixture. Another difference to the optimized Diels-Alder conditions is that nearly stoichiometric amounts of the ynamides 16 (1.1 equiv) are sufficient to obtain high yields, which is notable for a reaction that forms an all-carbon stereocenter at the bridgehead position of a highly strained unsaturated [3.2.0]bicycle. A rationale for the different optimized conditions of the two reaction classes is discussed in detail in section 4.3.
The results summarized in Table 2 show that the substituent at the \( \beta \)-position of the ynamide is pivotal for the outcome of the reaction. By and large, \( n \)-hexyl- and cyclohexyl-substituted ynamides give high yields (entries 1, 2, and 8-10). High enantioselectivity is achieved when \( R^1 \) is a phenyl or cyclohexyl group (entries 1-7). Thus, the donor character of the alkyl substituents is crucial for high chemical yields, whereas the steric bulk of the cyclic residues is necessary in order to obtain high enantioselectivity. Accordingly, the cyclohexyl-substituted ynamides 16a and 16b give the best combination of very high yields and enantioselectivities of up to 92% ee (entries 1,2). Product 17a was obtained as a single enantiomer by recrystallization from hexane. However, when the sterically even more bulky \textit{tert}-butyl analogue of ynamide 16a was used, no reaction occurred. Considering the highly crowded situation in the bicyclic products 17, this limit to the steric bulk tolerated by the systems hardly surprises. On the other hand, the Ru / PNNP system is mild enough to tolerate functionalizable moieties (entries 11-12), which are intrinsically less stable than their alkyl and aryl analogues.

The smaller ethyl ester 6b gives lower enantioselectivity (Scheme 53), which confirms that a bulky ester group is pivotal, as observed in the Diels-Alder reaction\(^{167}\) (chapter 2) and in the previously discussed transformations with the saturated analogues 3.\(^{20,22,214}\) These observations will be discussed in detail in chapter 4.

\[ + \text{Nu} \rightarrow \text{Cyclodimer} \]

\[ \text{Scheme 53: Enantioselective Ficini [2+2] cycloaddition with ethyl \( \beta \)-ketoester 6b.} \]

Preliminary tests suggested that the ethyl cyclohexenone derivative 6d performs similarly to its five-membered ring analogue 6b and that the six-membered ring \textit{tert}-butyl ester analogue 6e might have an analogous optimization potential. However, TLC analysis of the reaction solution shows that 6e decomposes considerably under the reaction conditions. Due to the moderate stability of the alkylidene \( \beta \)-ketoesters, partial degradation of the substrate competes with the catalytic cycloaddition reaction. The reaction of \textit{tert}-butyl ester 6e with
16a gives low yield and only slightly improved enantioselectivity as compared to the ethyl analogue 6d (Scheme 54). Therefore, cyclohexenone substrates were not further studied.

Scheme 54: Enantioselective Ficini [2+2] cycloaddition with six-membered ring substrates 6d and 6e.

3.2.2.1 Absolute Configuration of Amidocyclobutene 17a. Single crystals of enantiomerically pure tert-butyl-7-[N-benzyl-4-methylphenylsulfonamido]-6-cyclohexyl-2-oxobicyclo[3.2.0]-hept-6-ene-1-carboxylate (17a) were obtained by recrystallization from hexane. An X-ray study confirmed the proposed structure and showed the (1R,5S) absolute configuration, as indicated by the value of the Flack parameter (Figure 17).

Figure 17: Comparison between amidocyclobutene 17a and an analogous compound reported by Hsung.213
A comparison to a similar compound reported by Hsung\textsuperscript{213} shows that the bond lengths and angles of the amidocyclobutene motif are basically identical, although compound 17a features a relatively bulky cyclohexyl group on the vinylic C-atom, whereas Hsung’s compound only bears a methyl group in this position. This is a clear sign of the extraordinary rigidity of this highly strained structural motif. The presence of a quaternary stereocenter at C(1) leads to a significantly contracted C(2)–C(1)–C(7) angle (113.2(1)°) as compared to the corresponding angle in Hsung’s Ficini product (115.1(2)°) and to the corresponding angle at the C(5) bridgehead position of 17a (C(4)–C(5)–C(6): 118.9(1)°). An interesting effect is observed at the nitrogen centers in the two molecules. As indicated by the sum of the angles around the nitrogen atom, the conformation at N(1) is slightly less planar in Hsung’s compound (sum of angles = 354.8(2)°) than in 17a (sum of angles = 358.3(1)°). We attribute this fact to a reduction of the electron withdrawing effect of the sulfonyl group by the p-methoxy group in Hsung’s compound. This leads to less delocalization of the lone pair at the nitrogen atom into the sulfonyl group, as compared to the corresponding tosyl-substituted compound 17a.

The assignment of the absolute configuration of 17a was independently verified by reduction of the carbonyl function and esterification of the resulting alcohol 18c with (−)-camphanic acid chloride (Scheme 55).

![Scheme 55](image_url)

\textbf{Scheme 55:} Verification of the (1R,5S) configuration of 6a via its (−)-camphanic acid derivative 19c.

A single crystal of the camphanic acid ester 19c, obtained by slow evaporation of a diethylether solution, was analyzed by X-ray diffraction (Figure 18), which confirmed the (1R,5S) configuration of 17a.
3.2.2.2 Stereochemical Considerations. The observed configuration of amidocyclobutene 17a is in agreement with an attack of the ynamide 16a from the top enantioface of the coordinated enone (Figure 19). Once again, the shielding by one phenyl rings of the PNNP ligand ensures high enantioface selectivity, as in case of the Diels-Alder reactions with 6a and catalyst 2. As already discussed, the Ficini reaction is proposed to proceed via a stepwise nucleophilic attack of the β-C atom of the ynamide onto the electrophilic position of the enone.\textsuperscript{172} Thus, the electronic demand requires that the R\textsuperscript{1} and R\textsuperscript{2} substituents at nitrogen point against the complex. Such an attack has been modeled by MM calculations (Figure 19, left). The structure was obtained starting from the X-ray data of 7a and imposing a distance of 2.0 Å between C(1’) of the ynamide and C(3) of the enone. Interestingly, a C(1’)-C(2’)-C(3)-C(2)-torsion angle of 0° is obtained for the transition state without imposing any additional constraint. Further details are described in the experimental part of this thesis. The structure shows that the bulky R\textsuperscript{1} and R\textsuperscript{2} groups fold away from the PNNP backbone as ynamide 16a approaches the coordinated enone in the open chiral space of complex 7a, which minimizes the steric interactions in the transition state.

Additionally, the product-catalyst adduct was modeled by generating the C(1’)-C(2) and C(2’)-C(3) bonds and refining the structure of the putative complex [Ru(17a)(PNNP)]\textsuperscript{2+} containing product 17a, while keeping the coordinates of the Ru / PNNP fragment frozen. In order to account for the interactions of 16a with the PNNP ligand, a new refinement was started, in which only the coordination sphere of the ruthenium atom (Ru, P, N, and O atoms) was kept frozen (Figure 19). In spite of the large steric bulk of 17a its coordination seems
to be possible without incompatible steric interactions to the catalyst backbone. These considerations are highly relevant to the product release in the catalytic cycle, as discussed in section 4.3 of the next chapter.

3.3 Ficini Products as Stereogenic Ligand Backbone

As compound 17a can be obtained in enantiomerically pure form, we envisioned its application as stereogenic backbone for chelating ligands in asymmetric catalysis. Our primary target was to make use of the amidocyclobutene double bond by incorporating it into a diene ligand. However, as coordination of such compounds to rhodium(I) and iridium(I) precursors turned out to be difficult, the focus of the project was switched to phosphite-alkene and diphosphite ligands. The experimental work was mostly performed by Raphael Bigler and the results are described in detail in his Master thesis.215 The following section summarizes the insights obtained and gives an outlook for further developments of the project.

3.3.1 The Functionalization of Ficini Products

Using the Ficini products described in the previous section as a starting point for chiral ligands offers several advantages. Besides the possibility to obtain enantiomerically pure material at least in one case (cyclobutenamide 17a), we were intrigued by the large number of different ligand classes accessible in only a few reaction steps relying on basic organic
chemistry. Also, each ligand class would be highly modular as virtually any position of the bicyclo[3.2.0]heptene skeleton is modifiable either by the original Ficini cycloaddition or by simple organic transformations (Figure 20).

![Figure 20: Modifiable positions of the bicyclo[3.2.0]heptene skeleton.]

3.3.1.1 Diene Ligands. The primary goal of this project was the synthesis of diene ligands based on the bicyclo[3.2.0]hepta-1,4-diene skeleton, where one of the C=C double bonds is part of the enamide moiety generated in the [2+2] Ficini cycloaddition. Diene ligands are a relatively recent development, but highly efficient systems have already been reported, first and foremost by Hayashi and Carreira (Figure 21).

![Figure 21: Examples of chiral diene ligands by Hayashi and Carreira.]

In the course of this project, several structurally different, potential diene ligands were prepared (Scheme 56). The deprotonation of 17a in the α-position of the ketone with LiHMDS, followed by enolate trapping with TBDMSCl, gave access to the silyl enol ether 20a in good yield. The enol ether unit should render this diene rather electron rich.

The enone 20b was prepared because it has a low-lying π*-orbital and should thus be a good acceptor for back-donation from the transition metal. Diene 20b was obtained by phenylselenenylation and selenoxide elimination using hydrogen peroxide as an oxidant in 49% yield over two steps. The yield increased to 72% by not purifying the phenyl selenide
intermediately before the final oxidation/elimination reaction. Stereoselective 1,2-addition of methylmagnesium iodide onto 20b gave the allylic alcohol 20c in excellent yield and as a single diastereomer, which can be explained by the effective shielding of the α-side of 20b by the bulky substituents on the sulfonamide or by a directing effect of the ester group. Unfortunately, it was not possible to protect the tertiary alcohol 20c even when using sodium hydride as a base and methyl iodide as an electrophile, a fact that may be accounted for by the rather congested space between the double bonds. However, unprotected alcohol groups are generally not problematic in the coordination of dienes, as Rh(I) and Ir(I) are not particularly oxophilic. This argument is supported by the findings of Hayashi and Rawal.\textsuperscript{221,222}

Unfortunately, no coordination of the dienes 20a-c to [Rh(μ-Cl)(C\textsubscript{2}H\textsubscript{4})\textsubscript{2}] or [Rh(acac)(C\textsubscript{2}H\textsubscript{4})\textsubscript{2}] was observed in CDCl\textsubscript{3} at room temperature, as indicated by the unchanged olefin proton signals in the \textsuperscript{1}H NMR spectra. Changing the solvent from CDCl\textsubscript{3} to coordinating solvents like THF or MeCN failed to accelerate ligand exchange at the transition metal. Likewise, no reaction occurred upon heating the reaction solution to 45 °C or 65 °C. Going from Rh(I) to [Ir(μ-Cl)(coe)\textsubscript{2}] as Ir(I) precursor, which generally forms stronger bonds to olefins, did not lead to coordination either, irrespective of whether coordinating (Et\textsubscript{2}O, THF) or non-coordinating (CDCl\textsubscript{3}) solvents were used.

There are several possible explanations for the reluctance of ligands 20a-c to coordinate to d\textsuperscript{8} transition metals, such as the pronounced distortion of the bicyclo[3.2.0]hepta-1,4-diene skeleton, which leads to non-parallel double bonds and might hinder efficient backdonation from the transition metal into the π*-orbitals. Further possible explanations are
the high degree of delocalization and asymmetry of the enamide HOMO (unfavorable both for donation and back-donation) or too sterically demanding substituents on the enamide moiety.\(^{215}\)

![Scheme 57: Synthesis of the diene ligand 20d with reduced steric demand and cyclobutene-double bond polarization.](image)

In order to exclude some of these possible reasons, the phenylsulfide derivative 20d (Scheme 57) was prepared. Compound 20d should be structurally and electronically different from 20a, as there is only one substituent on the double bond (decreased steric demand), and the \(p\)-orbital of the sulfur atom should have a considerably reduced polarizing effect as compared to nitrogen. However, no coordination of 20d to \([\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]\) was observed even after three days in CHCl\(_3\) at room temperature. This result suggests that the low affinity of the dienes 20a-d towards Rh(I) and Ir(I) is not mainly due to the bulkiness of the substituents or to the electronic properties of these dienes. The lack of coordination rather points to the possibility that the bicyclo[3.2.0]hepta-1,4-diene skeleton is not suitable for chelation, probably due to the twisting of the double bonds or their spatial proximity leading to a too small bite angle. However, further investigations are needed in order to verify this hypothesis. Unfortunately, several attempts to crystallize dienes 20a-d by layering a CDCl\(_3\) solution of the respective compound with pentane or hexane were unsuccessful.

3.3.1.2 Phosphite-Alkene Ligands. In light of the difficulties encountered in the coordination of diene ligands 20a-d, we were eager to investigate whether the enamide double bond is generally suitable for coordination. Therefore, we envisioned the synthesis of phosphite-alkene complexes that ensure coordination to the transition metal through the phosphite moiety and possibly promote the coordination of the enamide double bond due to the chelate effect. The starting point for these ligands was compound 18c, the 2-hydroxy derivative of 17a, which is an intermediate in the synthesis of the camphanic acid derivative 19c described above (Scheme 55). Compound 18c was isolated in 94% yield from ena-
tiomerically pure 17a. The ensuing derivatization with phosphorochloridites derived from glycol, 2,2'-biphenol, and BINOL yielded the phosphite-alkene ligands 21a-c.

Scheme 58: Synthesis of phosphite-alkene ligands 21a-c.

Having successfully prepared the phosphite-alkene ligands 21a-c, their coordination behavior with Rh(I) and Ir(I) was investigated. In the case of Rh(I), several species were observed. Whereas phosphite 21a quickly decomposed to unidentified species in the presence of [Rh(acac)(C₂H₄)₂] or [Ir(μ-Cl)(coe)₂] in CDCl₃ at room temperature, ligands 21b and 21c formed several complexes in solution under the same conditions. It was not possible to unambiguously determine whether the multiple signals observed originate from the partial coordination of the double bond or formation of complexes with two P-coordinated phosphites with dangling C=C double bonds. Another possibility is the formation of atropisomers, which has to be considered when investigating compounds featuring a flexible biphenol (tropos) unit. The energy barrier for the rotation around the biphenol bond in such complexes is highly dependent on the substitution pattern of the tropos unit, bulkier residues usually resulting in higher barriers.

In a further study, a $^{13}$C NMR spectrum of the reaction solution containing 21c and [Ir(μ-Cl)(coe)₂] (0.5 equiv) showed no significant shift of the $^{13}$C resonances of the vinylic carbon atoms, which indicates that the alkene unit does not coordinate. In order to investigate whether reducing the steric bulk at the enamide moiety would promote its coordination, we prepared the analogous ligand 21d, having a methyl and a mesyl substituent at the
nitrogen center (Scheme 59). These groups represent the smallest alkyl-donor / sulfonyl-acceptor combination conceivable. However, the $^{13}$C NMR spectrum of the reaction solution of [Rh($\mu$-Cl)(C$_2$H$_4$)$_2$]$_2$ and 21d in CDCl$_3$ showed no significant shift of the vinylic carbon signals, and thus indicated that the double bond does not coordinate.

![Scheme 59: ORTEP plot of phosphite-alkene ligand 21d.](image)

Although the Ficini product was enantiomerically enriched (74% ee), ligand 21d crystallized from boiling hexane as a racemate. However, X-ray quality crystals were obtained, which were studied by X-ray diffractometry. The phosphite substituent on the cyclopentane ring adopts an equatorial position and points away from the enamide unit (Scheme 59). Also, there is very little space for the transition metal in the $\alpha$-face of 21d, which makes a bidentate coordination difficult. However, the crystal structure shows that the phosphite lone pair of 21d points in the direction of the ester group. This prompted us to investigate whether a chelate ring may be formed by the corresponding diphosphite ligands obtained by reduction of the ester group.

### 3.3.1.3 Diphosphite Ligands.

The starting material for the synthesis of the diphosphite ligands was the diol 18d, which was obtained in 69% yield by reduction of 17a with an excess of LiAlH$_4$ in diethyl ether. Diphosphite ligands 22a and 22b were obtained after derivatization with the corresponding phosphorochloridites in 61% and 47% yield, respectively (Scheme 60).
Both ligands formed more than one species with standard Rh(I) precursors like [Rh(nbd)$_2$]BF$_4$ and [Rh(acac)(C$_2$H$_4$)$_2$] (1 equiv) in CDCl$_3$, as observed by $^{31}$P NMR spectroscopy. This suggests that there is no clear preference for one of the possible atropisomers that originate from the flexible biphenol residues in 22a and 22b. Nevertheless, both ligands were tested in asymmetric rhodium-catalyzed hydrogenation and in palladium-catalyzed allylic alkylation reactions (Scheme 61).

Ligand 22a gave essentially racemic products both in the hydrogenation of dimethyl itaconate and in the allylic alkylation reaction of (E)-1,3-diphenylallyl acetate with dimethyl

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**Scheme 60:** Synthesis of diphosphite ligands 22a and 22b.

**Scheme 61:** Benchmark catalytic reactions with ligands 22a and 22b.
malonate. Therefore, the focus was shifted to ligand 22b, having the more bulky tetrakis-tert-butyl substituted biphenol substituents. The increase of steric bulk on these groups has been shown to considerably improve the enantioselectivity of allylic alkylation reactions with furanoside derived ligands.\textsuperscript{225} Indeed, the change from ligand 22a to 22b leads to a considerable increase in enantioselectivity in the hydrogenation of dimethyl itaconate (from 5% to 20% ee) and the allylic alkylation of (E)-1,3-diphenylallyl acetate (from 6% to 52% ee). The best results for each reaction class were obtained in the hydrogenation of methyl 2-acetamidoacrylate (30% ee) and the allylic alkylation of (E)-1,3-diphenylallyl acetate with dibenzyl malonate (57% ee). Though the enantioselectivity remains moderate at best, it is interesting to see the dramatic effect of rigidifying the ligand structure, which possibly leads to a more pronounced favorization of one atropisomer in the complex (see above), and hence increases the enantioselectivity.

3.3.2 Outlook of the Project

The dienes and phosphite-alkenes prepared in the course of this project turned out to be a difficult class of ligands, as no coordination of the enamide double bond was observed by NMR spectroscopy. A possibility to achieve coordination of the double bond after all might include the use of nosyl as a protecting group on the nitrogen to replace the very stable tosyl group. Since the nosyl group is easily cleavable, deprotection would give an enamine which should be a better ligand than an enamide. We deem that the coordination of such ligands containing an electron rich enamine might be possible. Also, the expansion of the five-membered ring might enable coordination by changing the relative orientation of the double bonds to each other (Figure 22, A).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure22.png}
\caption{Target structures for further development of the ligand system.}
\end{figure}

The diphosphite ligands show some potential in asymmetric catalysis, as ligand 22b achieved 57% ee in the asymmetric allylic alkylation of (E)-1,3-diphenylallyl acetate. Thus, further studies aimed at the optimization of the ligand may prove fruitful. First and foremost,
a further rigidification of the ligand seems attractive. While it is almost impossible to 
increase steric bulk on the phosphorochloridites, further structural variation on the diol 
component should be feasible. Diol B (Figure 22) might be prepared by selective oxidation 
of the primary alcohol group in 18d (Scheme 60) and stereoselective Grignard addition, 
whereas the diphenyl substituted compound C should easily be accessible by reacting the 
β-hydroxyester 18c with an excess of phenylmagnesium iodide. Both modifications should 
restrict the possible conformations as opposed to the very flexible primary alcohol group 
in 18d. A further target molecule is the diphosphine ligand D, which would probably 
form considerably more rigid structures after coordination to transition metals, due to the 
decreased ring size resulting from the elimination of the oxygen spacers from the ligand. This 
compound may be accessible by bistriflation of 18d with triflic acid anhydride, followed by 
double S_N2 substitution of the triflate moieties with diphenylphosphine.

3.4 Conclusion and Outlook

The first asymmetric [2+2] cycloaddition of ynamides to an enone (Ficini reaction) was real-
ized using complex [Ru(OEt_2)_2(PNNP)](PF_6)_2 (2) as Lewis acid catalyst. The scope of the 
reaction includes variously substituted ynamides and five- or six-membered ring unsaturated 
β-ketoesters. The combination of an electron-donating substitutent (R^2) and an electron 
withdrawing group (R^3) in ynamides imparts good reactivity of the ynamide. However, it is 
generally still low enough to inhibit the uncatalyzed background reaction at elevated tem-
peratures. The reason for the exceptional ability of the Ru / PNNP fragment to stabilize 
the intermediate enolate is probably founded in its double positive charge (see section 1.1). 
Therefore, the dicaticonic nature of 7a might be the key feature ensuring catalytic activity.

In view of the difficulties encountered by Hsung in the non-enantioselective Ficini reaction 
(see above), the high yields and enantioselectivities obtained here are remarkable. Moreover, 
the coordination of the unsaturated β-ketoester to the chiral, oxophilic Ru / PNNP fragment 
is a more efficient strategy for enantioselection than introducing a chiral auxiliary at the 
ynamide N atom,^{210,211,213} which is remote from the triple bond (see section 3.1.3). Besides 
using ynamides, the reaction is a further, but still rare example of the use of an unsaturated 
β-ketoester as substrate for a cycloaddition reaction (see section 1.4). Like the Diels-Alder 
reaction described in chapter 2, the Ficini reaction has a predictable stereochemistry due to 
the formation of well-defined catalyst-substrate adducts like complex 7a. This allows for a 
more detailed study of the catalytic system by stoichiometric reactions, which is discussed 
in the next chapter.
Investigations aiming at the use of enantiomerically pure 17a as a ligand backbone for late transition metal chemistry are still at an early stage. However, the high degree of modularity and functionalizability of Ficini products 17 may prove to be essential for the further development of the project.
4 Stoichiometric Reactions and NMR Studies

As discussed in chapters 2 and 3, catalyst [Ru(OEt)_2(PNNP)](PF_6)_2 (2) brought about a breakthrough in the application of alkylidene β-ketoesters such as 6a in Diels-Alder and Ficini reactions. The reactions with activated dienes such as Dane’s diene (14) give essentially quantitative yields with a quasi-stoichiometric amount of the reagent, whereas 2,3-dimethylbutadiene (8) had to be used in excess (10 equiv). Except for the reaction with 8, a CH_2Cl_2:Et_2O (1:1) solvent mixture was required to achieve high yields in a reproducible fashion, and the Ficini reaction required a temperature of 55 °C to give high yields after 24 h. Also, high enantioselectivity was only obtained with the bulky unsaturated β-ketoester 6a. In order to understand the above features of the Ru / PNNP system, we decided to investigate the structural aspects of the species involved in the cycloaddition reactions and to verify our results by stoichiometric reactions that simulate a single catalyst turnover.\(^{226}\)

4.1 Characterization of Complex [Ru(6a)(PNNP)](PF_6) (7a)

After the preliminary results by Martin Althaus described in chapter 1, some additional attempts were made in the course of this thesis, to isolate and fully characterize complex [Ru(6a)(PNNP)](PF_6)_2 (7a), which contains 2-tert-butoxycarbonyl-2-cyclopenten-1-one (6a) as alkylidene β-ketoester.

In a first attempt, complex 7a was prepared by adding unsaturated β-ketoester 6a to a CD_2Cl_2 solution of freshly prepared [Ru(OEt)_2(PNNP)](PF_6)_2 (2) (Scheme 62, d). The reaction is complete within 15 min, as indicated by a slight color change from reddish brown to orange red. The $^{31}$P NMR spectrum of the reaction solution shows the AX pattern of 7a as the only identifiable product, but small impurities (< 2% intensity) indicate that this synthetic pathway is less clean than the deprotonation-hydride abstraction route from the saturated β-ketoester complex 4a discovered by Martin Althaus\(^{25}\) (Scheme 62, a-c), hence scale up and isolation were not attempted.

The hydride abstraction reaction from enolato complex 5a (Scheme 62, c) was carried out on a larger scale (50 - 100 mg), in order to isolate either racemic or enantiopure 7a in the solid state. However, attempts to precipitate 7a from the CH_2Cl_2 reaction solutions with hexane led to the formation of impurities that were not present in solution, and only intractable oils were recovered. This behavior is analogous to that of its saturated analogue 4a, which is not surprising in view of the overall labile nature of the coordination bond.
between ruthenium and a neutral oxygen donor (see section 1.1). Therefore, the attempts were abandoned, and the following discussion is based on the spectroscopic data in solution and on the X-ray structure obtained by Martin Althaus,\textsuperscript{25} mentioned in section 1.1.1.

4.1.1 Structural Aspects of Complex 7a

The crystal structure of 7a shows that the coordination sphere of ruthenium is a distorted octahedron with the absolute configuration OC-6-42-A.\textsuperscript{227–230} The \((S,S)\)-PNNP ligand is arranged in the \(\Lambda\)-cis-\(\beta\) configuration and in a conformation that is very similar to those observed in the related enolato complex 5a, as well as in the previously reported \(\beta\)-keto acid complex \([\text{Ru}(\text{3a}–\text{tBu})(\text{PNNP})]^2+\) (4d), where \(3\text{a}–\text{tBu}\) is the acid obtained by hydrolysis of the \(\text{tBuOC(O)}\) ester group of \(3\text{a}\) (Figure 23). Complex 4d was formed, probably by acid-catalyzed hydrolysis, during an attempt to crystallize the \(\beta\)-ketoester complex 4a.\textsuperscript{21,25}

The unsaturated \(\beta\)-ketoester 6a binds with the keto oxygen O(1) \textit{trans} to N(1), and with the ester carbonyl oxygen O(2) \textit{trans} to P(2). This is the same configuration as in the enolato complex 5a, which suggests that the hydride abstraction occurs without a major structural rearrangement. The Ru–O(1) distance (\textit{trans} to N) is significantly shorter than Ru–O(2) (\textit{trans} to P) (2.107(2) vs 2.172(2) Å), as observed in 4d,\textsuperscript{21} which reflects the lower \textit{trans} influence of the imino donor as compared to phosphine (Figure 24).
4.1 Characterization of Complex $[\text{Ru}(6a)(\text{PNNP})](\text{PF}_6)$ (7a)

**Figure 23:** ORTEP plots of complex 7a and the acid complex $[\text{Ru}(3\text{a}^{	ext{t}}\text{-Bu})(\text{PNNP})]^2+$ (4d).\textsuperscript{22,25}

<table>
<thead>
<tr>
<th>Bond Lengths (Å)</th>
</tr>
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<tbody>
<tr>
<td>C-O : 1.43</td>
</tr>
<tr>
<td>C=O : 1.20</td>
</tr>
<tr>
<td>C-C : 1.54</td>
</tr>
<tr>
<td>C=C : 1.34</td>
</tr>
</tbody>
</table>

**Figure 24:** Bond lengths of the β-ketoester moieties in complexes 5a-c, 7a, and 4d.

The C-C and C-O bond distances in the coordinated enone ester differ only marginally from average values.\textsuperscript{231} Due to the polarization of the conjugated system, a certain level of conjugation between the C(48)–C(49) double bond and the carbonyl groups is expected, which would localize some charge density onto the Ru–O moiety. However, the lengthening of the carbonyl C=O bonds in 7a (both 1.235(4) Å) with respect to the saturated acid analogue 4d (1.224(6) and 1.230(6) Å)\textsuperscript{22} is barely significant. On the other hand, clear indications of the polarization of the conjugated system can be found by $^{13}$C NMR spectroscopy. In 7a, the $^{13}$C NMR signal of the olefin carbon atom at $\delta$ 188.3 is shifted considerably towards higher frequency compared with a related free enone ester ($\delta$ 171.9, Figure 25, right), which points to a considerable change in the shielding constant $\sigma$. The shielding constant for the
chemical shift of non-H nuclei is determined mainly by the paramagnetic term $\sigma_{\text{para}}$, which is influenced by the $p$-electron excitation energy $\Delta E$ and by the expectation value $r_{2p}$ for the distance between a $2p$-electron and the nucleus according to the following equation:

$$\sigma_{\text{para}} = \frac{1}{\Delta E \cdot r_{2p}^3}$$

In the present case, $\Delta E$ represents the energy difference for the $\pi \rightarrow \pi^*$ transition, and therefore, the HOMO-LUMO gap of the enone ester ligand, whereas $r_{2p}$ is determined mostly by the charge density at the corresponding carbon atom. Thus, the highly deshielded carbon resonance at $\delta 188.3$ originates either from a small $\Delta E$, a small $r_{2p}$, or both.$^{2,26}$ A small $\Delta E$ in complex 7a might arise from a lowering of the energy of the $\pi^*$-orbital with respect to the free enone ester. A small $r_{2p}$, that is, the contraction of the $p$-orbital coefficient, may result from the considerable cationic character of the carbon center due to polarization caused by the coordination to the dicationic Ru / PNNP fragment. Overall, the data reported in Figure 25 clearly show that the coordination to ruthenium enhances the polarization of the C=C double bond of 6a. The resulting withdrawal of electron density from the $\beta$-carbon atom of the enone moiety is expected to stabilize the corresponding LUMO and improve the interaction with the HOMO of electron-rich dienes in Diels-Alder reactions,$^{41}$ making the complex an efficient catalyst for these transformations.

### 4.1.2 Changes upon Hydride Abstraction from 5a

As discussed in section 1.1.1, the $\beta$-ketoester complex 7a and its enolato precursor 5a are structurally very similar, which can be attributed to the rigid backbone of the tetradentate PNNP ligand. This rigidity is reflected by the very similar Ru–P and Ru–N bond lengths of 5a and 7a (Table 3). The largest differences between the two complexes involve the C(48)–
C(49) bond of the coordinated $\beta$-ketoester, which is shortened from a single bond (1.513(4) Å) in the enolato complex 5a to a double bond in 7a (1.339(5) Å, Figure 24).

The C(45)–C(49) distance is longer in 7a (by 0.08 Å) because of the loss of conjugation in the unsaturated $\beta$-ketoester, which is also the reason for the shortening of the carbonyl O(1)–C(45) bond in 7a as compared to 5a (1.235(4) vs 1.281(4) Å). The effect is smaller for the O(2)–C(50) bond, as the ester moiety is less enolized than the ketone carbonyl and, therefore, gains less double bond character upon hydride abstraction. The Ru–O distances are slightly longer in 7a than in 5a, which reflects the weaker coordination of the neutral unsaturated $\beta$-ketoester in 7a as compared to the anionic enolato ligand in 5a.

The highly parallel alignment of the $\beta$-ketoester ring and the shielding C(1)–C(6) phenyl ring, as well as their close proximity, calls for a discussion of $\pi - \pi$ interactions between the two moieties in complexes 5a and 7a (Figure 26). On going from the enolato complex 5a to the enone derivative 7a, the C(1)···C(49) and C(4)···C(48) separations shrink, and the C(49)···Ru–P(1)–C(1) torsion angle is slightly reduced from –12.0(1) to –8.3(1)$^\circ$, respectively.

**Table 3**: Selected distances (Å) and angles ($^\circ$) of tert-butyl enolato complex 5a, its hydride abstracted analogue 7a, and the major (5b) and minor (5c) diastereoisomers of the corresponding methyl enolato complexes (see also Figure 24).

<table>
<thead>
<tr>
<th></th>
<th>5a</th>
<th>7a</th>
<th>5b</th>
<th>5c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ru–P(1)</td>
<td>2.2803(8)</td>
<td>2.2973(8)</td>
<td>2.2821(7)</td>
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<td>2.2600(6)</td>
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</tr>
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<td>2.047(3)</td>
<td>2.050(2)</td>
<td>2.029(6)</td>
</tr>
<tr>
<td>Ru–N(2)</td>
<td>2.097(3)</td>
<td>2.083(3)</td>
<td>2.091(2)</td>
<td>2.072(6)</td>
</tr>
<tr>
<td>Ru–O(1)</td>
<td>2.082(2)</td>
<td>2.107(2)</td>
<td>2.086(2)</td>
<td>2.109(5)</td>
</tr>
<tr>
<td>Ru–(O2)</td>
<td>2.144(2)</td>
<td>2.172(2)</td>
<td>2.128(2)</td>
<td>2.108(5)</td>
</tr>
<tr>
<td>C(1)···C(49)</td>
<td>3.554(5)</td>
<td>3.471(4)</td>
<td>3.572(4)</td>
<td>3.47(1)</td>
</tr>
<tr>
<td>C(4)···C(48)</td>
<td>4.058(5)</td>
<td>3.760(1)</td>
<td>3.974(4)</td>
<td>3.76(1)</td>
</tr>
<tr>
<td>P(1)–Ru–C(49)</td>
<td>92.52(6)</td>
<td>91.27(5)</td>
<td>94.85(5)</td>
<td>92.5(1)</td>
</tr>
<tr>
<td>C(49)···Ru–P(1)–C(1)</td>
<td>–12.0(1)</td>
<td>–8.3(1)</td>
<td>–11.4(1)</td>
<td>–4.9(3)</td>
</tr>
<tr>
<td>dihedral angle ($^\circ$)</td>
<td>23.3(4)</td>
<td>14.0(4)</td>
<td>26.6(2)</td>
<td>18.0(7)</td>
</tr>
</tbody>
</table>

* $^a$ Angle between the C(45)/C(49)/C(50) and C(1)/C(2)/C(3)-C(4)/C(5)/C(6) planes.
Furthermore, the dihedral angle between the plane defined by C45/C49/C50 of the β-ketoester and the plane of the shielding phenyl ring is reduced from 23.3° to 14.0° (Table 3). These changes are diagnostic of enhanced π–π-interactions between the C(1)–C(6) phenyl ring and the β-ketoester in 7a as compared to 5a and reflect the higher π-acidity of the electron-poor enone moiety in comparison to the enolato ligand. Hence, the two ring systems align and move closer to each other in 7a. Interestingly, this rearrangement does not involve a shift of the P(1) atom connected to the C(1)–C(6) phenyl ring. The C(49)–Ru–P(1) angle remains nearly unchanged (92.52(6) vs 91.27(5)°, Table 3) as compared to the large reductions of the torsion and dihedral angles discussed above.

![Partial ORTEP plots of 5a and 7a](image)

**Figure 26:** Partial ORTEP plots of 5a and 7a, focusing on the relative positions of coordinated substrate and the C(1)–C(6) phenyl ring.

Interestingly, Corey has proposed that the π–π-interaction between aromatic groups of the catalyst and acrolein- or enone-type substrates in the transition state is a major factor directing the enantioselectivity of cationic oxazaborolidine catalysts (see section 2.1.1.1 and...
4.2 Stereoselective Binding of \(\beta\)-Ketoesters

Substrate 6a, which bears a bulky tert-butyl residue in the ester group, gives the highest enantioselectivity both in the Diels-Alder reaction and in the [2+2] Ficini cycloaddition. We have seen above that the coordination of 6a to the Ru / PNNP fragment occurs with complete diastereoselectivity, as 7a is formed as a single diastereoisomer. To investigate the effect of the ester group on the diastereoselectivity of the binding of the unsaturated \(\beta\)-ketoester to ruthenium, we prepared the corresponding ethyl (6b) and methyl (6c) derivatives of the alkylidene \(\beta\)-ketoester complex 7a, as described below. For convenience, the different \(\beta\)-ketoester ligands of the discussed complexes are summarized in Figure 27.

After double chloride abstraction from dichloro complex 1, \([\text{Ru(OEt}_2(\text{PNNP})](\text{PF}_6)_2\) (2) was treated with 6a-c (1.2 equiv) in CD\(_2\)Cl\(_2\). After 15 min, the solutions were analyzed by \(^{31}\text{P}\) NMR spectroscopy. The tert-butyl ester 6a gave a single product showing an AX pattern at \(\delta\) 63.2/50.4, whereas two main species were observed with the ethyl ester derivative 6b (AX spin systems at \(\delta\) 63.1/ 49.6 and \(\delta\) 61.5/48.6, 5:1 ratio) and methyl ester 6c (\(\delta\) 64.3/ 50.5 and \(\delta\) 62.6/49.8, 7:1 ratio). We speculated that the large tert-butyl ester group in 6a is pivotal to the diastereoselective binding of the unsaturated \(\beta\)-ketoester, and is hence a prerequisite for high enantioselectivity, and that the two additional signals in case of 6b and 6c derive from minor diastereomers of the \([\text{Ru(6)(PNNP})]^ {2+}\) complexes.

To verify this hypothesis, the alleged diastereomeric complexes formed with the methyl ester derivative 6c were characterized and used in Diels-Alder reactions with Dane’s diene (Scheme 63). Thus, \([\text{Ru(OEt}_2(\text{PNNP})]^ {2+}\) (2) was treated with the saturated \(\beta\)-ketoester 2-methoxycarbonylcyclopentanone (3c) (1.1 equiv) in CD\(_2\)Cl\(_2\) (Scheme 63, a). The resulting
dicationic complexes \([\text{Ru}(3c)(\text{PNNP})]^2^+\) were formed as a 70:30 mixture of diastereoisomers (4b and 4c). Both complexes were deprotonated with triethylamine (1.2 equiv) to give the corresponding diastereomeric enolato complexes 5b and 5c (in the same ratio), as indicated by the AX patterns in the \(^{31}\text{P}\) NMR spectrum at \(\delta 50.5/64.3\) (5b) and \(\delta 49.8/62.5\) (5c) (Scheme 63, b). Complexes 5b and 5c were separated by column chromatography on silica. They show distinctly different physical and chemical properties, as 5b is a red crystalline solid that is highly soluble in CH\(_2\)Cl\(_2\) and CHCl\(_3\), whereas 5c is an orange powder, and is poorly soluble in CH\(_2\)Cl\(_2\) and CHCl\(_3\). Both complexes were fully characterized.

The structural assignment in solution is based on the observation of coupling involving one of the carbonyl moieties and a phosphine, which is diagnostic of a mutual trans arrangement of the corresponding moieties. The \(^{13}\text{C}\) NMR spectrum (125.8 MHz) of the major diastereoisomer 5b shows a \(^3J_{\text{P},\text{C}}\) coupling constant of 1.5 Hz to the ester moiety at \(\delta 167.5\) and no coupling to the enolized ketonic carbonyl at \(\delta 193.4\). In case of the minor diastereoisomer 5c, the situation is reversed, and a trans coupling of 1.6 Hz is observed only for the enolized keto moiety at \(\delta 191.2\) with no coupling to the ester carbonyl at \(\delta 168.0\). Diastereoisomer 5b has the same structure as the tert-butyl analogue 5a, which is formed as a single diastereoisomer in which the ester group of the metal-bound \(\beta\)-ketoester is cis to both imines and trans to P(2), as indicated by the \(^3J_{\text{P},\text{C}}\) coupling of 1.5 Hz to the ester carbonyl carbon resonating at \(\delta 165.7\).

The 500 MHz \(^1\text{H}\) NMR spectra of the diastereomeric methyl derivatives 5b and 5c are very similar, except for the methyl signal of the ester moiety, which is distinctively shifted to lower frequency in 5c (\(\delta 2.63\)) as compared to 5b (\(\delta 3.20\)). This shielding effect is probably caused by the ring current of the aromatic framework of the PNNP ligand, as indicated by the X-ray structure of 5c (Figure 28). Also, the chemical shift of the deshielded \(^{31}\text{P}\) signal is very similar for the two analogous complexes 5a (\(\delta 63.4\)) and 5b (\(\delta 63.7\)), whereas the shift is distinctly different for complex 5c (\(\delta 60.7\)), in which the substrate is coordinated in the reversed fashion. The stereochemical assignment is unambiguously confirmed by the crystal structures of 5b and 5c (see below). The enolato complexes 5b and 5c can be stored at room temperature under inert gas atmosphere in the solid state for months without signs of decomposition or interconversion. Also, no isomerization is observed in CD\(_2\)Cl\(_2\) solution over 24 h, even in the presence of diethyl ether as a coordinating solvent in a 1:1 ratio to CD\(_2\)Cl\(_2\).
4.2 Stereoselective Binding of β-Ketoesters

Scheme 63: Synthesis of 7b and 7c, after separation of the enolato-precursors 5b and 5c.
4.2.1 X-Ray Structures of 5b and 5c

After several attempts of crystallizing enantiomerically pure (S,S)-5b and (S,S)-5c, the enolato complex [Ru(3b–H)((rac)-PNNP)]PF$_6$ was prepared with the racemic (R,R+S,S)-PNNP ligand. The major (5b) and minor (5c) diastereoisomers were separated by column chromatography, and single crystals were obtained by layering n-pentane over CH$_2$Cl$_2$ and CHCl$_3$ solutions, respectively. The asymmetric units of 5b and 5c contain a discrete 5b (or 5c) cation and the hexafluorophosphate anion, as well as disordered solvent molecules. For both diastereoisomers 5b and 5c, the enantiomer containing the (S,S)-PNNP ligand (as used in catalysis) is depicted in Figure 28. Metrical data are given in Table 3 (page 73).

In the major diastereoisomer 5b, the coordination sphere of ruthenium is a distorted octahedron with the OC-6-42-A absolute configuration\textsuperscript{227–230} at ruthenium, and the (S,S)-PNNP ligand is in the $\Lambda$-cis-$\beta$ configuration as in 7a. The enolato ligand binds with the keto oxygen O(1) trans to N(1), and with the ester carbonyl oxygen O(2) trans to P(2), as in the tert-butyl analogues 5a and 7a. The minor diastereoisomer 5c exhibits the same cis-$\beta$ configuration of the (S,S)-PNNP ligand, but the enolato ligand exposes the opposite enantiomeric (re in 5b vs si in 5c). Thus, the absolute configuration is OC-6-43-A. For convenience, selected bond lengths and angles of 5b and 5c are compared with those of the tert-butyl analogue 5a and of the unsaturated analogue 6a in Table 3 and in Figure 24.

![Figure 28: ORTEP plot of the enantiomers of 5b and 5c containing the (S,S)-PNNP ligand.](image-url)
The structural data show that the overall conformation of the PNNP ligand, as well as the coordination sphere of ruthenium, are very similar in both diastereoisomers, which suggests that there is no strong steric preference for the major diastereoisomer 5b. The major differences between 5b and 5c involve the Ru–O(1) and Ru–O(2) distances, which are markedly different in 5b (2.086(2) vs 2.128(2) Å, Figure 24). This results from the cumulated effects of enolization (the carbonyl oxygen O(1) bears the larger negative partial charge) and trans influence, which is higher for phosphine than for imine, resulting in a particularly weak Ru–O(2) bond involving the ester group in 5b. In the minor isomer 5c, Ru–O(1) and Ru–O(2) are identical within experimental error, which indicates that the effects of the enolization and of the different trans influences cancel each other out and suggests that this configuration is electronically disfavored.

Cerius$^2$ MM space-filling models based on the X-ray data of the diastereoisomers 5b and 5c show that the small methyl ester group can easily be accommodated in both complexes (Figure 29), which suggests that the diastereoselectivity of the methyl ester coordination mainly results from the electronic factors discussed above.

![Figure 29: Spacefilling models of compounds 5b (major) and 5c (minor), illustrating the lack of steric interactions of the PNNP ligand to the methyl ester group in both diastereoisomers.](image)

The electronic preference can be estimated to be similar in the methyl derivatives 5b/5c and in the tert-butyl analogue 5a. Therefore, it is reasonable to assume that this factor would impose roughly a 70:30 diastereoselectivity in favor of 5a, as observed in case of the methyl complexes 5b/5c. The additional steric effect exerted by the large tert-butyl ester group in 5a is responsible for the drastic increase in selectivity from a weak electronic trend to perfect diastereoselectivity in favor of the only observed diastereoisomer 5a. This indicates that in the tert-butyl ester complex the steric influence on diastereoselectivity is considerably larger than the electronic contributions. Thus, the crystal structures of 5a, 5b,
and 5c give the rare opportunity of assessing the relative importance of steric and electronic effects.

4.2.2 Hydride Abstraction from Enolato Complex 5b or 5c

To prepare the corresponding alkylidene β-ketoester adducts, the enolato complexes 5b and 5c were treated with (Ph₃C)PF₆ (1.05 equiv) under the same conditions as for 5a (Scheme 63, c, page 77). The hydride abstraction is instantaneous, as indicated by the color change of the reaction solution from red-orange to yellow. When the 70:30 diastereomeric mixture of 5b and 5c was used instead, the corresponding hydride-abstracted complexes 7b and 7c were formed in approximately the same ratio. It should be noted that the diastereomeric ratio between complexes 7b and 7c is different when they are prepared directly from the diether complex 2 by addition of alkylidene β-ketoester 6c (87:13 instead of 70:30, Scheme 64, Methods A and C, respectively).

![Scheme 64](image)

Method A: 87:13 mixture of 7b/7c by direct coordination of 6c to 2.
Method B: diastereomerically pure 7b by H⁺ abstraction from isolated 5b.
   or: diastereomerically pure 7c by H⁺ abstraction from isolated 5c.
Method C: 70:30 mixture of 7b/7c by H⁺ abstraction from 70:30 mixture of 5b/5c.

The hydride abstraction from the pure major isomer 5b gives 7b as the only product, whereas only 7c is formed from 5c (Method B). Thus, the reaction is stereospecific and renders the two diastereoisomers of the catalytically active complexes 7b and 7c independently available. After 12 h in CD₂Cl₂ solution, pure 7b or 7c undergo partial decomposition to unidentified products, but there is no conversion to the other diastereoisomer. Thus, the degradation of the complexes is faster than the exchange between 7b and 7c. The same be-
havior is observed when diethyl ether is used as a coordinating co-solvent (1:1 with CD$_2$Cl$_2$) to promote ligand exchange.

Like 7a, the highly reactive and catalytically active complexes 7b and 7c cannot be isolated and were therefore characterized in solution by $^1$H, $^{31}$P, and $^{13}$C NMR spectroscopy by analogy to 7a. As in the case of 5b and 5c, a distinctive shift of the signal for the methyl group of the ester moiety to lower frequency is observable for 7b and 7c (7b: $\delta$ 3.62, 7c: $\delta$ 2.94). The small characteristic $^3$J$_{P,C}$ trans coupling to the carbonyl groups (see above) in 5b and 5c is not resolved in 7c, while it is still observable in 7b ($^3$J$_{P,C} = 1.5$ Hz). The remaining spectroscopic data of 7a, 7b, and 7c are consistent with the trends observed between the analogously related complexes 5a, 5b, and 5c. Thus, the enolato complexes 5a - 5c are stable precursors for the reactive alkylidene $\beta$-ketoester complexes 7a - 7c, which are generated in situ by the stereospecific hydride abstraction reaction. The resulting complexes 7a - 7c were used in a series of stoichiometric reactions with Dane’s diene (14) that model a single catalytic cycle and as catalysts to study the stereochemical course of the catalytic reaction (see below).

### 4.2.3 Stoichiometric Diels-Alder Reactions

The diastereomerically pure complexes containing either the tert-butyl (7a) or the methyl (7b or 7c) alkoxy carbonyl-2-cyclopenten-1-one derivatives were formed in situ in CD$_2$Cl$_2$ by hydride abstraction from 5b or 5c (Scheme 64, Method B) and treated with Dane’s diene (14) (1.1 equiv) (Scheme 63, d, page 77). After addition of an excess of tetrabutylammonium chloride (Bu$_4$NCl) to displace the product from ruthenium, 15b or 15c were isolated and the enantioselectivity of the stoichiometric Diels-Alder reaction was determined by chiral HPLC analysis. The tert-butyl derivative 7a gave (8R,13S,14S)-13-tert-butoxycarbonyl-3-methoxy-7,8,12,13,15,16-hexahydro-6H-cyclopenta[a]phenanthren-17(14H)-one (15a) in 87% yield and with 90% ee (Table 4, entry 1). With the methylester derivative 6c, the reaction of the major diastereoisomer 7b with Dane’s diene gave the corresponding 8R,13S,14S enantiomer (entry 4), whereas the minor diastereoisomer 7c reacted with the opposite sense of induction to give the minor 8S,13R,14R enantiomer (entry 5). These results are in agreement with an attack from the upper face of the substrate and confirm the proposed stereochemical model.

An intriguing result is that the stoichiometric reaction of the minor diastereoisomer 7c with 14 gave higher enantioselectivity than 7b (97 and 87% ee, respectively, entries 5, 4). We suggest an explanation based on the X-ray structures of the related enolato complexes 5b and 5c, which can act as models for the substrate adducts 7b and 7c. This comparison
is reasonable, as the X-ray structures of the tert-butyl analogues 5a and 7a indicate that little structural rearrangement occurs upon hydride abstraction from the enolato complex (see section 4.1.2).

Table 4: Stoichiometric and Catalytic Reactions of 7 with Dane’s diene (14).\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>complex</th>
<th>mol%</th>
<th>added substrate</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Ru(6a)(PNNP)](^{2+}) (7a)</td>
<td>100</td>
<td>-</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>[Ru(6a)(PNNP)](^{2+}) (7a)</td>
<td>10</td>
<td>6a (R(_1) = tBu)</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>[Ru(OEt(_2))(PNNP)](^{2+}) (2)(^b)</td>
<td>10</td>
<td>6a (R(_1) = tBu)</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>[Ru(6b)(PNNP)](^{2+}) (7b)</td>
<td>100</td>
<td>-</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>[Ru(6c)(PNNP)](^{2+}) (7c)</td>
<td>100</td>
<td>-</td>
<td>97(^c)</td>
</tr>
<tr>
<td>6</td>
<td>[Ru(OEt(_2))(PNNP)](^{2+}) (2)</td>
<td>100</td>
<td>3c (R(_1) = Me)(^d)</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>[Ru(OEt(_2))(PNNP)](^{2+}) (2)</td>
<td>100</td>
<td>6c (R(_1) = Me)</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>[Ru(OEt(_2))(PNNP)](^{2+}) (2)(^b)</td>
<td>10</td>
<td>6c (R(_1) = Me)</td>
<td>51</td>
</tr>
<tr>
<td>9</td>
<td>[Ru(6b)(PNNP)](^{2+}) (7b)</td>
<td>10</td>
<td>6c (R(_1) = Me)</td>
<td>72</td>
</tr>
<tr>
<td>10</td>
<td>[Ru(6b)(PNNP)](^{2+}) (7b)(^e)</td>
<td>5</td>
<td>6c (R(_1) = Me)</td>
<td>79</td>
</tr>
<tr>
<td>11</td>
<td>[Ru(6c)(PNNP)](^{2+}) (7c)(^e)</td>
<td>5</td>
<td>6c (R(_1) = Me)</td>
<td>60</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: see experimental section, absolute configuration of the product is 8R,13S,14S, unless otherwise stated. \(^b\) See catalytic reactions chapter 2.1.1.3. \(^c\) Absolute configuration is 8S,13R,14R (see text). \(^d\) Addition of 14 after deprotonation of 4b/c (70:30) and hydride abstraction. \(^e\) Reaction time was 48 h.

The C(49)⋯Ru–P(1)–C(1) torsion angle (−4.9(3)\(^a\) vs −11.4(1)\(^a\)) and the C(1)⋯C(49) and C(4)⋯C(48) separations are much smaller in 5c than in 5b (Figure 30). Thus, the C(1)⋯C(6) phenyl ring is closer and better aligned with the enolato moiety in the minor diastereoisomer 5c, which enhances the shielding of the re face of the alkylidene β-ketoester and explains the higher enantioselectivity of the corresponding stoichiometric reaction of 7c with Dane’s diene 14. We have seen above that, in the enone complex 7a, the C(49)⋯Ru–P(1)–C(1) torsion angle is smaller than in the corresponding enolato derivative 5a because of the increased π − π interactions in the former complex (see section 4.1.2 and Table 3). Therefore, it is reasonable to assume that the shielding in the enone complexes 7b and 7c is more efficient, and the difference between the two complexes more pronounced, than indicated by the C(49)⋯Ru–P(1)–C(1) values available for the enolato complexes 5b and 5c.
4.2 Stereoselective Binding of β-Ketoesters

Finally, the relation between the diastereoselectivity of the substrate binding and the enantioselectivity of product formation was tested by performing the chloride abstraction - coordination - deprotonation - hydride abstraction - Diels-Alder reaction sequence, without separation of the diastereomeric complexes 5b and 5c (Scheme 64, method C). Thus, complexes 4b and 4c were prepared as a mixture by adding the saturated β-ketoester 3c to complex 2, followed by deprotonation with triethylamine and hydride abstraction with tritylium hexafluorophosphate. The 31P NMR spectra of the reaction solution taken at each step (Figure 31) showed that the 70:30 diastereoisomeric ratio remained constant throughout the reaction sequence.

After addition of Dane’s diene (14), the major (8R,13S,14S) enantiomer of the estrone derivative 15b was obtained with 34% ee (entry 6). This is very close to the theoretical value of 36% ee calculated from the initial 5b:5c diastereoisomer ratio (which is the same as 7b:7c) and the inherent enantioselectivity of the cycloaddition reaction between the pure

Figure 30: Partial ORTEP plots of 5b and 5c, focusing on the relative positions of coordinated substrate and the C(1)–C(6) phenyl ring.
diastereomers 7b and 7c and Dane’s diene 14 (as determined from the above stoichiometric reactions).

**Figure 31:** Stacked $^{31}$P spectra (162 MHz, 25 °C) of the reaction sequence leading from complexes 4b/c to [Ru(15b)(PNNP)]$^{2+}$ via deprotonation, hydride abstraction and Diels-Alder reaction. The 4 additional signals in the spectrum of 4b/c belong to unknown impurities, which disappear after deprotonation with triethylamine.

When the isomeric mixture of 7b and 7c was prepared by addition of the unsaturated $\beta$-ketoester 6c (1 equiv) to a solution of [Ru(OEt)$_2$(PNNP)](PF$_6$)$_2$ (2) (Scheme 64, method A), followed by addition of Dane’s diene (14), 15 was formed with an enantioselectivity of 56% ee (Table 4, entry 7). This reflects the fact that the coordination of the unsaturated $\beta$-ketoester 6c to 2 occurs with higher diastereoselectivity (87:13, Method A) than that of the saturated $\beta$-ketoester 3c (70:30, Method C). These observations indicate that the enantioselectivity of the Diels-Alder reaction is controlled by the diastereoselectivity of the coordination of the unsaturated $\beta$-ketoester to ruthenium and confirm that there is no exchange between 7b and 7c, as observed by $^{31}$P NMR spectroscopy.
4.2.4 Reactions with [Ru(6)(PNNP)]^{2+} (7) as Catalyst

The fast and clean formation of the enone complexes 7 by hydride abstraction prompted us to test them as catalysts in Diels-Alder reactions with Dane’s diene (14). The reactions with tert-butyl ester 6a gave essentially the same enantioselectivity (86 and 85% ee), irrespective of whether the substrate adduct 7a or the Et_{2}O complex 2 was used as catalyst (Table 4, entries 2, 3). This is in agreement with the observation that the adduct 7a is formed as a single diastereoisomer both by hydride abstraction from 5a and by reaction of 2 with \( \beta \)-ketoester 6a. These values are only slightly lower than those found in the corresponding stoichiometric reaction (90% ee, entry 1), which indicates that there are no major contributions to product formation by a background reaction.

To study the effect of the initial stereochemistry of the enone complex onto the enantioselectivity of the catalytic reaction, the diastereoisomerically pure methylester substrate adducts 7b and 7c (10 mol%) were tested in the catalytic Diels-Alder reaction with the methyl ester enone 6c and Dane’s diene (14) in CH_{2}Cl_{2}:Et_{2}O (1:1).

The major diastereoisomer 7b gave 15b with 72 % ee with a catalyst loading of 10 mol% (Scheme 65, b), which is significantly higher than obtained with 2 (10 mol%) as catalyst (51% ee, a). This increase is too large to be caused by the high enantioselectivity obtained in the first catalytic cycle, which must be close to 87% ee, as indicated by the corresponding stoichiometric reaction (Table 4, entry 4). We speculate that this effect may be related to the generally cleaner catalyst formation by hydride abstraction. We also attempted to exploit this improved method of catalyst formation to reduce the catalyst loading of the reaction. Thus, the reaction was repeated with 5 mol% of 7b in instead of 10 mol%. However, the TLC analysis of the reaction mixture showed that the conversion of 6c is not quantitative even

\[
\begin{align*}
\text{MeO} & \quad + \quad \text{MeO} \\
\text{14} & \quad \quad \quad \text{CH}_2\text{Cl}_2:\text{Et}_2\text{O} (1:1) \\
\text{MeO} & \quad \quad \quad \text{MeO}
\end{align*}
\]

\begin{align*}
(a) \text{Method A} & \quad (7b/c 87:13, 10 \text{ mol%}): \quad 51\% \text{ ee} \\
(b) \text{Method B} & \quad (\text{pure } 7b, \text{ 10 mol%}): \quad 72\% \text{ ee} \\
(c) \text{Method B} & \quad (\text{pure } 7b, \text{ 5 mol%}): \quad 79\% \text{ ee} \\
(d) \text{Method B} & \quad (\text{pure } 7c, \text{ 5 mol%}): \quad 60\% \text{ ee}
\end{align*}

\[\text{Scheme 65: Catalytic reactions of methyl ester enone 6c and Dane’s diene (14) with different catalyst preparation (see Scheme 64).}\]
after 48 h. The available data offer no explanation for the slight increase in enantioselectivity to 79% ee under these conditions (Scheme 65, c).

Finally, to check whether the higher enantioselectivity using diastereomerically pure 7b instead of the ether complex 2 as catalyst may be due to a memory effect in which the substitution of the product by the substrate occurs with retention of configuration at the metal, we monitored the reaction of substrate 6c with Dane’s diene (14) and 7b (5 mol%) over 72 h.

Table 5: Enantioselectivity vs reaction time in the reaction of 6c with 14 catalyzed by 7b. a

<table>
<thead>
<tr>
<th>entry</th>
<th>time (h)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>76</td>
</tr>
</tbody>
</table>

a Conditions: A standard catalytic run with 5 mol% of 7b was performed and samples of 0.1 mL were taken with a syringe at the given times. The samples were filtered through a pad of silica and analyzed by chiral HPLC (see exp. section).

The reaction showed a gradual decrease of the enantioselectivity from 83 to 76% ee (Table 5). This trend is in agreement with the evolution of the catalyst from the diastereomerically pure 7b, which can be assumed to form 15b with 87% ee in the first catalytic cycle, to a diastereomeric mixture of 7b and 7c upon coordination of a new molecule of substrate 6c. The buildup of the minor isomer 7c accounts - at least in part - for the formation of the opposite enantiomer of the Diels-Alder product 15b and for the decreasing enantioselectivity, which is represented by the succession of reactions A and B in Scheme 66.

The absence of a memory effect was confirmed by using the minor diastereoisomer 7c as catalyst (5 mol%) ceteris paribus (Scheme 65, d), which gave the same sense of induction as 2 and the major diastereoisomer 7b. However, the enantioselectivity is lower with 7c than with 7b (60 vs 79% ee, d and c, respectively), obviously because of the inverse sense of induction in the first catalytic cycle (reaction C in Scheme 66), but surprisingly higher than with catalyst 2 (51% ee, a). The reason for the increased enantioselectivity observed upon activation by the hydride abstraction pathway is probably related to the higher purity of the catalysts obtained with this method as compared to double chloride abstraction from.
4.3 Limiting Factors on Reactivity

In the Diels-Alder reaction, both catalysts 2 and 7b (or 7c) require a loading of 10 mol% to give quantitative yield within 24 h. At a catalyst loading of 5 mol%, slightly lower yields (60 - 79%) are obtained even after 48 h (Table 4, entries 10, 11). To determine the factors that limit the catalyst activity, diastereomERICALLY pure 7b was treated with diene 14 (1 equiv) in CD$_2$Cl$_2$ in an NMR tube, which simulates a single turnover of the catalytic cycle. The $^{31}$P NMR spectra of the reaction solution showed that 7b had reacted quantitatively within 15 min. Apart from trace impurities, the only signals observed after this time were two AX patterns ($\delta$ 39.1/62.9 (major) and $\delta$ 47.1/61.8 (minor)) that we assign to [Ru(15b)(PNNP)]$^{2+}$ (Scheme 67) on the basis of comparison with an authentic sample prepared from 2 and isolated 15b in a CD$_2$Cl$_2$ solution.

**Scheme 66:** Relations between the active complexes 7b and 7c during the catalytic reaction.

the dichloro complex 1 with (Et$_3$O)PF$_6$. In fact, (Et$_3$O)PF$_6$ is a highly reactive species whose slow degradation upon storing produces traces of strong acids that may interfere with the catalytic reaction. A further advantage of the hydride abstraction protocol is that the reaction is instantaneous instead of progressing overnight, like the generation of 2 from 1 by chloride abstraction with (OEt$_3$)PF$_6$.
Then, β-ketoester 6c (1 equiv) was added to the above solution of [Ru(15b)(PNNP)]^{2+}, and the regeneration of the active species 7b/c was monitored by $^{31}$P NMR spectroscopy (Table 6, entry 1). After 30 min, the product adduct [Ru(15b)(PNNP)]^{2+} was still the main species present in solution (ca. 65%). The formation of the diastereoisomeric substrate adducts 7b and 7c was quantitative only after 3 h.

Scheme 67: Investigation of cycloaddition reaction and product displacement in the Diels-Alder reaction with Dane’s diene (14).

The rate of regeneration of 7b/7c was not significantly affected by a large excess of substrate 6c (9 equiv) (entry 2), whereas the use of a CD$_2$Cl$_2$/Et$_2$O (1:1) solvent mixture significantly accelerated the product/substrate exchange (entry 3). The stoichiometric reaction of the sterically more demanding tert-butyl-β-ketoester complex 7a with Dane’s diene 14 took about 30 min to reach completion instead of less than 15 min with 7b (entry 4). On the other hand, the dissociation of the corresponding product 15a was faster, as the addition of 6a (1 equiv) at this stage regenerated [Ru(6a)(PNNP)]^{2+} (7a) (60%) after 30 min in CD$_2$Cl$_2$ (entry 4) as opposed to 35% in case of the exchange of the ruthenium-bound product 15b for 6b (entry 1). These compensating influences possibly explain why 6a and 6c give similar reaction profiles in the catalytic reaction.

The above results show that (i) the equilibrium between [Ru(15b)(PNNP)]^{2+} and [Ru(6c)(PNNP)]^{2+} lies completely on the side of substrate coordination, (ii) the product/substrate exchange is slower than the cycloaddition reaction, and that (iii) the resulting inhibition is operative already at the onset of the catalytic reaction (when most of the sub-
strate is still present). We conclude that, in the reaction between 6c and diene 14, product release from the catalyst is slow as compared to the cycloaddition reaction, which makes it a prime candidate for the rate-determining step of the catalytic cycle. This effect is kinetic in nature, as the substrate/product ratio does not significantly affect the rate of the exchange reaction. Therefore, it should not be confused with the thermodynamic product inhibition often observed in enzyme catalysis, in which both substrate and product bind to the catalyst (the enzyme) in rapidly established equilibria that progressively shift toward product coordination as the substrate concentration decreases.233

Table 6: Product displacement by substrates 6a/b after 30 min.

| entry | reagent | substrate (equiv) | solvent    | T (°C) | regeneration of 7b/c
<table>
<thead>
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</tr>
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<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>6c (1)</td>
<td>CD₂Cl₂</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>6c (9)</td>
<td>CD₂Cl₂</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>6c (1)</td>
<td>CD₂Cl₂:Et₂O b</td>
<td>25</td>
<td>70</td>
</tr>
<tr>
<td>4 c</td>
<td>14</td>
<td>6a (1)</td>
<td>CD₂Cl₂</td>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>6c (1)</td>
<td>CD₂Cl₂</td>
<td>25</td>
<td>5 - 10</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>6c (1)</td>
<td>CD₂Cl₂:Et₂O b</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>6c (1)</td>
<td>CD₂Cl₂</td>
<td>55</td>
<td>100</td>
</tr>
</tbody>
</table>

a In case of the methyl ester complexes, both 7b/c and the two corresponding diastereoisomers of [Ru(15b)(PNNP)]²⁺ were included in the integration. b In a 1:1 ratio. c The initial reaction between 7a and 14 took 30 minutes instead of 15 min with 7b/c.

Finally, the accelerated regeneration of the substrate-catalyst adduct that we observed with Et₂O (Table 6, entry 3), which possibly assists product displacement, explains why a 1:1 mixture of CD₂Cl₂ and Et₂O (1:1) gives the best results in catalysis with electron rich, highly reactive dienes 9, 10, and 14 (Table 1, entries 4-9 and Scheme 29).167,234 In contrast, the optimized Diels-Alder conditions for 2,3-dimethylbutadiene (8) require pure CH₂Cl₂ as solvent (Table 1, entries 1-3, values in parenthesis).167,234 To understand the latter feature, the stoichiometric Diels-Alder reaction of 7b was repeated with diene 8 under the same conditions (Scheme 68).

After 15 min, only 10% of 7b had reacted with 8, whereas its conversion with Dane’s diene (14) was quantitative within 15 min. In fact, complex 7b started to decompose before
Scheme 68: Stoichiometric Diels-Alder reaction of complex 7b with 2,3-dimethylbutadiene (8).

full conversion was achieved. When an excess of 2,3-dimethylbutadiene (8) (10 equiv) was used in the stoichiometric reaction in pure CD$_2$Cl$_2$, 70% conversion of 7b was observed after 10 min. Thus, the rate of cycloaddition is probably the limiting factor with diene 8, and a coordinating co-solvent such as Et$_2$O decreases the Lewis acidity of the system, leading to lower yield (Table 1, entry 2, page 33). The low reactivity of 2,3-dimethylbutadiene also explains why the catalytic reaction requires an excess of 8 (10 equiv) (entries 1-3), which, as shown above, by and large fixes the reactivity problem.

4.3.1 Stoichiometric Ficini Reaction

For the sake of comparison, the stoichiometric [2+2] Ficini cycloaddition$^{189,190}$ between 7b and $N$-benzyl-$N$-(cyclohexylethynyl)-4-methylbenzene-sulfonamide (16a) was performed under the same conditions (Scheme 69). Also in this case, complex 7b reacted quantitatively within 15 min to form the diastereoisomers of complex [Ru(17o)(PNNP)]$^{2+}$ (δ 45.2/61.5 (major) and 43.9/59.7 (minor), checked with an authentic sample prepared from 2 and 17o), which has methyl-7-$[N$-benzyl-4-methylphenylsulfonamido]-6-cyclohexyl-2-oxobicyclo[3.2.0]hept-6-ene-1-carboxylate (17o) coordinated to the Ru / PNNP fragment. However, the product/substrate exchange gave only about 5-10% of 7b/7c after 30 min (Table 6, entry 5), in contrast to 35% observed with diene 14 (entry 1).

The product/substrate exchange is accelerated in a 1:1 solvent mixture of CD$_2$Cl$_2$ and Et$_2$O (entry 6) as in case of the Diels-Alder reaction (entry 3), but the effect is not large enough to even reach the rate observed in the Diels-Alder reaction with 14 in pure CD$_2$Cl$_2$ (entry 1). Thus, although the [2+2] cycloaddition product 17o is very sterically demanding, the product release is even slower than in case of the Diels-Alder reaction with Dane’s diene (14).

Finally, a solution of the product-catalyst adduct [Ru(17o)(PNNP)]$^{2+}$ (formed as above at room temperature) and 6c in pure CH$_2$Cl$_2$ was heated at 55 °C in a sealed tube for 30 min,
followed by cooling the solution to room temperature in a water bath and quickly recording the $^{31}$P NMR spectrum. Under these conditions, the regeneration of the catalyst-substrate 7b/c adduct was quantitative after 30 minutes (entry 7). This experiment also shows that the coordination equilibrium lies completely on the side of [Ru(6c)PNNP]$^{2+}$ (7b/c), as in the case of the Diels-Alder reaction. Once again, the conditions that overcome the kinetic inhibition in the stoichiometric reaction correspond closely to those of the optimized catalytic reaction described above. The origin of the slow release of the cycloaddition product from the catalyst are found in the special properties of the involved ruthenium complexes, which all feature a low-spin d$^6$ configuration, as discussed in the next section.

4.4 The Properties of Ru(II) Low-Spin d$^6$ Complexes

An appealing feature of the Ru / PNNP system is that the substrate-catalyst adducts are well-defined complexes that can be structurally characterized. As observed by Evans, structural information about the catalyst and the catalyst-substrate complexes is the sine qua non for mechanistic understanding, which is the key to the broad applicability of Diels-Alder catalysts (see page 22). The question is, why this vital information is readily obtainable for the Ru / PNNP system, whereas it is often out of reach for other catalytic systems (see section 2.1.1.3).

A perusal of the literature shows that relatively stable substrate-catalyst adducts can be isolated for a number of ruthenium(II) Diels-Alder catalysts such as chiral Ru(II) half-sandwich complexes, whose adducts with methyl vinyl ketone and methacrolein have...
been characterized (Figure 32). Together with the already mentioned Ir(III) catalysts for the Nazarov cyclization (see section 1.1.1, page 4), these are low-spin d\textsuperscript{6} octahedral complexes of 4d and 5d metals with middle- to strong-field ligands, and hence among the most stable coordination compounds, as indicated by elementary crystal field arguments.\textsuperscript{236}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure32.png}
\caption{Low-spin d\textsuperscript{6} octahedral catalyst-substrate adducts by Kündig,\textsuperscript{124} Carmona,\textsuperscript{235} and Eisenberg.\textsuperscript{36}}
\end{figure}

However, d\textsuperscript{6} octahedral complexes with soft phosphine donors typically lack the most conspicuous property of a Lewis acidic catalyst, that is, the affinity for oxygen-donor ligands. Therefore, special features must be introduced in these catalysts, such as a high positive charge (or high formal oxidation state), hard ancillary ligands, and/or strong π-acceptors (see section 1.1.1).\textsuperscript{237} Accordingly, the above mentioned ruthenium half-sandwich complexes either contain a strongly π-accepting bis(perfluorophenyl)diphosphinite ligand\textsuperscript{124} or bear a double positive charge in combination with a hard nitrogen donor,\textsuperscript{235} whereas Eisenberg’s dicationic iridium(III) complex contain CO as ancillary ligand (see page 6).\textsuperscript{36,37} In case of [Ru(6a)(PNNP)]\textsuperscript{2+} (7a), the factors that increase the oxophilicity are the two hard nitrogen donors of the PNNP ligand and the dicationic nature of the complex (section 1.1). As for the latter issue, we have shown that the monocationic adducts [RuCl(OR\textsubscript{2})(PNNP)]\textsuperscript{+} (R = H or Et) are labile and exist in CD\textsubscript{2}Cl\textsubscript{2} solution in equilibrium with the five-coordinate complex [RuCl(PNNP)]\textsuperscript{+}, which will be discussed in chapter 6.

Low-spin d\textsuperscript{6} octahedral complexes are also exceptionally inert, as they have the highest energy difference between their ground state and the possible intermediates of ligand substitution.\textsuperscript{238,239} These five- or seven-coordinate intermediates are models for the respective transition states of the substitution reactions, which are either a dissociative or a associative process. Thus, the energy differences of the intermediates are a measure of the activation energy of these exchange processes. Accordingly, the low-spin d\textsuperscript{6} configuration is the key feature that gives a reduced rate of exchange in solution, which makes the reactive interme-
diates amenable to investigation by NMR spectroscopy, and even allows for their isolation, as demonstrated in this chapter. At the same time, the inertness of the complexes is also the main disadvantage of the dicationic Ru / PNNP catalyst, as product release can be a significant issue (see section 4.3).

In summary, we attribute the inert nature of complexes 7 to the combination of the stable and inert d\textsuperscript{6} low spin configuration, of the chelate effect associated with the bidentate β-ketoesters, and of the double positive charge of the complexes. Unfortunately, the very properties that give access to a broad array of vital information of the catalytic system are also causing its main synthetic limitation.

4.5 Conclusion and Outlook

Hydride abstraction from the enolato Ru / PNNP complexes 5a-c gives well-defined, easily characterizable dicationic complexes containing alkylidene β-ketoesters that are efficient asymmetric catalysts for Diels-Alder and Ficini reactions with dienes and ynamides, respectively. It should be noted that the synthetic routes to alkylidene β-ketoesters usually apply highly toxic primary oxidants and often suffer from moderate yields and narrow substrate scope (see section 1.3). The tandem deprotonation / hydride abstraction reaction described in this section is an elegant and clean protocol for the preparation of unsaturated β-ketoesters on a small scale, which is, beyond fundamental aspects, chemically useful for the in situ preparation of pure catalysts.

Complex 7a is a rare example of a fully characterized catalyst-substrate adduct. The structure and stoichiometric reactions of the substrate-catalyst adducts of type 7 are easily studied and yield valuable information on the stereochemical course of the reaction and on the relative rate of the cycloaddition and product release steps. It is reasonable to assume that the dicationic nature of catalyst 7 and the combination of hard (N) and soft (P) donors successfully contribute to give a highly oxophilic, though mild Lewis acid that is able of activating alkylidene β-ketoesters without triggering undesired side-reactions such as polymerization.

The above studies show that these catalytic reactions are on a narrow path between low reactivity of the alkylidene β-ketoester toward the diene and slow product release, which possibly provides another explanation why these reactions have eluded their efficient realization for so long.

In perspective, the Ru / PNNP catalyst may allow for a fast screening and optimization of the catalytic system with different substrates and reagents. This includes the tuning
of the PNNP ligand with electron-withdrawing or -donating substituents to fine-tune the Lewis acidity of the system. In fact, PNNP ligands are easily modified, and form a family of ligands that may find broad application in organic synthesis.
5 Cu(I/II)-Catalyzed Cyclo- and Michael Additions

In view of the lack of simple and efficient non-enantioselective synthetic protocols for the Diels-Alder and Ficini reaction with alkylidene \( \beta \)-ketoesters, we were confronted with the necessity of developing a new method to prepare racemic reference substances such as 1-ethoxycarbonyl-3,4-dimethyl-9-oxo-bicyclo[4.3.0]oct-3-ene (11b) and ethyl-8-\([N\)-benzyl-4-methylphenylsulfonamido]-7-cyclohexyl-2-oxobicyclo[4.2.0]oct-7-ene-1-carboxylate (17l) for the determination of the enantioselectivity of the Ru / PNNP catalytic system.\(^{167,190}\) The synthesis of these products as a racemate is the topic of this chapter. As most of these products have not been reported in literature before, this chemistry is relevant to organic synthesis on its own and has been published independently.\(^{169}\)

5.1 A Lack of Efficiency

The results discussed in chapters 2 and 3 are a breakthrough in the application of alkylidene \( \beta \)-ketoesters in Diels-Alder and Ficini reactions, for which no simple and straightforward protocols were available (see 2.1.2 and 3.1.3). However, as discussed in section 1.4, the use of unsaturated \( \beta \)-ketoesters in catalytic cycloadditions is rare in general also beyond Diels-Alder and Ficini reactions, as briefly sketched below.

The [2+2] cycloaddition of alkynyl sulfanes and the Michael addition of heteroaromatic rings to unsaturated \( \beta \)-ketoesters are two reactions that have not been discussed yet in this thesis, but feature a similar mode of enone activation as Diels-Alder and Ficini reactions. Although examples of both reactions have been reported, no efficient and high yielding protocol existed prior to our report.\(^{169}\) For example, ethynyl(phenyl)sulfane (23) was used to prepare an intermediate in the synthesis of tricycloclavulone, an unusual prostanoid-related compound.\(^{247}\) The protocol features high catalytic loadings of copper(II) triflate (30 mol\%) and gives moderate yields (Scheme 70). The resulting [3.2.0]cyclohept-5-ene ring system is subsequently transformed into the tricyclic system of the target molecule.

Hetereoaromatic compounds can react with dienophiles in either Diels-Alder or Michael addition reactions. An example of the Michael addition of furan to a \( \gamma \)-dimethyl substituted unsaturated \( \beta \)-ketoester was reported by Browne in 1992 (Scheme 71).\(^{148}\) Various Lewis acids were screened, and the best results were obtained with stoichiometric amounts of BF\(_3\)·OEt\(_2\) over 28 h with a large excess (10 equiv) of furan. However, even under these conditions, only moderate yields were obtained. With stoichiometric amounts of SnCl\(_4\), only substrate
Scheme 70: 2+2 cycloaddition of 23 to 6c in the synthesis of an intermediate towards tricycloclavulone.

decomposition was observed, which supports our conclusion that strong Lewis acids are not well suited for the generally sensitive unsaturated β-ketoesters (see 2.1.2). Another example is the Michael addition of 2-(trialkylsilyloxy)furans to - among others - alkylidene β-ketoesters catalyzed by various Lewis acids reported by Chabaud and Guillou.

Scheme 71: Michael addition of furan to a γ-dimethyl substituted unsaturated β-ketoester.

5.2 Cu(I) and Cu(II) Triflate as Lewis Acid Catalysts

As copper-based catalysts are commonly used Lewis-acidic catalysts and have found application in related reactions with α-thioacrylates and alkylidene malonates, we tested the copper(I) triflate benzene complex \([\text{Cu}_2(\mu^2-O_3SCF_3)_2(\mu^2-\eta^2-C_6H_6)]_n\) (24) as a mild Lewis acid. In fact, complex 24 turned out to catalyze the Diels-Alder and Ficini reactions with a number of cyclic unsaturated β-ketoesters (Scheme 72).

Thus, we decided to optimize the catalytic system and explore its scope by employing cyclic 6b and acyclic 6f as representative substrates. We further aimed to extend its applicability to the related [2+2] cycloaddition of ethynyl(phenyl)sulfane (23) and Michael addition of 1,2,5-trimethyl-1H-pyrrole (25) (Scheme 73). In the standard procedure with the Cu(I) catalyst, β-ketoesters 6b or 6f, reagents 16a, 23, or 25 (1.1 equiv), and the Cu(I) complex 24 (1-2 mol%) were stirred in CH₂Cl₂ until TLC analysis showed that the β-ketoester had been quantitatively converted. In the case of diene 8, a large excess (5 equiv)
5.2 Cu(I) and Cu(II) Triflate as Lewis Acid Catalysts

**Scheme 72:** Diels-Alder and Ficini reactions catalyzed by copper(I) (24) or copper(II) (28) triflate.

of the reagent was required to drive the reaction to completion, due to the low reactivity of 2,3-dimethylbuta-1,3-diene.

**Scheme 73:** [2+2] Cycloaddition reactions with ethynyl(phenyl)sulfane (23) and Michael addition reactions with 1,2,5-trimethyl-1H-pyrrole (25).

Total reaction times were between 30 min and 3 h. Copper(I) triflate 24 is only moderately soluble in CH$_2$Cl$_2$ and does not dissolve completely under these reaction conditions, which is probably due to its complex polymeric structure (Figure 33). The above protocol gives
the desired products in 48 - 99% yield without the need for anhydrous solvents or protective gas atmosphere (Table 7).

![Polymeric structure of copper(I) triflate (24).](image)

**Figure 33:** Polymeric structure of copper(I) triflate (24).

<table>
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<tr>
<th>entry</th>
<th>β-ketoester</th>
<th>reagent</th>
<th>catalyst</th>
<th>loading</th>
<th>time (h)</th>
<th>product</th>
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<td>64</td>
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^a Total yield of 26b’/26b (4:1 ratio).

Cyclic and acyclic β-ketoesters were converted under mild conditions in short reaction times and, apart from flash column chromatography, no workup of the reaction solution was required. The copper(I) catalyst 24 is much more active than the [RuCl$_2$(PNNP)]-based system,$^{167,190}$ and the catalyst loading can be reduced to 1 or 2 mol% while maintaining full conversion after 0.5 to 3 h. This is remarkable in particular for the cycloaddition reactions, which involve the formation of a sterically crowded quaternary all-carbon center.
In the Ficini reaction with 16a, both the cyclic (6b) and acyclic (6f) unsaturated β-ketoester gave the regioisomer expected on the basis of electronic preference as the only product (Scheme 72, 17l and 17p, respectively). In contrast, the [2+2] cycloaddition of ethynyl(phenyl)sulfane (23) onto the acyclic substrate 6f gives a 4:1 mixture of the regioisomers 26b and 26b’, in which the sterically favored isomer 26b’ is the major component (Scheme 73). This is unusual, since sulfanes and ynamides are nucleophilic at the β-position to the heteroatom, which normally efficiently directs the regioselectivity of these formal [2+2] cycloadditions notwithstanding the steric situation (Scheme 37, page 45).

The inverse regioselectivity is probably caused by the lower electronic induction of the sulfane as compared to the amide group, in combination with the substantial steric difference between the doubly substituted α- and the unsubstituted β-position of enone 6f. This difference is smaller in 6b, in which the β-position is part of the five-membered ring, and hence only the electronically favored regioisomer 26a is formed. In comparison to the reported protocol (Scheme 70), the Cu(I)-catalyzed reaction of 6b with 23 is run at room temperature (instead of 0 °C), and a much smaller catalyst loading is applied (1% instead of 30 mol%).

Using the highly nucleophilic 1,2,5-trimethyl-1H-pyrrole (25) with enones 6b and 6f leads to Michael addition instead of cycloaddition reactions (Scheme 73). The corresponding Michael addition products 27a and 27b were formed in 99% and 64% yield, respectively (Table 7, entries 7 and 11). The reaction proceeds smoothly with 1% of 24 during 30 min, which is much more efficient than the corresponding stoichiometric procedure with furan and BF₃·OEt₂ (see section 5.1).

For comparison, we also tested copper(II) triflate (28) in selected instances, such as the Diels-Alder reaction of 6b, which gives 11b in excellent yield (Table 7, entry 2). Monitoring of the reaction course by TLC analysis showed that, overall, the reactions with Cu(OTf)$_2$ (28) are complete after a shorter reaction time than with the less Lewis-acidic Cu(I) complex 24 (even with a catalytic loading of 1 mol%). Also, 28 gives a slightly higher yield with the less reactive ethynyl(phenyl)sulfane (23) than Cu(I) (79 and 70%, respectively, entries 6 and 5). On the other hand, the mild copper(I) catalyst 24 gives much better yields in combination with acid-sensitive substrates, such as ynamide 16a, whose reaction with 6b gives 17l in 99% yield with 24, but only 52% yield with 28 (entries 3 and 4).

To test whether small amounts of a copper(II) species, formed by oxidation or dismutation of 24, may account for catalytic activity, we repeated the reaction between 6b and diene 8 with [Cu$_2$(μ²-O₃SCF₃)$_2$(μ²-η²-CH₃C₆H₅)]ₙ, the toluene analogue of 24. The latter complex is commercially available in 99.9% purity, whereas the batch of 24 used in this study was
of technical grade (90%). The reaction was carried out under argon in the dark, and the solution remained colorless throughout the reaction, which indicates that no sizeable amounts of Cu(II) are formed (for comparison, the reaction solutions with 24 were brownish). As the yield obtained under these conditions (88%) is similar to that observed with 24 (95%) (Table 8, entries 1 and 2), it can be assumed that Cu(I) is competent for the catalytic reaction.

Finally, some experiments were carried out for the sake of comparison with existing methods. The best literature protocol\textsuperscript{58} for the Diels-Alder reaction of unsaturated \( \beta \)-ketoesters with 2,3-dimethylbutadiene (8), which is based on the much stronger Lewis acid SnCl\textsubscript{4} (in anhydrous diethylether), gives a significantly lower yield of 11b than the copper(I) catalyst 24 (55 vs 95\% with 24, Table 8, entries 3 and 1), which is probably due to partial polymerization\textsuperscript{148} of 6b under these conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>([\text{Cu}_2(\mu^2-O_3\text{SCF}_3)_2(\mu^2-\eta^2-\text{CH}_3\text{C}_6\text{H}_5)]_n) (2 mol%), under argon</td>
<td>88</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>SnCl\textsubscript{4} (50 mol%)</td>
<td>55</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>24 (2 mol%), in air</td>
<td>95</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>28 (1 mol%)</td>
<td>94</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>24 + Ph-BOX (20 mol%)</td>
<td>47</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>28 + Ph-BOX (20 mol%)</td>
<td>66</td>
<td>19</td>
</tr>
</tbody>
</table>

\textsuperscript{a} See experimental part for reaction conditions.

To test an enantioselective catalyst other than Ru / PNNP,\textsuperscript{167} we used (S,S)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline) ((S,S)-Ph-BOX) as chiral ligand in combination with Cu(I) and Cu(II) in the Diels-Alder reaction of 6b with diene 8. Copper(I) or copper(II) triflate (20 mol\%), ligand Ph-BOX (1.1 equiv vs metal), and 6b were dissolved in dichloromethane under argon, and 8 (1.5 equiv) was added thereto.

\[\text{Figure 34:} \ (S,S)-2,2'-\text{isopropylidenebis}(4\text{-phenyl}-2\text{-oxazoline}) \ ((S,S)-\text{Ph-BOX})\]
Copper(II) gave full conversion after 1 h at room temperature, whereas the reaction with the copper(I) system reached completion upon stirring overnight (Table 8, entries 4 and 5). A reasonable explanation is that the ligand further reduces the already modest Lewis acidity of copper(I) and thus deactivates the system considerably. Some asymmetric induction was observed, but the enantioselectivity was low (19 - 23% ee) and the yields were only moderate (47 - 66%).

![Scheme 74: Attempted ozonolysis of compound 17a under reductive, neutral, or oxidative conditions.](image)

Finally, preliminary experiments were dedicated to the functionalization of Ficini product 17a by ozonolysis of the cyclobutenamide double bond. The reaction was performed in CH₂Cl₂, MeOH, and mixtures thereof at various temperatures between –78 and 25 °C. Furthermore, reductive (NaBH₄), neutral (PPh₃, dimethylsulfane), and oxidative (H₂O₂) workup conditions were explored (Scheme 74). However, no well defined cleavage products were isolated from the reaction mixtures.

### 5.3 Conclusion

The results show that the [RuCl₂(PNNP)]-based catalyst remains unchallenged in terms of enantioselective catalysis, although the results with copper may possibly be improved by investigating a larger array of ligands. When no asymmetric induction is required, the Cu(I)/Cu(II) protocol is preferential to Ru / PNNP, as it is more convenient, less expensive, and faster. The protocol makes these challenging bicyclic products easily available as racemate and may prove to be a starting point for their application in organic synthesis, including the extension to asymmetric reactions.
6 Monocationic Aqua and Et$_2$O Ru / PNNP Complexes

The results discussed in chapter 4 show that Ru / PNNP complexes of the type [Ru(O–O)(PNNP)]$^{2+}$ are unexpectedly stable and inert, which provides the opportunity for detailed investigations on these systems. However, their high oxophilicity limits their catalytic efficiency, as product release from the catalyst proved to be problematic. A related class of Ru / PNNP complexes are the aqua and Et$_2$O adducts of [RuCl(PNNP)](PF$_6$) (29). These complexes with the general formula [RuCl(OR$_2$)(PNNP)]$^+$ (R = H, 30 (Cl–H$_2$O-cis) and 31 (Cl–H$_2$O-trans); R = Et, 32) have been used as epoxidation,$^3$ cyclopropanation,$^4$–$^6$ and imine aziridination$^7$ catalysts. These monocationic complexes are less stable and less inert than the dicationic species discussed above. The investigation of their behavior in solution, which is the topic of the present chapter, gives insight into the factors that control the oxophilicity of the Ru / PNNP complexes, as well as precious quantitative data.

6.1 Introduction

Single chloride abstraction from [RuCl$_2$(PNNP)] (1) with Tl(I)$^8$ or Ag(I)$^6$ salts gives the monocationic, five-coordinate complex [RuCl(PNNP)]$^+$ (29) (Scheme 75, a). If the abstraction is performed with 1 equivalent of (Et$_3$O)PF$_6$, the diethyl ether formed in the reaction coordinates to the monocationic Ru / PNNP fragment (Scheme 75, b).

Scheme 75: Activation of complex 1 by single chloride abstraction with TlPF$_6$ (a) or (Et$_3$O)PF$_6$ (b).

Complex 29 and its aqua (30/31) and Et$_2$O (32) derivatives catalyze enantioselective atom-transfer reactions such as epoxidation,$^8$ cyclopropanation,$^4$–$^6$ and aziridination$^7$ (see page 1). The coordination of oxygen donors (such as water, diethyl ether, THF, or acetone) modifies the catalytic activity and selectivity of [RuCl(PNNP)]$^+$ (29). In epoxidation and
cyclopropanation, the presence of water or other oxygen donors reduces the activity and enantioselectivity of the catalyst.$^{4-6,8}$ In contrast, previous work from this laboratory has shown that the monocationic six-coordinate adducts $[\text{RuCl}(\text{L})(\text{PNNP})]^+$ ($\text{L} = \text{OH}_2$ or $\text{OEt}_2$) are the most suitable ruthenium PNNP complexes for the aziridination of imines with ethyl diazoacetate.$^7,250$ In particular, the temperature effects observed in the imine aziridination reaction catalyzed by these aqua and Et$_2$O adducts called for a better understanding of the thermodynamic and kinetic aspects of the dissociation and cis-trans equilibria involving these species.$^7$

Therefore, for comparison with the dicationic oxygen donor adducts described in this thesis, we re-investigated the aqua complex $\text{cis-β-[RuCl}(\text{OH}_2)(\text{PNNP})]\text{PF}_6$ (30), its trans analogue 31, and the elusive Et$_2$O adduct $[\text{RuCl}(\text{OEt}_2)(\text{PNNP})]\text{PF}_6$ (32)$^{5,250}$ The structural features and dissociation equilibria of these complexes in solution are discussed below.

### 6.2 Addition of Water to $[\text{RuCl}(\text{PNNP})]\text{PF}_6$

The five-coordinate complex $[\text{RuCl}(\text{PNNP})]\text{PF}_6$ (2) was prepared by chloride abstraction from $[\text{RuCl}_2(\text{PNNP})]$ (1) with TlPF$_6$ (1 equiv) in CD$_2$Cl$_2$ according to the usual procedure (Scheme 75)$^8$. Upon addition of water (1 equiv), the water droplet dissolved into CD$_2$Cl$_2$ within 1 min, and broad signals of the $\text{cis-β}$ aqua complex $[\text{RuCl}(\text{OH}_2)(\text{PNNP})]\text{PF}_6$ (30) (63%) appeared in the room-temperature inverse-gated decoupled $^{31}\text{P}$ NMR spectrum of the reaction solution. The other species present were unreacted 29 (29%) and $\text{trans-[RuCl}(\text{OH}_2)(\text{PNNP})]\text{PF}_6$ (31) (8%). The room temperature ($^{31}\text{P},^{31}\text{P}$)-EXSY spectrum (202 MHz, mixing time = 50 ms) shows that five-coordinate 29 and the $\text{cis-β}$ aqua complex 30 are in mutual exchange (Figure 35). The observation of individual, non-averaged signals for 29 and 30 indicates that the system is in the slow exchange regime. No detectable exchange process involves the trans isomer 31, which implies that it either does not dissociate or that its dissociation is slow on the NMR time scale at room temperature.

The equilibria involving the five-coordinate complex 29 and the aqua derivatives 30 and 31 are summarized in Scheme 76. The ($^{31}\text{P},^{31}\text{P}$)-EXSY NMR spectrum at $-10^\circ \text{C}$ (202 MHz, mixing time = 40 ms, 29 + 1 equiv H$_2$O) shows that 29 and 30 are still slowly exchanging, whereas no exchange is detected at $-15^\circ \text{C}$. A series of ($^{31}\text{P},^{31}\text{P}$)-EXSY experiments at room temperature with different mixing times gave a value of $47(9) \text{s}^{-1}$ for the exchange rate constant $k$ (see section 7.6.1).
Upon increasing the overall amount of water from 1 to 5 equivalents (vs ruthenium), all $^{31}$P NMR signals sharpened up, and the overall conversion of the five-coordinate species 29 to the aqua complexes 30 and 31 increased from 71% to 93% (82 and 11% for 30 and 31, respectively). The composition of the solution (81% 30, 13% 31, 6% 29) and the chemical shifts of 30 and 31 did not change (within experimental error) upon increasing the excess of water to a total of 20 equivalents (Table 9). In the range between 1 and 20 equivalents H$_2$O, the 30:31 cis:trans ratio remained essentially constant at ca. 6:1.
6.2 Addition of Water to [RuCl(PNNP)]PF$_6$

Table 9: $^{31}$P NMR spectroscopic data of complexes 29, 30, 31, and 32.

<table>
<thead>
<tr>
<th>complex</th>
<th>solvent</th>
<th>T (°C)</th>
<th>H$_2$O (equiv)</th>
<th>$\delta_A$</th>
<th>$\delta_B$</th>
<th>$^2J_{P,P'}$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[RuCl(PNNP)]PF$_6$ (29)</td>
<td>CD$_2$Cl$_2$</td>
<td>0</td>
<td>0</td>
<td>60.5</td>
<td>51.0</td>
<td>28.3</td>
</tr>
<tr>
<td>cis-$\beta$-[RuCl(OH$_2$)(PNNP)]PF$_6$ (30)</td>
<td>CD$_2$Cl$_2$</td>
<td>25</td>
<td>20</td>
<td>62.8</td>
<td>45.4</td>
<td>32.0</td>
</tr>
<tr>
<td>(by addition of H$_2$O to 29)</td>
<td>CD$_2$Cl$_2$</td>
<td>25</td>
<td>5</td>
<td>62.9</td>
<td>45.4</td>
<td>31.8</td>
</tr>
<tr>
<td></td>
<td>CD$_2$Cl$_2$</td>
<td>25</td>
<td>1</td>
<td>64.0</td>
<td>45.3</td>
<td>31.1$^a$</td>
</tr>
<tr>
<td></td>
<td>CD$_2$Cl$_2$</td>
<td>–20</td>
<td>1</td>
<td>63.1</td>
<td>45.6</td>
<td>32.0</td>
</tr>
<tr>
<td>cis-$\beta$-[RuCl(OH$_2$)(PNNP)]PF$_6$ (30)</td>
<td>CDCl$_3$</td>
<td>25</td>
<td>0</td>
<td>69.2</td>
<td>46.0</td>
<td>br</td>
</tr>
<tr>
<td>(isolated)</td>
<td>CDCl$_3$</td>
<td>25</td>
<td>20</td>
<td>63.4</td>
<td>45.6</td>
<td>32.0</td>
</tr>
<tr>
<td></td>
<td>CD$_2$Cl$_2$</td>
<td>25</td>
<td>0</td>
<td>67.0</td>
<td>45.9</td>
<td>br</td>
</tr>
<tr>
<td></td>
<td>CD$_2$Cl$_2$</td>
<td>25</td>
<td>&gt;20</td>
<td>62.7</td>
<td>45.5</td>
<td>31.6</td>
</tr>
<tr>
<td>trans-[RuCl(OH$_2$)(PNNP)]PF$_6$ (31)</td>
<td>CD$_2$Cl$_2$</td>
<td>25</td>
<td>20</td>
<td>50.6</td>
<td>44.1</td>
<td>27.1</td>
</tr>
<tr>
<td>(by addition of H$_2$O to 29)</td>
<td>CD$_2$Cl$_2$</td>
<td>25</td>
<td>5</td>
<td>50.6</td>
<td>44.1</td>
<td>27.1</td>
</tr>
<tr>
<td></td>
<td>CD$_2$Cl$_2$</td>
<td>25</td>
<td>1</td>
<td>50.7</td>
<td>43.8</td>
<td>27.1</td>
</tr>
<tr>
<td></td>
<td>CD$_2$Cl$_2$</td>
<td>–20</td>
<td>1</td>
<td>51.1</td>
<td>43.8</td>
<td>26.9</td>
</tr>
<tr>
<td>trans-[RuCl(OH$_2$)(PNNP)]PF$_6$ (31)</td>
<td>CDCl$_3$</td>
<td>25</td>
<td>0</td>
<td>52.2</td>
<td>44.2</td>
<td>26.6</td>
</tr>
<tr>
<td>(isolated)</td>
<td>CDCl$_3$</td>
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<td>20</td>
<td>50.7</td>
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</tr>
<tr>
<td></td>
<td>CD$_2$Cl$_2$</td>
<td>25</td>
<td>0</td>
<td>52.0</td>
<td>45.0</td>
<td>27.3</td>
</tr>
<tr>
<td></td>
<td>CD$_2$Cl$_2$</td>
<td>25</td>
<td>&gt;20</td>
<td>50.6</td>
<td>44.1</td>
<td>26.5</td>
</tr>
<tr>
<td>cis-$\beta$-[RuCl(OEt$_2$)(PNNP)]PF$_6$ (32)</td>
<td>CD$_2$Cl$_2$</td>
<td>25</td>
<td>-</td>
<td>41</td>
<td>41</td>
<td>$^b$</td>
</tr>
<tr>
<td></td>
<td>CD$_2$Cl$_2$</td>
<td>–78</td>
<td>-</td>
<td>55.5</td>
<td>36.9</td>
<td>29.6</td>
</tr>
</tbody>
</table>

$^a$ The signal at $\delta$ 64.0 is broad and exhibits a reduced $^2J_{P,P'}$ constant of 25 Hz. $^b$ The signal at $\delta$ 41 is broad and featureless.

The stereochemistry of the isomeric aqua complexes 30 and 31, prepared by adding water (20 equiv) to five-coordinate 29 in CD$_2$Cl$_2$, was inferred from the 202 MHz ($^{31}$P,$^1$H)-HMQC spectrum, which was recorded at $–60$ °C to prevent possible cross peaks caused by chemical exchange. In the major isomer 30, the deshielded $^{31}$P NMR signal at $\delta$ 62.8 does not correlate to either imine proton, whereas the low-frequency phosphine signal shows a cross peak to the imine signal at $\delta$ 8.85 with a resolved P,H coupling across the P–Ru–N=C–H moiety (Figure 36).
The $^4J_{P,H}$ coupling constant of 9.6 Hz is diagnostic of a mutual trans arrangement of the phosphine and imine. In fact, its magnitude depends on the same electronic effects that influence the value of the $^2J_{P,P'}$ coupling constant, which is known to be larger in trans complexes than in cis ones. Accordingly, the other imine proton gives a slightly broadened singlet at $\delta$ 8.73 in the $^1H$ NMR spectrum with no correlation to phosphorus. In fact, when the phosphino and imino ligands are mutually cis, the $^4J_{P,H}$ coupling is too small to be resolved (< 3 Hz). In the minor isomer 31, each imine proton ($\delta$ 9.26 and 8.98) exhibits a resolved $^4J_{P,H}$ coupling ($^4J_{P,H} = 9$ Hz for both signals) and a strong cross peak to one of the phosphines, which is indicative of two trans P–Ru–N=C–H moieties, that is, of trans stereochemistry for the complex.

The above assignment is supported by the observation that one of the phosphines in the cis-β isomer 30 resonates at a much higher frequency (ca. $\delta$ 63) than the other one (ca. $\delta$ 45). This indicates that these P donors are trans to ligands with a largely different trans influence, such as aqua and imine, and is hence diagnostic of a cis-β configuration, which is confirmed by an X-ray study (see below). The same pattern has been observed for the $^{31}P$ NMR chemical shifts in [Ru(OH)$_2$(PNNP)]$^{2+}$. In the trans isomer 31, the P atoms resonate at similar and significantly lower frequencies ($\delta$ 50.6 and 44.1, Table 9), as they are.
6.3 Isolated [RuCl(OH₂)(PNNP)]PF₆

trans to the same donor type, that is, imine. Based on these results, the previous tentative assignment of the signals of 31 to a cis-β complex⁸ has to be corrected.

Figure 37: \(^{(31)P,1H}\)-HMQC spectrum (202 MHz, –60 °C) of [RuCl(PNNP)]PF₆ (29).

For comparison, we measured a \(^{(31)P,1H}\)-HMQC NMR spectrum of the five-coordinate complex [RuCl(PNNP)]PF₆ (29) at –60 °C (Figure 37). As usually observed despite all precautions, the aqua complexes 30 and (traces of) 31 are present as impurities. An interesting feature is that the \(^1H\) NMR signals of the imine protons of 29 overlap with those of the cis-β aqua complex 30. This suggests that the PNNP ligand assumes a cis-β configuration in both complexes and lends further support⁵² to our assignment of the pseudo trigonal bipyramidal geometry to the five-coordinate complex 29 (Scheme 76). Distorted trigonal-bipyramidal geometries are electronically favored for complexes of the type [MXL₄]ⁿ⁺ in which M is a d⁶ metal ion (here Ru(II)) and X is a π-donor (here Cl).⁵²

6.3 Isolated [RuCl(OH₂)(PNNP)]PF₆

The aqua complexes 30 and 31 were prepared and isolated as previously reported⁸ by adding a CH₂Cl₂ solution of five-coordinate 29 to a water/2-propanol solution (1:1), followed by
evaporation of CH$_2$Cl$_2$. The $^{31}$P NMR spectrum of the yellow-orange solid in CDCl$_3$ showed the signals of 30 and 31 in an approximate 7:3 ratio as previously observed. The signals of the trans isomer 31 appear as a sharp AX pattern (27% of the total intensity) at δ 52.2 and 44.2, which indicates slow or no dissociation of the aqua ligand, and the diastereomeric composition remains constant over 6 h. In contrast, the cis-β isomer 30 (64%) gives broad doublets at δ 69.2 and 46.0, and low-intensity, featureless signals at δ 60.4 and 51.1 are assigned to five-coordinate 29 (9%).

The observation that the cis-β aqua complex 30 dissociates to a small extent in carefully dried CDCl$_3$ contrasts with an earlier report, in which 30 was found to be stable in CDCl$_3$. We conclude that the solvents used in the earlier study contained a substantially larger amount of adventitious water than in the present case. Accordingly, the signals of the cis-β isomer 30 sharpen up upon addition of water (10 equiv) to the CDCl$_3$ solution (Table 9), and, to some extent, in aged samples (24 h).

For comparison with the detailed solution studies described above, the isomer mixture of 30 and 31 was then dissolved in carefully dried CD$_2$Cl$_2$, and a $^{31}$P NMR spectrum was recorded immediately. The products observed under these conditions are the cis-β isomer 30 (61%), five-coordinate 29 (31%), and the trans aqua complex 31 (8%). The signals of 29 and 30 are broad as these species are in chemical exchange in CD$_2$Cl$_2$ at room temperature (see above). Five-coordinate 29, as well as some minor, unknown impurities, were converted to the aqua complexes 30 (87%) and 31 (13%) upon addition of water (10 equiv). The equilibration of the 7:3 isomeric mixture of 30 and 31 is a very interesting result, as it shows that the trans aqua complex 31 undergoes dissociation in CD$_2$Cl$_2$, too. However, the process is slow on the NMR time scale, as indicated by the absence of exchange involving 31 under these conditions (Figure 35).

Overall, the $^{31}$P NMR data show that the cis aqua complex 30 is more labile than the trans isomer 31, in agreement with the higher trans influence of phosphine as compared to the chloro ligand. This is consistent with the earlier observation that the aqua ligand trans to the phosphine in cis-β-[Ru(OH)$_2$(PNNP)]$^{2+}$ is much more labile than the one trans to the imine. Furthermore, the solvent affects both the rate of water dissociation and the position of the equilibria between 29, 30, and 31. Thus, we find now that the trans isomer 31 is more inert in CDCl$_3$ than in CD$_2$Cl$_2$, which was not noticed previously as the NMR spectra were recorded in CDCl$_3$ only. Also, the equilibria in Scheme 76 are less shifted toward 29 in CDCl$_3$ than in CD$_2$Cl$_2$. These observations suggest that dichloromethane plays a role in the stabilization of the five-coordinate complex 29, its higher polarity with respect to chloroform being the most straightforward explanation.
An intriguing issue concerning the nature of the chloride-abstracted species \([\text{RuCl}(\text{PNNP})]\text{PF}_6\) (29) emerges from the bulk of the \(^{31}\text{P}\) NMR data. As Table 9 shows, the chemical shift of the deshielded phosphine \(P_A\), which is *trans* to the aqua ligand in the *cis*-\(\beta\) complex 30, approaches its low-exchange \(\delta\) value of 62.8 from higher frequencies, which strongly suggests that the exchange partner is a species with a higher \(\delta\) value. This is inconsistent with the corresponding chemical shift of \(P_A\) in 29, which is lower (\(\delta\) 60.5). Therefore, we suspect that a further species is present in solution, which is either in fast exchange or in low concentration and hence remains undetected. Future investigations will address the existence and nature of such a species.

An X-ray study of *cis*-\(\beta\)-[RuCl(OH\(_2\))(PNNP)]PF\(_6\) (30) complements the solution study. X-ray quality crystals were obtained during the author’s Master’s thesis,\(^{253}\) while trying to crystallize the five-coordinate complex 29 at low temperature, in the presence of adventitious water.\(^{237,250,253}\) Figure 38 shows a comparison between the ORTEP plots of the alkylidene \(\beta\)-ketoester adduct 7a (discussed in chapter 4) and the aqua complex 30. Both complexes feature a *cis*-\(\beta\) configuration. The conformation of the PNNP ligand is similar in both complexes, however, there is a profound difference in the Ru–O(1) and Ru–P(2) bond lengths. In the monocationic aqua complex (30), the Ru–O(1) bond is considerably longer than in dicationic 7a (2.215(2) vs 2.172(2) Å), which indicates a weaker bond to the oxygen donor in 30. In return, the Ru–P(2) bond is shortened in complex 30 (2.2437(6) vs 2.2692(8) Å). The reduced strength of the oxygen donor coordination in the monocationic complex 30 is in agreement with the kinetic data obtained in solution, which show a more labile coordination of the aqua ligand.

The successful isolation of the *cis*-aqua complex 30 confirms that [RuCl(PNNP)]\(^+\) (29) is relatively oxophilic for a late transition metal (see section 1.1),\(^{2,24}\) although less so than the double chloride abstracted Ru / PNNP fragment, which is at the core of this thesis. The higher stability and inertness of [Ru(O–O)(PNNP)]\(^{2+}\) (7), as opposed to complexes of type [RuCl(OR\(_2\))(PNNP)]\(^+\) (R = H or Et), can be partially attributed to their double positive charge, as discussed in chapter 4. A second stabilizing factor is the chelate coordination of the unsaturated \(\beta\)-ketoesters 6 in contrast to the monodentate coordination of water or diethyl ether to monocationic complex 29.
6.4 Comparison to cis-β-[RuCl(OEt$_2$)(PNNP)]PF$_6$

Previous studies from our laboratory have shown that dichloro complex 1 reacts with (Et$_3$O)PF$_6$ (1 equiv) in dichloromethane to give a complex that was formulated as the ether adduct [RuCl(OEt$_2$)(PNNP)]PF$_6$ (32).$^5$ Prompted by recent studies on imine aziridination by Marco Ranocchiari,$^7,250$ the reaction was re-investigated by NMR spectroscopy.$^{237}$ While sharp signals were recorded for 29 and 32 at $-78$ °C (Table 9), only one broad signal at $\delta$ 41 (along with those of minor impurities) was visible in the room temperature spectrum, which shows that the dynamic mixture is more or less at its point of coalescence.$^{237}$ The chemical analogy with the cis-β aqua complex 30 suggests that the dynamic process involved is the equilibrium between five-coordinate 29 and the Et$_2$O adduct 32 (Scheme 77).

\[
\begin{align*}
\text{Ru-O(1)} &= 2.215(2) \\
\text{Ru-P(2)} &= 2.2437(6) \\
\text{Ru-O(1)} &= 2.172(2) \\
\text{Ru-P(2)} &= 2.2692(8)
\end{align*}
\]

Scheme 77: Equilibrium between five-coordinate complex 29 and its diethyl ether complex 32.

The rate of the exchange process can be roughly estimated from the frequency difference between the corresponding signals of the main exchanging species 29 and 32. At 202 MHz,
6.5 Discussion and Outlook

A difference of 1054 Hz is estimated for the high-frequency $P_A$ signals and 2800 Hz for the low-frequency $P_B$ resonances (on the basis of the sharp signals of the 202 MHz $^{31}$P NMR spectrum of 32 at −78 °C). As both signal pairs are close to their coalescence points at room temperature, the rate constant has to be close to, or in between these values, that is, around $2 \times 10^3$ s$^{-1}$. If the rate constant were considerably smaller than 1054 s$^{-1}$, the shielded $P_B$ ($\Delta \nu = 2800$ Hz between 29 and 32) would still give resolved, individual signals around room temperature. At a larger rate constant, the $P_A$ signals ($\Delta \nu = 1054$ Hz) would have passed their coalescence point and would form a sharp averaged signal at room temperature. Hence, as the exchange between five-coordinate (29) and the cis-β aqua complex 30 has a rate constant of 47(9) s$^{-1}$ at room temperature, we estimate that the corresponding process of the ether complex is faster by 1-2 orders of magnitude.

6.5 Discussion and Outlook

To the best of our knowledge, ethers form stable ruthenium phosphine complexes only if the oxygen donor is incorporated in a chelate ring.\cite{254-256} The above investigations confirm the general trend that ether adducts are less stable than aqua complexes. However, the five-coordinate complex [RuCl(PNNP)]PF$_6$ (29), exhibits similar affinity for water and Et$_2$O. In fact, both 30 and 32 undergo dissociation to a significant extent when the oxygen donor L (L = H$_2$O or Et$_2$O) is present in a 1:1 ratio to ruthenium. The most evident difference between the aqua and Et$_2$O complexes 30 and 32 is the kinetic behavior. For the exchange between five-coordinate (29) and the cis-β aqua complex 30, the rate constant was determined to be 47(9) s$^{-1}$, whereas the exchange between 29 and the ether complex 32 is 1-2 orders of magnitude faster. This indicates that the Et$_2$O adduct 32 is significantly more labile. Factors that may account for this difference are the O-H···Cl hydrogen bonding, which is only possible in the aqua complex (Figure 38),\cite{237,250,253} and the larger steric bulk of Et$_2$O as compared to water.

These conclusions are highly relevant to the recently reported aziridination of imines with ethyl diazoacetate, which is catalyzed by five-coordinate 29 and its aqua and Et$_2$O derivatives 30 and 32.\cite{246} In particular, the six-coordinate adducts 30 and 32 show similar catalytic behavior, provided that a temperature gradient between −78 and 25 °C is used with the Et$_2$O adduct 32 as catalyst. The NMR spectroscopic studies discussed above suggest that the temperature gradient is required to inhibit (thermodynamically and/or kinetically) the dissociation of 32. Therefore, the present results offer a handle to fine tune the reactivity of catalysts based on the 16-electron complex [RuCl(PNNP)]$^+$ (29) in a rational fashion.
Furthermore, this study shows that monocationic complexes containing neutral oxygen donor molecules (30, 31, and 32) are less stable and more labile than the dicationic complexes with chelating alkylidene $\beta$-ketoesters such as the catalyst-substrate adducts 7. In fact, all of the investigated monocationic complexes exist in equilibrium with pentacoordinate compound 29 (Scheme 78, a), whereas no exchange was observed for the two diastereoisomers of the dicationic methyl $\beta$-ketoester complexes 7b and 7c (Scheme 78, b; see chapter 4).

Scheme 78: Overview between exchange phenomena in monocationic and dicationic Ru / PNNP complexes.

Since slow product displacement from the dicationic Ru / PNNP fragment has proven to be problematic in Diels-Alder and Ficini reactions (Scheme 78, c; see section 4.3), investigating the more labile monocationic species with single point binding dienophiles seems viable. However, the well defined structure of the catalyst-substrate adduct 7a would be lost in this approach. Thus, it would remain to be investigated whether the five-coordinate species 29 may coordinate single point binding dienophiles in a way that provides a similarly effective shielding as in complexes of type 7.
General Conclusion and Outlook

The application of the Ru / PNNP complex \([\text{Ru(OEt}_2\text{)}_2\text{(PNNP)}][\text{PF}_6]_2\) 2 in Lewis acid-catalyzed transformations on alkylidene \(\beta\)-ketoesters represents a breakthrough in the chemistry of these challenging and scarcely explored substrates. The Diels-Alder and Ficini cycloadditions are performed under mild conditions and can be conveniently run at room temperature or 55 °C, respectively (Scheme 79). The protocols yield a large number of versatile bicyclic products, featuring quaternary all-carbon stereocenters, with high yield and enantioselectivity. Most of these products have not been reported before, not even as racemates. The application of the protocols for the synthesis of estrone derivatives, featuring an ester group as a synthetic handle at the C-18 position, and for the preparation of Ficini product-based ligands demonstrates the synthetic usefulness of the system. In this context, one should remember that the absence of a background reaction with poorly reactive dienophiles, as observed in the case of the reaction of alkylidene \(\beta\)-ketoesters with dienes and ynamides, is considered to be an unfavorable basis for highly enantioselective catalytic Diels-Alder reactions.\(^{119}\)

The hydride abstraction reaction from stable enolato complexes 5 represents an activation method for the catalytic system that gives fast and clean access to the well defined catalyst-substrate adduct complexes \([\text{Ru}(6)(\text{PNNP})]^{2+}\) (7), as an alternative to the reaction of 2 with the alkylidene \(\beta\)-ketoesters 6. The d\(^6\) low spin configuration of complexes 7 renders them stable enough to perform detailed studies on the stereochemistry and reactivity of the catalytic system. The investigations revealed that the two coordination sites of the alkylidene \(\beta\)-ketoester are differentiated based on their electronic and steric properties, and that the large tert-butyl ester moiety is vital for diastereoselective substrate coordination and, therefore, for the enantioselectivity of the catalytic reaction. These insights make the stereochemical outcome of the Diels-Alder and Ficini reactions highly predictable.

The special aptitude of the Ru / PNNP fragment for the activation of unsaturated \(\beta\)-ketoesters is most probably related to its dicationic nature and to the combination of hard (N) and soft (P) donors. The resulting highly oxophilic, though mild Lewis acid is able of activating these sensitive and poorly reactive substrates without triggering undesired side-reactions such as polymerization. However, the investigations in chapter 4 have shown that the reactions are on a narrow path between low reactivity of the alkylidene \(\beta\)-ketoester and slow product release, which renders a further optimization of the system a challenging task.
In further developments, the Lewis acidity of the Ru / PNNP system may be easily tuned by variation of the substituents on the phenyl ring at the phosphorus atoms. In the majority of cases where slow product release has been identified as a problem, a slight reduction of Lewis acidity by using more electron rich substituents, like \( p \)-methoxyphenyl, might prove beneficial. Moreover, the increase in electron density in the \( \pi \)-system of the aromatic ring may improve the \( \pi-\pi \)-interactions to the coordinated substrate, thus leading to a more efficient shielding and higher enantioselectivity. Another approach to facilitate product release would be the use of monocationic complexes like 29, whose monodentate binding of oxygen donors was found to be considerably weaker. However, this radical change of strategy would sacrifice the well defined catalyst-substrate adduct structure of complexes 7.

The copper(I) and copper(II) triflate based systems used for the preparation of racemic reference compounds do not seem to show any signs of slow product release. These catalytic systems are faster, more efficient, more convenient, and less expensive than the Ru / PNNP based protocol. However, no reasonable levels of enantioselection have been observed with either copper(I) or copper(II) triflate using the standard Ph-BOX ligand.
Besides the optimization of the Ru / PNNP system, much future attention should be directed at extending the reaction scope. Many Lewis acid-catalyzed reactions, like [3+2] cycloadditions, Michael additions, and Nazarov cyclizations are suitable targets for the application of the dicationic Ru / PNNP fragment in complex 2. Also, one might consider extending the substrate scope of the already reported Diels-Alder and Ficini cycloaddition reactions to other classes of chelating enones. However, close attention has to be paid to a sufficient differentiation of the two binding sites of the substrates by either electronic or steric factors. A possible substrate class relying mainly on the latter are bulky unsaturated $\alpha$-alkoxycarbonyl lactones. In analogy to alkylidene $\beta$-ketoesters, they are prepared from their saturated analogues and might be subjected to a number of different transformations after the enantioselective cycloaddition reaction.

Since the first observation of the double chloride abstraction from complex 1, the dicationic framework in diether complex 2 has found a number of applications with both saturated and unsaturated $\beta$-ketoesters. Given a continued rational development of the system, Ru / PNNP may experience widespread application in the fields of organic synthesis and homogeneous catalysis.
7 Experimental

7.1 General Procedures

7.1.1 Chemicals

All solvents used for synthetic purposes were of puriss. p. a. grade, purchased from Fluka-Chemie AG or Armar Chemicals. The solvents for air- or moisture-sensitive manipulations were freshly distilled from an appropriate drying agent under argon (EtOH from Na/diethyl phthalate; toluene from Na; CH₂Cl₂ from CaH₂; Et₂O, THF, hexane and pentane from Na/benzophenone). Deuterated solvents for NMR spectroscopy were purchased from Cambridge Isotope Laboratories (CD₂Cl₂) or Armar Chemicals (CDCl₃). For sensitive compounds, CD₂Cl₂ was dried by heating under reflux for 12 h over CaH₂, then purified by distillation and degassed by three freeze-pump-thaw cycles. Triethoxy oxonium hexafluorophosphate (stabilized with 10% diethyl ether) was purchased from Aldrich and used without further purification. 2,3-Dimethylbutadiene was stirred over CaH₂ for 6 h and distilled prior to use. Cyclopentadiene was freshly cracked prior to use. The purities of the applied copper catalysts are as follows: 24 (90%, technical grade), Cu(OTf)₂ (28) (98%), [Cu₂(µ²-O₃SCF₃)₂(µ²-η²-CH₃C₆H₅)]ₙ (99.9%). All other commercially available chemicals were obtained in puriss. p. a. grade from Fluka-Chemie AG, Aldrich-Fine Chemicals, Acros, ABCR-Chemicals, TCI-Deutschland GmbH or Strem Chemicals, and were used without further purification, unless stated otherwise.

[RuCl₂(PNNP)] (1), 1 2,3-(dimethoxy)butadiene (9), 257 2,3-(dibenzyloxy)butadiene (10), 258 Dane’s diene (7-methoxy-4-vinyl-1,2-dihydronaphthalene (14)) and ethynyl(phenyl)sulfane (23) 260 were prepared according to known literature procedures. Ethyl 2-benzoylacrylate (6f) was prepared by a slightly modified literature procedure. 261 Ethyl 3-oxo-3-phenylpropanoate and paraformaldehyde (3 equiv) were heated at reflux under a protective gas atmosphere for 2 h, and then for additional 2 h after adding another 2 equivalents of paraformaldehyde.

7.1.2 Techniques and Instruments

All manipulations with air or moisture sensitive materials were carried out at a vacuum/argon line with standard Schlenk techniques, or in a glovebox (MBRAUN MB-150B- G-II) under an atmosphere of purified nitrogen.
NMR: The $^1$H, $^{13}$C{$^1$H}, $^{19}$F and $^{31}$P{$^1$H} NMR spectra were measured on the following instruments (frequencies in MHz): Bruker Avance AC 200 ($^1$H, 200.1; $^{19}$F, 188.3), Bruker Avance DPX 250 ($^1$H, 250.1; $^{13}$C{$^1$H}, 62.5; $^{31}$P{$^1$H}, 101.3), Bruker Avance DPX 300 ($^1$H, 300.1; $^{13}$C{$^1$H}, 75.5; $^{31}$P{$^1$H}, 121.5), Bruker Avance DPX 400 ($^1$H, 400.1; $^{13}$C{$^1$H}, 100.6; $^{31}$P{$^1$H}, 162.0), Bruker Avance DPX 500 ($^1$H, 500.2; $^{13}$C{$^1$H}, 125.8; $^{31}$P{$^1$H}, 202.5), and Bruker Avance DPX 700 ($^1$H, 700.1; $^{13}$C{$^1$H}, 176.0; $^{31}$P{$^1$H}, 283.4). Two-dimensional and variable-temperature NMR spectra were recorded on the Bruker Avance DPX 500 or DPX 700 instruments. $^1$H and $^{13}$C positive chemical shifts $\delta$ (in ppm) are downfield from tetramethylsilane, and are referenced to the residual solvent signal. $^{19}$F NMR signals are referenced to external CFCl$_3$, and $^{31}$P NMR signals to external 85% H$_3$PO$_4$. Coupling constants $J$ are given in Hertz. If not specified, $J$ represents $J_{H,H}$. The multiplicity is denoted by the following abbreviations: s: singlet; d: doublet; t: triplet; q: quartet; sept: septet; m: multiplet; br: broad. Chiral GC: Enantiomeric excesses of compounds 11a-c and 12c were determined by chiral GC on a Thermo Finnigan TraceGC ultra with a Thermo Finnigan AS2000 autosampler. Column: Supelco $\beta$-DEX 120 (30 m x 0.25 mm, film 0.25 $\mu$m). Inlet: Split injector (42 mL/min, 200 °C). Carrier: Helium (1.4 mL/min). Detector: FID (Air/H$_2$ 350/35, 250 °C). Analytic HPLC: Enantiomeric excesses of all other compounds were determined on a Hewlett-Packard 1050 Series or an Agilent 1100 Series with UV/VIS detection. The applied column (Daicel Chiralcel OD-H or AD-H), flow rate (in mL/min), ratio of the eluents ($n$-hexane and 2-propanol), wavelength and sample injection volume (in $\mu$L, sample concentration 1 - 3 mg/mL) are specified for each compound. Preparative HPLC: A Gilson system with the modules 306 Pump, 806 Manometric Module, UV/VIS-156 detector and FC 204 Fraction Collector was used with a Daicel Chiralcel OJ column. MS: EI-, ESI- and MALDI-MS were measured by the MS-service of the Laboratory of Organic Chemistry (ETH Zurich). M.p.: Melting points were determined on a Büchi Melting Point B-540 apparatus and are uncorrected. EA: Elemental analyses were carried out by the Laboratory of Microelemental Analysis (ETH Zurich); all measurements are within a deviation of ± 0.4 of the calculated values. Polarimeter: Perkin Elmer 341; cell 1 dm, solvent CHCl$_3$, c in g/100 mL. IR: Infrared spectra were recorded on a Perkin-Elmer BX II using ATR FT-IR technology and are reported as absorption maxima in cm$^{-1}$. Crystallography: X-ray structural measurements were carried out by Raphael Aardoom and Katrin Niedermann. Intensity data of single crystals glued to a glass capillary were collected at the given temperature (usually 100 K) on a Bruker SMART APEX platform with CCD detector and graphite monochromated Mo-K$_{\alpha}$ radiation ($\lambda = 0.71073$ Å). The Program SMART served for data collection; integration was performed with the software SAINT (SAINT+, Software for CCD Diffractometers, v. 6.01; Bruker AXS, Inc., Madison, WI, 2001 and SAINT, v. 6.02.).
7 Experimental

The structures were solved by direct methods or Patterson methods, respectively, using the program SHELXS 97\textsuperscript{262}. The refinement and all further calculations were carried out using SHELXL 97.\textsuperscript{263} All non-hydrogen atoms were refined anisotropically using weighted full-matrix least squares on F\textsuperscript{2}. The hydrogen atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. In the end, absorption correction was applied (SADABS)\textsuperscript{264} and weights were optimized in the final refinement cycles. The absolute configuration of chiral compounds was determined on the basis of the Flack parameter\textsuperscript{265,266} or by derivatization with (1\textit{S},4\textit{R})-champhanic chloride. The standard uncertainties (s.u.) are rounded according to the "Notes for Authors" of Acta Crystallographica.\textsuperscript{267}

7.2 Synthesis of Substrates and Reagents

7.2.1 Unsaturated \(\beta\)-Ketoesters

**Preparation of the Cyclic Unsaturated \(\beta\)-Ketoesters 6a-e.** The unsaturated \(\beta\)-ketoesters 6a-e were obtained from their saturated analogues using a selenide oxidation / elimination reaction.\textsuperscript{62} In order to minimize polymerization and maximize product yields, the purification of the reaction products by distillation should be performed rapidly and at minimal pressure. Because of this distillation step, batch sizes of under 1 g should be avoided. Furthermore, it is crucial to achieve complete conversion of the saturated \(\beta\)-ketoesters 3, which are difficult to remove completely under the rapid distillation conditions. Thus, an excess of sodium hydride (1.5 equiv), perfectly anhydrous conditions (water leads to reprotoonation and reformation of compounds 3) and a slight excess of phenyl selenyl chloride (1.05 - 1.1 equiv) are required in the selenylation step. In contrast, the oxidation step is generally uncomplicated and insensitive to a larger excess of hydrogen peroxide (up to 6 equiv). In the case of unsaturated \(\beta\)-ketoester 6a, residues of 3a can be reduced by recrystallization from pentane. To that end, 6a was dissolved in warm pentane (40 °C) and the solution was placed in the freezer (–17 °C) for several hours, after which the cold solution was removed from solid 6a with a syringe. All isolated unsaturated \(\beta\)-ketoesters were stored in a glovebox under a nitrogen atmosphere at –17 °C.

2-\textit{tert}-Butoxycarbonyl-2-cyclopenten-1-one (6a): \(^1\text{H} \text{NMR} (300 \text{ MHz, CDCl}_3) \delta 8.29 (t, J = 2.5 \text{ Hz}, 1\text{H}), 2.76 – 2.63 (m, 2\text{H}), 2.58 – 2.48 (m, 2\text{H}), 1.54 (s, 9\text{H}).

2-Ethoxycarbonyl-2-cyclopenten-1-one (6b): \(^1\text{H} \text{NMR} (300 \text{ MHz, CDCl}_3) \delta 8.41 (t, J = 2.7 \text{ Hz}, 1\text{H}), 4.32 (q, J = 7.1 \text{ Hz}, 2\text{H}), 2.82 – 2.69 (m, 2\text{H}), 2.52 - 2.60 (m, 2\text{H}), 1.35 (t, J = 7.1 \text{ Hz}, 3\text{H}).
2-Methoxycarbonyl-2-cyclopenten-1-one (6c): ¹H NMR (300 MHz, CDCl₃) δ 8.42 (t, J = 2.8 Hz, 1H), 3.80 (s, 3H), 2.82 – 2.69 (m, 2H), 2.60 – 2.48 (m, 2H).

2-Ethoxycarbonyl-2-cyclohexen-1-one (6d): ¹H NMR (250 MHz, CDCl₃) δ 7.67 (t, J = 4.1 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 2.70 - 2.45 (m, 4H), 2.25 - 1.89 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H).

2-tert-Butoxycarbonyl-2-cyclohexen-1-one (6e): ¹H NMR (300 MHz, CDCl₃) δ 7.62 - 7.44 (t, J = 4.1 Hz, 1H), 2.55 - 2.43 (m, 4H), 2.12 - 1.99 (m, 2H), 1.57 - 1.50 (s, 9H).

7.2.2 Ynamides

Preparation of Ynamides (16a-k): All ynamides were prepared from the alkynyl bromides via the copper sulfate-catalyzed amidation reaction published by Hsung.²⁰⁰ Typical yields range from 70-90%.

N-Benzyl-N-(cyclohexylethynyl)-4-methylbenzenesulfonamide (16a): ¹H NMR (300 MHz, CDCl₃) δ 7.77 (d, J = 8.3 Hz, 2H), 7.40 – 7.24 (m, 7H), 4.45 (s, 2H), 2.47 (s, 3H), 2.39 (m, 1H), 1.74 – 1.15 (m, 10H).

N-(Cyclohexylethynyl)-N,4-dimethylbenzenesulfonamide (16b): ¹H NMR (500 MHz, CDCl₃) δ 7.81 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 3.04 (s, 3H), 2.49 (s, 3H), 2.46 (m, 1H), 1.83 – 1.73 (m, 2H), 1.72 – 1.65 (m, 2H), 1.56 – 1.26 (m, 6H).

N-Benzyl-4-methyl-N-(phenylethynyl)benzenesulfonamide (16c): ¹H NMR (200 MHz, CDCl₃) δ 7.85 (d, J = 8.3 Hz, 2H), 7.48 – 7.13 (m, 12H), 4.63 (s, 2H), 2.49 (s, 3H).

N,4-Dimethyl-N-(phenylethynyl)benzenesulfonamide (16d): ¹H NMR (300 MHz, CDCl₃) δ 7.87 (d, J = 8.2 Hz, 2H), 7.44 – 7.29 (m, 7H), 3.18 (s, 3H), 2.48 (s, 3H).

N-Methyl-N-(phenylethynyl)methanesulfonamide (16e): ¹H NMR (300 MHz, CDCl₃) δ 7.43 (m, 2H), 7.36 – 7.29 (m, 3H), 3.32 (s, 3H), 3.15 (s, 3H).

4-Methoxy-N-methyl-N-(phenylethynyl)benzenesulfonamide (16f): ¹H NMR (250 MHz, CDCl₃) δ 7.92 (d, J = 8.8 Hz, 2H), 7.51 – 7.16 (m, 5H), 7.06 (d, J = 8.8 Hz, 2H), 3.92 (s, 3H), 3.18 (s, 3H).

N-Benzyl-4-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide (16g): ¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, J = 8.3 Hz, 2H), 7.33 (m, 7H), 4.48 (s, 2H), 2.47 (s, 3H), 2.19 (t, J = 7.0 Hz, 2H), 1.43 – 1.16 (m, 8H), 0.90 (t, J = 7.1 Hz, 3H).
N-Methyl-N-(oct-1-yn-1-yl)methanesulfonamide (16h): $^1$H NMR (250 MHz, CDCl$_3$) δ 3.18 (s, 3H), 3.06 (s, 3H), 2.37 – 2.20 (m, 2H), 1.60 – 1.02 (m, 8H), 0.91 (t, J = 6.3 Hz, 3H).

4-Methoxy-N-methyl-N-(oct-1-yn-1-yl)benzenesulfonamide (16i): $^1$H NMR (250 MHz, CDCl$_3$) δ 7.86 (d, J = 8.9 Hz, 2H), 7.04 (d, J = 8.9 Hz, 2H), 3.92 (s, 3H), 3.04 (s, 3H), 2.26 (t, J = 6.8 Hz, 2H), 1.54 – 1.10 (m, 8H), 0.91 (t, J = 6.1 Hz, 3H).

N-(3-(Benzyloxy)prop-1-yn-1-yl)-N,4-dimethylbenzenesulfonamide (16j): $^1$H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, J = 8.3 Hz, 2H), 7.42 – 7.31 (m, 7H), 4.56 (s, 2H), 4.32 (s, 2H), 3.12 (s, 3H), 2.47 (s, 3H).

N-Benzyl-N-(4-((tert-butyldimethylsilyl)oxy)but-1-yn-1-yl)-4-methylbenzenesulfonamide (16k): $^1$H NMR (300 MHz, CDCl$_3$) δ 7.76 (d, J = 8.2 Hz, 2H), 7.30 (m, 7H), 4.46 (s, 2H), 3.57 (t, J = 7.3 Hz, 2H), 2.46 (s, 3H), 2.41 (d, J = 7.3 Hz, 2H), 0.88 (s, 9H), 0.03 (s, 6H).

7.3 Synthesis of Complexes

2-Methoxycarbonylcyclopentanoato{N,N’-bis[2-(diphenylphosphino)benzylidene]diaminocyclohexane}ruthenium(II) Hexafluorophosphate (5b + 5c.) A solution of 1 (700 mg, 0.8 mmol, 1 equiv) and (Et$_3$O)PF$_6$ (441 mg, 1.6 mmol, 2 equiv) in CH$_2$Cl$_2$ (33 mL) was stirred at room temperature for 16 h. Then, 2-methoxycarbonylcyclopentanone (3c) (119 µL, 0.961 mmol, 1.2 equiv) in CH$_2$Cl$_2$ (3 mL) was added, and the resulting solution was stirred for 3 h at room temperature. After adding triethylamine (126 µL, 0.91 mmol, 1.13 equiv) and stirring for further 15 min, the solvent was evaporated under reduced pressure. The crude mixture of diastereoisomers was subjected to column chromatography on silica starting with CH$_2$Cl$_2$ as eluent. Under these conditions only (OC-6-42-A-(S,S))-5b is eluted. When the solvent leaving the column was almost colorless, 0.25% of methanol were added to the eluent and elution was continued. The color of the eluent leaving the column intensified once more and the minor diastereoisomer (OC-6-43-A-(S,S))-5c was obtained. The intermediate fractions were checked for purity by $^{31}$P NMR spectroscopy and the clean fractions were added to 5b or 5c respectively. After evaporation of the solvent and drying under high vacuum, the analytically pure products were obtained as a red crystalline solid (5b) and as an orange powder (5c). Yield: 450 mg (0.43 mmol, 54%) of 5b and 200 mg (0.191 mmol, 24%) of 5c.
Complex 5b: $^1$H NMR (500 MHz, CD$_2$Cl$_2$) $\delta$ 8.89 (s, 1H), 8.70 (d, $J = 9.0$ Hz, 1H), 7.92 – 7.78 (m, 1H), 7.77 – 7.66 (m, 2H), 7.66 – 7.53 (m, 2H), 7.53 – 7.44 (m, 3H), 7.42 – 7.14 (m, 10H), 7.07 (dt, $J = 18.0$, 7.9 Hz, 5H), 6.95 (dt, $J = 14.9$, 7.2 Hz, 4H), 6.52 (t, $J = 8.6$ Hz, 1H), 3.68 (t, $J = 9.1$ Hz, 1H), 3.20 (s, 3H), 2.52 (d, $J = 10.6$ Hz, 1H), 2.41 (d, $J = 9.9$ Hz, 1H), 2.36 – 2.22 (m, 1H), 2.17 – 2.03 (m, 2H), 1.99 – 1.88 (m, 2H), 1.87 – 1.62 (m, 3H), 1.51 – 1.36 (m, 2H), 1.36 – 1.13 (m, 2H), 0.98 – 0.81 (m, 1H). $^{31}$P{1H} NMR (101 MHz, CD$_2$Cl$_2$): $\delta$ 63.7 (d, $J_{P,P'} = 30.8$ Hz, 1P), 52.3 (d, $J_{P,P'} = 30.8$ Hz, 1P), –142.6 (sept, $J_{P,F} = 712$ Hz, 1P, PF$_6$).

$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ 193.4 (C=O), 167.5 (d, $J_{C,P} = 1.5$ Hz, 1C, COOMe), 166.8 (d, $J_{C,P} = 3.7$ Hz, 1C, C=N), 163.1 (d, $J_{C,P} = 5.1$ Hz, 1C, C=N), 139.0 – 121.0 (arom. C), 91.8, 78.4 (C-N), 51.5, 38.8, 32.3, 31.6, 28.0, 25.1, 24.1, 20.4. HRMS (ESI): Calcd. for C$_{51}$H$_{49}$N$_2$O$_3$P$_2$Ru (= M – PF$_6$) $m/z$ 901.2270, found $m/z$ 901.2258. EA: Calcd. for C$_{51}$H$_{49}$F$_6$N$_2$O$_3$P$_3$Ru·CH$_2$Cl$_2$ (1130.86): C, 55.23; H, 4.55; N, 2.48; found: C, 55.05; H, 4.55; N, 2.49.

Complex 5c: $^1$H NMR (500 MHz, CD$_2$Cl$_2$) $\delta$ 8.82 (s, 1H), 8.66 (d, $J = 9.5$ Hz, 1H), 7.86 – 7.74 (m, 1H), 7.73 – 7.61 (m, 3H), 7.61 – 7.55 (m, 1H), 7.54 – 7.47 (m, 3H), 7.45 – 7.39 (m, 1H), 7.39 – 7.27 (m, 5H), 7.20 (dd, $J = 16.3$, 7.9 Hz, 5H), 7.11 – 6.93 (m, 6H), 6.87 (t, $J = 7.0$ Hz, 2H), 6.45 (t, $J = 8.5$ Hz, 1H), 3.81 (t, $J = 10.6$ Hz, 1H), 2.63 (s, 3H), 2.47 (d, $J = 11.3$ Hz, 1H), 2.32 (d, $J = 9.6$ Hz, 1H), 2.11 – 1.82 (m, 5H), 1.82 – 1.64 (m, 3H), 1.53 – 1.32 (m, 2H), 1.31 – 1.15 (m, 2H), 0.92 – 0.75 (m, 1H). $^{31}$P{1H} NMR (101 MHz, CD$_2$Cl$_2$): $\delta$ 60.7 (d, $J_{P,P'} = 28.8$ Hz, 1P), 52.3 (d, $J_{P,P'} = 28.8$ Hz, 1P), –143.2 (sept, $J_{P,F} = 711$ Hz, 1P, PF$_6$). $^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ 191.2 (d, $J_{C,F} = 1.6$ Hz, 1C, C=O), 168.0 (COOMe), 166.7 (d, $J_{C,P} = 4.3$ Hz, 1C, C=N), 162.2 (d, $J_{C,P} = 4.9$ Hz, 1C, C=N), 91.7, 78.8, 68.8, 51.0, 39.3 (d, $J_{C,P} = 4.5$ Hz, 1C), 32.2, 31.7, 28.1, 25.1, 23.9, 19.7. HRMS (ESI): Calcd. for C$_{51}$H$_{49}$N$_2$O$_3$P$_2$Ru (= M – PF$_6$) $m/z$ 901.2270, found $m/z$ 901.2262. EA: Calcd. for C$_{51}$H$_{49}$F$_6$N$_2$O$_3$P$_3$Ru·CH$_2$Cl$_2$ (1130.86): C, 55.23; H, 4.55; N, 2.48; found: C, 54.99; H, 4.79; N, 2.48.

2-Methoxycarbonyl-2-cyclopenten-1-one{N,N'-bis[2-(di-phenylphosphino)benzylidene]cyclohexane-1,2-diamine}ruthenium(II) Bis(hexafluorophosphate) (7b and 7c). A solution of complex 5b or 5c (30 mg, 29 µmol) in CD$_2$Cl$_2$ (0.5 mL) was added to tritylium hexafluorophosphate (Ph$_3$C)PF$_6$ (11.9 mg, 30 µmol, 1.05 equiv). The color of the solution immediately changed from orange to bright yellow. The NMR spectroscopic analysis of the reaction mixture showed the formation of pure (OC-6-
42-A-(S,S))-7b or (OC-6-43-A-(S,S))-7c besides the secondary reaction product triphenylmethane (characteristic $^1$H NMR signal: $\delta$ 5.59 (s, 1H, Ph$_3$CH)).

Complex 7b: $^1$H NMR (CD$_2$Cl$_2$, 700.2 MHz): $\delta$ 8.90 (s, 1H, HC=N), 8.90 (d, $J_{P,H}$ = 9.0 Hz, 1H, HC=N), 8.48 (dd, $J$ = 2.4, 2.4 Hz, 1H), 8.00 – 7.91 (m, 2H, arom. H), 7.80 – 7.66 (m, 2H, arom. H), 7.63 – 7.57 (m, 2H, arom. H), 7.52 – 7.37 (m, 6H, arom. H), 7.29 – 7.23 (m, 5H, arom. H), 7.14 – 7.04 (m, 4H, arom. H), 7.03 – 6.93 (m, 4H, arom. H), 6.57 (br dd, $J$ = 8.8, 8.8 Hz, 1H, arom. H), 6.32 (s, 3H, CH$_3$) 3.40 (br dd, $J$ = 10.3 Hz, 1H, HC-N) 2.84 (br dd, $J$ = 22.8, 3.9 Hz, 1H), 2.78 (br d, $J$ = 10.5 Hz, 1H), 2.62 (br dd, $J$ = 22.3, 5.1 Hz, 1H), 2.40 – 2.25 (m, 2H), 2.03 – 1.82 (m, 4H), 1.76 (dddd, $J$ = 11.8, 11.8, 11.8, 2.3 Hz, 1H), 1.36 – 1.26 (m, 1H), 1.16 – 1.07 (m, 1H), 0.79 (br ddd, $J$ = 13.2, 13.2, 13.2 Hz, 1H). $^{31}$P{$^1$H} NMR (CD$_2$Cl$_2$, 202.5 MHz): $\delta$ 64.3 (d, $J_{P,P'}$ = 29.3 Hz, 1P), 50.5 (d, $J_{P,P'}$ = 29.3 Hz, 1P), −144.3 (sept, $J_{P,F}$ = 711 Hz, 2 P, PF$_6$). $^{13}$C{$^1$H} NMR (CD$_2$Cl$_2$, 176 MHz): $\delta$ 215.5 (C=O), 188.5, 169.5 (C=N), 167.1 (d, $J_{C,P}$ = 5.2 Hz, 1C, C=N), 166.8 (d, $J_{C,P}$ = 1.6 Hz, 1C, COOMe), 143.5 – 123.0 (arom. C), 77.7 (C=N), 69.6 (C=N), 56.8, 54.9, 37.5, 31.7, 31.2, 29.7, 24.7, 23.4.

Complex 7c: $^1$H NMR (CD$_2$Cl$_2$, 700.2 MHz): $\delta$ 8.90 (d, $J_{P,H}$ = 9.6 Hz, 1H, HC=N), 8.88 (s, 1H, HC=N), 8.44 (dd, $J$ = 2.4, 2.4 Hz, 1H), 7.99 – 7.90 (m, 2H, arom. H), 7.81 – 7.66 (m, 4H, arom. H), 7.63 – 7.57 (m, 2H, arom. H), 7.54 – 7.50 (m, 1H, arom. H), 7.48 – 7.42 (m, 2H, arom. H), 7.30 – 7.24 (m, 5H, arom. H), 7.14 – 7.04 (m, 4H, arom. H), 6.99 – 6.89 (m, 4H, arom. H), 6.48 (br dd, $J$ = 8.9, 8.9 Hz, 1H, arom. H), 3.46 (br dd, $J$ = 9.9, 9.9 Hz, 1H, HC-N) 2.99 – 2.89 (m, 1H), 2.95 (s, 3H, CH$_3$) 2.81 (br d, $J$ = 11.3, 1H) 2.77 (br dd, $J$ = 21.0, 5.8 Hz, 1H), 2.57 (br dd, $J$ = 17.6, 5.0 Hz, 1H), 2.40 (br dd, $J$ = 21.0, 5.7 Hz, 1H), 2.38 – 2.34 (m, 1H), 2.01 – 1.83 (m, 2H), 1.78 (ddd, $J$ = 12.6, 12.6, 12.6, 3.7 Hz, 1H), 1.38 – 1.26 (m, 1H), 1.17 – 1.07 (m, 1H), 0.78 (br ddd, $J$ = 13.3, 13.3, 13.3 Hz, 1H). $^{31}$P{$^1$H} NMR (CD$_2$Cl$_2$, 202.5 MHz): $\delta$ 62.5 (d, $J_{P,P'}$ = 29.0 Hz, 1P), 49.8 (d, $J_{P,P'}$ = 29.0 Hz, 1P), −143.4 (sept, $J_{P,F}$ = 713 Hz, 2 P, PF$_6$). $^{13}$C{$^1$H} NMR (CD$_2$Cl$_2$, 176 MHz): $\delta$ 215.6 (C=O), 188.6, 169.9 (br d, $J_{C,P}$ = 4.5 Hz, 1C, C=N), 166.6 (d, $J_{C,P}$ = 4.5 Hz, 1C, C=N), 166.6 (COOMe), 143.5 – 126.0 (arom. C), 78.0 (C=N), 69.6 (C=N), 56.8, 54.1, 37.9, 31.7, 31.2, 29.8, 24.7, 23.3.
7.4 Catalytic Reactions

Background Reaction: A CH₂Cl₂ solution (1 mL) of the unsaturated β-ketoester 6a-f (0.12 mmol, 1 equiv) and the respective diene 8, 9, 10, 14 or ynamide 16a-k (1.1 - 10 equiv, according to conditions of the Ru / PNNP-catalyzed reaction) were stirred in a sealed tube at rt (Diels-Alder) or 55 °C (Ficini reaction) overnight. TLC analysis showed that no or only minimal background reaction had occurred.

General Procedure for Racemic Products: To the above solution, copper(I) trifluoromethanesulfonate benzene complex (24) (0.12 mmol, 0.1 equiv) was added, and the mixture was stirred for 1 h. The solvent was evaporated under reduced pressure, and the oily residue was subjected to flash chromatography on silica. When determined, typical yields were in the range of 70 – 90%. For a refined protocol for copper-catalyzed reactions see page 138.

7.4.1 Catalytic Diels-Alder Reactions

7.4.1.1 General Procedure for Preliminary Experiments. A CH₂Cl₂ solution (2 mL) of [RuCl₂(PNNP)] (1) (20 mg, 0.024 mmol, 0.1 equiv) and (Et₃O)PF₆ (12.2 mg, 0.049 mmol, 0.2 equiv) was stirred at room temperature overnight. A color change from red to brown indicated the formation of the catalytically active complex. The dienophile (0.24 mmol, 1 equiv) was added as CH₂Cl₂ solution (2 mL). After 10 min, freshly cracked cyclopentadiene, 2,5-dimethylfuran, 1,2,5-trimethyl-1H-pyrrole (25), or 2,3-dimethylbutadiene (8) (10 equiv) was added, and the progress of the reaction was monitored by TLC. After completion, the reaction was quenched by addition of tetrabutylammonium chloride (20 mg, 0.072 mmol, 0.3 equiv) to deactivate the catalyst. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica. In case of cyclopentadiene, the crude ¹H NMR spectrum showed major amounts of polycyclopentadiene. Therefore, the amount of rubbery contaminants was reduced by extracting the Diels-Alder products from the crude mixture with diethyl ether (3 x 3 mL), before performing flash column chromatography.

Ethyl 5-oxo-1,4,4a,5,6,7,8,8a-octahydro-1,4-methanonaphthalene-4a-carboxylate: The reaction of 6d and cyclopentadiene gave the Diels-Alder product as a colorless oil. Yield: ca. 11 mg, ca. 0.05 mmol, ca. 20% (3:1 - 12:1 varying mixture of diastereoisomers). ¹H NMR (400 MHz, CDCl₃) characteristic signals of the minor diastereoisomer are given when they are resolved from the major diastereoisomer δ 0.87 (m, minor), 0.97 (qd, J = 13.2, 2.8 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H),
1.25 - 1.43 (m, 2H), 1.45 - 1.52 (m, minor), 1.63 - 1.67 (m, minor), 1.71 - 1.80 (m, minor), 1.82 - 2.18 (m, 3H), 2.24 - 2.37 (m, 1H), 2.45 - 2.56 (m, 2H), 2.58 (br s, 1H), 2.82 - 2.92 (m, minor), 3.01 (br, 1H, CH (bridgehead, major)), 3.11 (br, 1H, CH (bridgehead)), 3.26 (br, 1H, CH (bridgehead)), 3.40 (br, 1H, CH (bridgehead)), 6.08 - 6.14 (m, 1H, olef. H (major)), 6.22 - 6.30 (m, 3H, 1 olef. H (major) + 2 olef. H (minor)). Chiral GC: β-DEX column, 135 °C isotherm, retention times $t_R$ (major, 1) = 203.7 min, $t_R$ (minor, 1) = 206.3 min; both diastereoisomers racemic.

**Ethyl 3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoindene-3a-carboxylate:** The reaction of 6b and cyclopentadiene gave the Diels-Alder product as a colorless oil. Yield: 31.0 mg, 0.141 mmol, 58% (2:1 mixture of diastereoisomers). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.21 - 1.37 (m, 10H, CH$_3$ (major + minor) + CH$_2$ (CP-bridge, major + minor)), 1.45 - 1.65 (m, aliph. H, both diastereoisomers), 2.10 - 2.65 (m, aliph. H, both diastereoisomers), 2.70 - 2.85 (m, aliph. H, both diastereoisomers), 3.01 (br, 1H, CH (bridgehead, major)), 3.18 (m, 1H, CH (bridgehead)), 3.34 (br, 1H, CH (bridgehead, minor)), 3.47 (br, 1H, CH (bridgehead, major)), 4.00 - 4.25 (m, 4H, OCH$_2$), 6.10 - 6.16 (m, 1H, olef. H (major)), 6.24 - 6.33 (m, 3H, 1 olef. H (major) + 2 olef. H (minor)). Chiral GC: β-DEX column, 110 °C isotherm, retention times $t_R$ (major, 1) = 185.3 min, $t_R$ (major, 2) = 192.4 min, $t_R$ (minor, 1) = 203.7 min, $t_R$ (minor, 2) = 206.3 min; both diastereoisomers racemic.

**tert-Butyl 3-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoindene-3a-carboxylate:** The reaction of 6a and cyclopentadiene gave the Diels-Alder product as a yellowish oil (all amounts reduced by 50% as compared to general procedure). Yield: 23.0 mg, 0.105 mmol, 86% (1.2:1 mixture of diastereoisomers). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.25 - 1.34 (m, 2H, CH$_2$ (CP-bridge, both diastereoisomers)), 1.41 (s, 9H, $^1$Bu (major)), 1.45 (s, 9H, $^1$Bu (minor)), 1.5 - 1.7 (m, aliph. H, both diastereoisomers), 2.03 - 2.85 (m, aliph. H, both diastereoisomers), 2.98 (br, 1H, CH (bridgehead)), 3.11 (br, 1H, CH (bridgehead)), 3.26 (br, 1H, CH (bridgehead)), 3.40 (br, 1H, CH (bridgehead)), 6.08 - 6.14 (m, 1H, olef. H (major)), 6.22 - 6.30 (m, 3H, 1 olef. H (major) + 2 olef. H (minor)). Chiral GC: β-DEX column, 135 °C isotherm, retention times $t_R$ (major,
1) = 48.4 min, $t_R$ (major, 2) = 49.3 min, $t_R$ (minor, 1) = 52.2 min, $t_R$ (minor, 2) = 53.0 min; both diastereoisomers racemic.

**Ethyl 2-oxo-5-(1,2,5-trimethyl-1H-pyrrol-3-yl)cyclopentanecarboxylate (27a):** The reaction of 6b and 25 gave 27a as a slightly red oil. Yield: 55.9 mg, 0.212 mmol, 88% of racemic product. For characterization see page 139.

**Ethyl 2-(2,5-dimethylfuran-3-yl)-5-oxocyclopentanecarboxylate:** The reaction of 6b and 2,5-dimethylfuran gave a light yellow oil. Yield: 42.6 mg, 0.117 mmol, 70%. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.92 - 5.77 (s, 1H), 4.27 - 4.08 (m, 2H), 3.68 - 3.51 (td, $J$ = 11.8, 6.4 Hz, 1H), 3.18 - 3.03 (d, $J$ = 11.8 Hz, 1H), 2.61 - 2.33 (m, 2H), 2.33 - 2.17 (m, 7H), 1.98 - 1.82 (m, 1H), 1.31 - 1.22 (t, $J$ = 7.1 Hz, 3H). Chiral GC: $\beta$-DEX column, 100 °C isotherm, retention times $t_R$ = 132.1 min, $t_R$ = 140.6 min, racemic.

**1-Methoxycarbonyl-8,9-dimethyl-2-oxo-bicyclo[4.3.0]oct-8-ene:** The reaction of 2-methoxycarbonyl-2-cyclohexen-1-one and 2,3-dimethylbutadiene (8) gave the Diels-Alder product as a colorless oil. Yield: 44.6 mg, 0.189 mmol, 78%. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.84 - 3.63 (s, 3H), 2.77 - 2.63 (m, 1H), 2.61 - 2.26 (m, 4H), 2.12 - 1.94 (m, 2H), 1.92 - 1.68 (m, 4H), 1.67 - 1.62 (s, 3H), 1.61 - 1.54 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 208.2, 172.8, 123.1, 121.6, 61.6, 52.3, 38.1, 37.5, 33.8, 33.5, 26.8, 24.0, 19.0, 18.5. Chiral GC: $\beta$-DEX column, 126 °C isotherm, retention times $t_R$ = 176.3 min (minor), $t_R$ = 178.8 min (major); 43% ee.

**1-Methoxycarbonyl-3,4-dimethyl-9-oxo-bicyclo[4.3.0]oct-3-ene (11c):** See page 126.

### 7.4.1.2 General Procedure for 2,3-dimethylbutadiene (8).
A CH$_2$Cl$_2$ solution (1 mL) of [RuCl$_2$(PNNP)] (1) (10 mg, 0.012 mmol, 0.1 equiv) and (Et$_3$O)PF$_6$ (7 mg, 0.025 mmol, 0.21 equiv) was stirred at room temperature overnight. A color change from red to brown indicated the formation of the catalytically active complex. The dienophile (0.12 mmol, 1 equiv) was added as CH$_2$Cl$_2$ (0.5 mL, Method A) or diethyl ether (1 mL, Method B) solution. After 10 min, 2,3-dimethylbutadiene (8) (0.137 mL, 1.2 mmol, 10 equiv) was added, and the progress of the reaction was monitored by TLC. After completion, the reaction was quenched by addition of tetrabutylammonium chloride (10 mg, 0.036 mmol, 0.3 equiv) to deactivate the catalyst. The solvent was evaporated under reduced pressure, and the oily residue was subjected to flash chromatography on silica. Yields refer to isolated products.
1-tert-Butoxycarbonyl-3,4-dimethyl-9-oxo-bicyclo[4.3.0]oct-3-ene (11a): The reaction of 6a and 8 gave 11a as a colorless oil. Yield: 26.2 mg, 0.099 mmol, 82% (Method B: 52%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.46 (s, 9H, C(CH$_3$)$_3$), 1.65 (s, 3H, CCH$_3$), 1.68 (s, 3H, CCH$_3$), 1.66 - 1.72 (m, 1H, H$_{aliph}$), 1.83 (m, 1H, H$_{aliph}$), 2.03 - 2.11 (m, 2H, H$_{aliph}$), 2.24 - 2.50 (m, 4H, H$_{aliph}$), 2.84 (m, 1H, CH$_2$CHCH$_2$). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 19.0, 19.5, 26.2, 28.3, 30.8, 33.1, 36.6, 38.9, 60.8, 81.7, 122.9, 123.8, 171.3, 214.4. IR (liquid film, cm$^{-1}$): 1723.9 (s, carbonyl C=O), 1745.4 (s, carbonyl C=O), 2916.3 (m, C-H). Chiral GC: $\beta$-DEX column, 120 °C isotherm, retention times $t_R$ (major) = 158.1 min, $t_R$ (minor) = 160.9 min; 67% ee (Method B: 84%). $[\alpha]_D^{20}$ = –96.4 (c = 1.0, CHCl$_3$). HRMS (EI): Calcd. for C$_{16}$H$_{24}$O$_3$ m/z 264.0410, found m/z 264.1099. EA: Calcd. for C$_{16}$H$_{24}$O$_3$ (264.36): C, 72.69; H, 9.15; found: C, 72.75; H, 9.21.

1-Ethoxycarbonyl-3,4-dimethyl-9-oxo-bicyclo[4.3.0]oct-3-ene (11b): The reaction of 6b and 8 gave 11b as a colorless oil. Yield: 25.0 mg, 0.110 mmol, 87% (Method B: 59%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.27 (t, J = 7.1 Hz, 3H, CH$_2$CH$_3$), 1.65 (s, 3H, CCH$_3$), 1.68 (s, 3H, CCH$_3$), 1.66 - 1.72 (m, 1H, aliph. $H$, 1.85 (d, J = 17.2 Hz, 1H, aliph. $H$, 2.02 - 2.11 (m, 2H, aliph. $H$, 2.24 - 2.55 (m, 4H, aliph. $H$, 2.93 (m, 1H, CH$_2$CHCH$_2$), 4.20 (m, 2H, OCH$_2$CH$_3$). $^{13}$C NMR (76 MHz, CDCl$_3$) $\delta$ 14.1, 18.8, 19.1, 25.7, 30.1, 32.2, 36.3, 38.1, 59.7, 61.2, 122.0, 123.2, 171.5, 213.7. IR (liquid film, cm$^{-1}$): 1722.5 (s, carbonyl C-O), 1746.5 (s, carbonyl C-O), 2910.8 (m, C-H). Chiral GC: $\beta$-DEX column, 120 °C isotherm, retention times $t_R$ (major) = 164.1 min, $t_R$ (minor) = 167.3 min; 60% ee (Method B: 60%). $[\alpha]_D^{20}$ = –140.1 (c = 1.0, CHCl$_3$). HRMS (EI): Calcd. for C$_{14}$H$_{20}$O$_3$ m/z 236.1407, found m/z 236.1409. EA: Calcd. for C$_{14}$H$_{20}$O$_3$ (236.31): C, 71.16; H, 8.53; found: C, 71.17; H, 8.61.

1-Methoxycarbonyl-3,4-dimethyl-9-oxo-bicyclo[4.3.0]oct-3-ene (11c):$^{57}$ The reaction of 6c and 8 gave 11c as a colorless oil. Yield: 23.0 mg, 0.105 mmol, 86% (Method B: 67%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.65 (s, 3H, CCH$_3$), 1.68 (s, 3H, CCH$_3$), 1.66 - 1.72 (m, 1H, aliph. $H$, 1.84 (d, J = 17.7 Hz, 1H, aliph. $H$, 2.02 - 2.11 (m, 2H, aliph. $H$, 2.24 - 2.55 (m, 4H, aliph. $H$, 2.89 (m, 1H, CH$_2$CHCH$_2$), 3.72 (s, 3H, OCH$_3$). $^{13}$C NMR (76 MHz, CDCl$_3$) $\delta$ 18.8, 19.1, 25.7, 30.1, 32.2, 36.3, 38.1, 52.5, 59.7, 121.9, 123.6, 172.0, 213.6. IR (liquid film, cm$^{-1}$): 1727.4 (s, carbonyl C-O), 1748.9 (s, carbonyl C-O), 2910.7 (m, C-H). Chiral GC: $\beta$-DEX column, 115 °C isotherm, retention times $t_R$ (major, $S,S$) = 180.0 min, $t_R$ (minor, $R,R$) = 182.5 min; 69% ee (Method B: 67%). $[\alpha]_D^{20}$ = –128.8 (c = 1.0, CHCl$_3$). HRMS (EI): Calcd. for C$_{15}$H$_{18}$O$_3$ m/z 222.1251, found m/z 222.1252.
The absolute configuration of the major enantiomer is (1S,6S), as determined by reduction to alcohol 18a and esterification with (1S,4R)-camphanic acid chloride to give a diastereomeric mixture that was separated by preparative HPLC, followed X-ray analysis of the minor (1S,4R,1’R,6’R,9’R) diastereoisomer (see page xxiv).

7.4.1.3 General Procedure for 2,3-dimethoxybutadiene (9). A CH$_2$Cl$_2$ solution (1 mL) of [RuCl$_2$(PNNP)] (1) (10 mg, 0.012 mmol, 0.1 equiv) and (Et$_3$O)PF$_6$ (7 mg, 0.025 mmol, 0.21 equiv) was stirred at room temperature overnight. A color change from red to brown indicated the formation of the catalytically active complex. The dienophile (0.12 mmol, 1 equiv) was added as diethyl ether solution (1 mL, Method B). After 10 min, 2,3-dimethoxybutadiene (9) (0.12 mmol, 13.8 mg, 15 µL, 1 equiv) was added via microsyringe. The diene addition was repeated after 4 and 8 h. The progress of the reaction was monitored by TLC. After completion, the reaction was quenched by addition of tetrabutylammonium chloride (10 mg, 0.036 mmol, 0.3 equiv) to deactivate the catalyst. The solvent was evaporated under reduced pressure, and the oily residue was subjected to flash chromatography on silica. Yields refer to isolated products.

1-tert-Butoxycarbonyl-3,4-dimethoxy-9-oxo-bicyclo[4.3.0]-oct-3-ene (12a): The reaction of 6a and 9 gave 12a as a light yellow oil. Yield: 30.5 mg, 0.103 mmol, 86%. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.45 (s, 9H, OC(CH$_3$)$_3$), 1.65 - 1.85 (m, 1H, aliph. H), 2.01 - 2.55 (m, 6H, aliph. H), 2.76 (d, $J = 17.1$ Hz, 1H, aliph. H), 2.91 (m, 1H, CH$_2$CHCH$_2$), 3.61 (s, 6H, OCH$_3$). $^{13}$C NMR (76 MHz, CDCl$_3$) $\delta$ 24.7, 25.5, 26.9, 27.9, 35.9, 38.3, 57.47, 57.53, 60.3, 81.9, 134.2, 136.0, 169.8, 212.5. IR (liquid film, cm$^{-1}$): 1721.8 (s, carbonyl C-O), 1746.0 (s, carbonyl C-O), 2975.8 (m, C-H). HPLC: Chiralcel AD-H (hexane/i-PrOH 90/10, flow rate 0.6 mL/min, $\lambda = 210.8$ nm), retention times $t_R$ (minor) = 11.9 min, $t_R$ (major) = 19.3 min; 64% ee. $[\alpha]_{D}^{20} = -93.2$ (c = 1, CHCl$_3$). HRMS (EI): Calcd. for C$_{16}$H$_{24}$O$_5$ m/z 296.1619, found m/z 296.1623.

3,4-Dimethoxy-1-ethoxycarbonyl-9-oxobicyclo[4.3.0]oct-3-ene (12b): The reaction of 6b and 9 gave 12b as a light yellow oil. Yield: 29.7 mg, 0.111 mmol, 92%. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.27 (t, $J = 7.0$ Hz, 3H, OCH$_2$CH$_3$), 1.70-1.85 (m, 1H, aliph. H), 2.09 (d, 2H, $J = 19.0$ Hz, aliph. H), 2.23 (d, $J = 17.1$ Hz, 1H, aliph. H), 2.31 - 2.59 (m, 3H, aliph. H), 2.84 (d, $J = 17.1$ Hz, 1H, aliph. H), 2.98 (m, 1H, CH$_2$CHCH$_2$), 3.61 (s, 6H, OCH$_3$), 4.12 (q, $J = 7.1$ Hz, 2H, OCH$_2$CH$_3$). $^{13}$C NMR (76 MHz, CDCl$_3$) $\delta$ 14.1, 24.7, 25.5, 26.8, 36.0, 38.1, 57.49, 57.55, 59.6, 61.7, 133.9, 136.1, 170.6, 212.1. IR (liquid film, cm$^{-1}$): 1728.8 (s, carbonyl C-O), 1754.5 (s, carbonyl C-O), 2975.8 (m, C-H). HPLC: Chiralcel AD-H (hexane/i-PrOH 90/10, flow rate 0.6 mL/min, $\lambda = 210.8$ nm), retention times $t_R$ (minor) = 11.9 min, $t_R$ (major) = 19.3 min; 64% ee. $[\alpha]_{D}^{20} = -93.2$ (c = 1, CHCl$_3$). HRMS (EI): Calcd. for C$_{16}$H$_{24}$O$_5$ m/z 296.1619, found m/z 296.1623.
3.4-Dimethoxy-1-methoxycarbonyl-9-oxobicyclo[4.3.0]oct-3-ene (12c): The reaction of 6c and 9 gave 12c as a light yellow oil. Yield: 19.1 mg, 0.075 mmol, 62%. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.70 - 1.85 (m, 1H, aliph. H), 2.09 (m, 2H, aliph. H), 2.24 (dt, \(J = 17.1, 2.1\) Hz, 1H, aliph. H), 2.30 - 2.60 (m, 3H, aliph. H), 2.84 (m, 1H, aliph. H), 2.99 (m, 1H, CH\(_2\)CHCH\(_2\)), 3.61 (s, 6H, OCH\(_3\)), 3.77 (s, 3H, CO\(_2\)C\(_6\)H\(_5\)). \(^13\)C NMR (76 MHz, CDCl\(_3\)) \(\delta\) 25.2, 25.9, 27.2, 35.5, 38.5, 53.2, 57.9, 58.0, 60.1, 134.1, 136.5, 171.5, 212.5. IR (liquid film, cm\(^{-1}\)): 1727.3 (s, carbonyl C-O), 1748.5 (s, carbonyl C-O), 2951.7 (m, C-H). Chiral GC: \(\beta\)-DEX column, 135 °C isotherm, retention times \(t_R \) (major) = 188.3 min, \(t_R \) (minor) = 190.3 min; 66% ee. \([\alpha]_{20}^D\) = –97.5 (c = 0.93, CHCl\(_3\)). HRMS (EI): Calcd. for C\(_{13}\)H\(_{18}\)O\(_5\) m/z 254.1149, found m/z 254.1146.

7.4.1.4 General Procedure for 2,3-(dibenzylxylo)butadiene (10) and Dane’s Diene (14). A CH\(_2\)Cl\(_2\) solution (1 mL) of [RuCl\(_2\)(PNNP)] (1) (10 mg, 0.012 mmol, 0.1 equiv) and (Et\(_3\)O)PF\(_6\) (7 mg, 0.025 mmol, 0.21 equiv) was stirred at room temperature overnight. A color change from red to brown indicated the formation of the catalytically active complex. The dienophile (0.12 mmol, 1 equiv) was added as a diethyl ether solution (1 mL, Method B). After 10 min, 2,3-(dibenzylxylo)butadiene (10) (48.1 mg, 0.18 mmol, 1.5 equiv) or Dane’s diene 14 (24.7 mg, 0.132 mmol, 21 \(\mu\)L, 1.1 equiv) was added. The progress of the reaction was monitored by TLC. After completion, the reaction was quenched by addition of tetrabutylammonium chloride (10 mg, 0.036 mmol, 0.3 equiv) to deactivate the catalyst. The solvent was evaporated under reduced pressure, and the oily residue was subjected to flash chromatography on silica. Yields refer to isolated products.

3,4-Dibenzylxylo-1-tert-butoxycarbonyl-9-oxobicyclo[4.3.0]oct-3-ene (13a): The reaction of 6a and 10 gave 13a as a light yellow oil. Yield: 50.0 mg, 0.109 mmol, 91%. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.48 (s, 9H, OC(CH\(_3\))\(_3\)), 1.60 (m, 1H, aliph. H), 2.00 (m, 1H, aliph. H), 2.05 (m, 1H, aliph. H), 2.19 (m, 1H, aliph. H), 2.31 - 2.54 (m, 3H, aliph. H), 2.88 (m, 2H, aliph. H), 4.88 (m, 4H, CH\(_2\)Ph), 7.27 - 7.45 (m, 10H, arom. H). \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 25.7, 26.4, 28.3, 28.6, 36.3, 38.8, 60.7, 72.4, 72.5, 82.3, 128.2, 128.37, 128.40, 128.74, 128.76, 135.2, 136.8, 138.3, 138.4, 170.1, 212.9. IR (liquid film, cm\(^{-1}\)): 1725.8 (s, carbonyl C-O),
1748.8 (s, carbonyl C=O), 2919.0 (m, C-H). HPLC: Chiralcel AD-H (hexane/i-PrOH 99/1, flow rate 0.6 mL/min, λ = 210.8 nm), retention times $t_R$ (major) = 60.8 min, $t_R$ (minor) = 66.2 min; 93% ee. \([\alpha]^{20}_D = -40.8 (c = 1, \text{CHCl}_3)\). HRMS (ESI): Calcd. for C$_{28}$H$_{32}$NaO$_5$ m/z 471.2142, found m/z 471.2133.

3,4-Dibenzyloxy-1-ethoxycarbonyl-9-oxobicyclo[4.3.0]oct-3-ene (13b): The reaction of 6b and 10 gave 13b as a light yellow oil.

Yield: 50.3 mg, 0.12 mmol, 99%.

$^1$H NMR (300 MHz, CDCl$_3$) \(\delta\) 1.26 (t, $J = 7.1$ Hz, 3H, OCH$_2$C$_6$H$_5$), 1.61 (m, 1H, aliph. H), 1.93 – 2.22 (m, 3H, aliph. H), 2.25 – 2.56 (m, 3H, aliph. H), 2.91 (m, 2H, aliph. H), 4.12 (dq, $^1J = 2.2$ Hz, $^3J = 7.1$ Hz, OCH$_2$CH$_3$), 4.88 (m, 4H, CH$_2$Ph), 7.22 – 7.43 (m, 10H, arom. H).

$^{13}$C NMR (126 MHz, CDCl$_3$) \(\delta\) 14.6, 25.7, 26.4, 28.5, 36.4, 38.7, 60.0, 62.1, 72.46, 72.48, 128.24, 128.26, 128.40, 128.44, 128.74, 128.75, 134.9, 136.9, 138.2, 138.3, 170.9, 212.0.

IR (liquid film, cm$^{-1}$): 1723.0 (s, carbonyl C=O), 1748.6 (s, carbonyl C=O), 2900.1 (m, C-H). HPLC: Chiralcel OD-H (hexane/i-PrOH 96.5/3.5, flow rate 0.8 mL/min, \(\lambda = 210.8\) nm), retention times $t_R$ (major) = 20.4 min, $t_R$ (minor) = 22.5 min; 77% ee. \([\alpha]^{20}_D = -52.4 (c = 1, \text{CHCl}_3)\).

HRMS (ESI): Calcd. for C$_{26}$H$_{28}$NaO$_5$ m/z 443.1829, found m/z 443.1835.

EA: Calcd. for C$_{26}$H$_{28}$O$_5$ (420.50): C, 74.26; H, 6.71; found: C, 74.09; H, 6.86.

3,4-Dibenzyloxy-1-methoxycarbonyl-9-oxobicyclo[4.3.0]oct-3-ene (13c): The reaction of 6c and 10 gave 13c as a light yellow oil.

Yield: 44.2 mg, 0.109 mmol, 90%.

$^1$H NMR (500 MHz, CDCl$_3$) \(\delta\) 1.49 - 1.85 (m, 1H, aliph. H), 1.99 (m, 1H, aliph. H), 2.07 (m, 1H, aliph. H), 2.17 (m, 1H, aliph. H), 2.35 (m, 1H, aliph. H), 2.47 (m, 2H, aliph. H), 2.91 (m, 2H, aliph. H), 3.72 (s, 3H, CO$_2$CH$_3$), 4.88 (m, 4H, CH$_2$Ph), 7.20 – 7.45 (m, 10H, arom. H).

$^{13}$C NMR (76 MHz, CDCl$_3$) \(\delta\) 25.2, 26.1, 28.0, 36.0, 38.2, 52.8, 59.7, 65.3, 72.0, 72.1, 127.84, 127.87, 128.0, 128.1, 128.33, 128.34, 134.4, 136.5, 137.79, 137.83, 171.0, 212.0.

IR (liquid film, cm$^{-1}$): 1726.6 (s, carbonyl C=O), 1749.4 (s, carbonyl C=O), 2950.6 (m, C-H). HPLC: Chiralcel OD-H (hexane/i-PrOH 95/5, flow rate 0.8 mL/min, \(\lambda = 210.8\) nm), retention times $t_R$ (major) = 20.4 min, $t_R$ (minor) = 22.5 min; 77% ee. \([\alpha]^{20}_D = -52.4 (c = 1, \text{CHCl}_3)\).

HRMS (ESI): Calcd. for C$_{25}$H$_{26}$NaO$_5$ m/z 426.1672, found m/z 426.1686.

(8R,13S,14S)-13-tert-Butoxycarbonyl-3-methoxy-7,8, 12,13,15,16-hexahydro-6H-cyclopenta[a]phenanthren-17 (14H)-one (15a): The reaction of 6a and 14 gave 15a as a white crystalline solid.

Yield: 44.3 mg, 0.120 mmol, 99% (85% after single recrystallization from isopropanol). The crystals obtained after recrystallization were suitable for X-ray analysis. M.p. (recryst): 130.0 °C. $^1$H NMR (500 MHz, CDCl$_3$) \(\delta\)
Experimental

1.48 (s, 9H), 1.55 – 1.73 (m, 2H), 1.98 (m, 1H), 2.06 (m, 1H), 2.28 (m, 1H), 2.32 – 2.53 (m, 2H), 2.58 (m, 1H), 2.88 (m, 3H), 3.05 (m, 1H), 3.82 (s, 3H), 6.19 (m, 1H), 6.63 (m, 1H), 6.74 (m, 1H), 7.55 (m, 1H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 21.8, 25.7, 27.0, 28.4, 30.8, 35.0, 37.3, 44.9, 55.6, 60.2, 82.0, 113.2, 113.7, 114.7, 125.0, 127.3, 133.8, 138.5, 159.0, 170.9, 214.4. IR (liquid film, cm\(^{-1}\)): 1716.3 (s, carbonyl C-O), 1745.9 (s, carbonyl C-O), 2934.3 (m, C-H). HPLC: Chiralcel AD-H (hexane/i-PrOH 92/8, flow rate 0.6 mL/min, \(\lambda = 210.8\) nm), retention times \(t_R\) (ester-exo diastereoisomer, major) = 11.6 min, \(t_R\) (ester-endo diastereoisomer, minor) = 14.7 min, \(t_R\) (ester-exo diastereoisomer, major) = 16.2 min, (endo diastereoisomer, major) = 17.5 min. 86% ee, d.r. (ester-exo:endo) = 27:1 (after single recrystallization: 99% ee, d.r. = 145:1). [\(\alpha\)]\(_{20}\)\(D\) = –199.7 (c = 1, CHCl\(_3\)). HRMS (EI): Calcd. for C\(_{23}\)H\(_{28}\)O\(_4\) m/z 368.1982, found m/z 368.1983. EA: Calcd. for C\(_{23}\)H\(_{28}\)O\(_4\) (368.47): C, 74.97; H, 7.66; found: C, 75.10; H, 7.72. The absolute configuration is \(8R,13S,14S\), as indicated by the X-ray crystallographic analysis of the camphanic acid ester derivative (see page xxviii).

3-Methoxy-13-methoxycarbonyl-7,8,12,13,15,16-hexahydro-6H-cyclopenta[a]phenanthren-17(14H)-one (15b):

The reaction of 6c and 14 gave 15b as a white crystalline solid. Yield: 35.0 mg, 0.107 mmol, 89% (56% after single recrystallization from 2-propanol). Diastereoselectivity (determined by \(^1\)H NMR spectroscopy): approx. 3:1 (approx. 7:1 after recrystallization). M.p.: 125 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.60 – 1.70 (m, 2H), 1.97 (m, 1H), 2.09 (m, 1H), 2.33 – 2.53 (m, 2H), 2.59 (m, 1H), 2.86 (m, 2H), 2.96 (m, 1H), 3.08 (m, 1H), 3.77 (s, 3H) 3.82 (s, 3H), 6.19 (m, 1H), 6.64 (m, 1H), 6.75 (m, 1H), 7.56 (m, 1H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 21.5, 25.6, 27.0, 30.8, 34.6, 37.1, 44.4, 53.2, 55.6, 59.5, 113.2, 113.7, 114.0, 125.0, 127.0, 133.8, 138.5, 159.1, 172.1, 213.7. IR (FT-ATR, cm\(^{-1}\)): 1726.1 (s, carbonyl C-O), 1736.0 (s, carbonyl C-O), 2910.2 (m, C-H). HPLC: Chiralcel OD-H (hexane/i-PrOH 97/3, flow rate 0.8 mL/min, \(\lambda = 230.4\) nm), retention times \(t_R\) (ester-exo diastereoisomer, minor) = 34 min, \(t_R\) (ester-exo diastereoisomer, major) = 41 min. 51% ee (99% after recrystallization from isopropanol), ester-endo diastereoisomers not separated. [\(\alpha\)]\(_{20}\)\(D\) = –189.1 (c = 1, CHCl\(_3\)). HRMS (EI): Calcd. for C\(_{20}\)H\(_{22}\)O\(_4\) m/z 326.1513, found m/z 326.1515. EA: Calcd. for C\(_{20}\)H\(_{22}\)O\(_4\) (326.39): C, 73.60; H, 6.79; found: C, 73.20; H, 6.85.

Catalytic Diels-Alder Reactions Starting from 5a-c. A solution of complex 5a-c (0.006 or 0.012 mmol, 0.05 or 0.1 equiv) in CH\(_2\)Cl\(_2\) (1 mL) was added to tritylium hexafluorophosphate (Ph\(_3\)C)PF\(_6\) (2.4 or 4.8 mg, 6.3 or 12.6 mmol, 0.0525 or 0.105 equiv) in a Young schlenk tube. The color of the solution immediately changed from orange to bright yellow. 6a or 6b (0.114 or 0.108 mmol, 0.95 or 0.9 equiv) was added in 1 mL of diethyl
ether, followed by 21 µL (0.132 mmol, 1.1 equiv) of Dane’s diene (14) after 10 minutes. The reaction was stirred overnight (in case of 5% catalyst for 48 h) and then quenched with an excess of tetrabutylammonium chloride. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica. The analytical data of the products matched the values obtained from the reactions catalyzed by 2.

### 7.4.2 Catalytic [2+2] Ficini Cycloadditions

**General Procedure for the Enantioselective Ficini Reaction:** [RuCl$_2$(PNP)] (1) (10 mg, 0.012 mmol, 0.1 equiv) and (Et$_3$O)PF$_6$ (6 mg, 0.024 mmol, 0.2 equiv) were stirred in CH$_2$Cl$_2$ (1 mL) in a Schlenk tube fitted with a Young valve at room temperature overnight. A color change from red to brown indicated the formation of the catalytically active complex. The unsaturated β-ketoester 6a-d (0.12 mmol, 1 equiv) was added as CH$_2$Cl$_2$ (1 mL) solution. After 10 min, the ynamide 16a-k (0.13 mmol, 1.1 equiv) was added. The Schlenk tube was closed and the mixture was heated to 55 °C in the dark. After 24 h, the solvent was evaporated under reduced pressure, and the oily residue was subjected to flash column chromatography on silica.

**Note:** Commercial (Et$_3$O)PF$_6$ (Meerwein salt) contains a not exactly specified amount (about 10%) of diethyl ether for stabilization. We observed that this amount decreases over long periods of time. Thus, when aged samples of Meerwein salt are used in the activation of 1, a slight excess of (Et$_3$O)PF$_6$ is introduced if the declared composition (90 % purity) is used. This results in the formation of an unidentified side product (visible on the TLC directly below the product spot) and slightly reduced amidocyclobutene yield. We obtained the most consistent results by assuming that the commercial (Et$_3$O)PF$_6$ salt is pure, that is, no stabilizer is present. The catalysis reactions performed in this manner show the best yields, high product purity, and no relevant decrease in reactivity, although one would assume incomplete catalyst activation with new (Et$_3$O)PF$_6$ batches.

(1R,5S)-tert-Butyl-7-[N-benzyl-4-methylphenylsulfonamido]-6-cyclohexyl-2-oxobicyclo[3.2.0]hept-6-ene-1-carboxylate (17a): The reaction of 6a and 16a gave 17a as a colorless oil. Yield: 64.3 mg, 0.117 mmol, 97%. A single recrystallization from hexane gave 17a as large colorless crystals. Yield: 49.6 mg, 0.090 mmol, 75%. **Note:** The use of aged (Et$_3$O)PF$_6$ batches for the activation of 1 resulted in the formation of an unknown impurity (see above), which cannot be removed by column chromatography. In these cases, recrystallization from hexane occasionally gave oils instead of crystals, whereas good yields of pure product were obtained from methanol. The colorless crystals formed are smaller.
than the crystals obtained from hexane, but still chemically and enantiomerically pure. When needed, large crystals were obtained by a second recrystallization from hexane. M.p.: 144.4 °C. 

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.86 (d, $J = 8.3$ Hz, 2H), 7.41 – 7.23 (m, 7H), 4.58 (d, $J = 15.0$ Hz, 1H), 4.43 (d, $J = 15.0$ Hz, 1H), 3.36 – 3.25 (m, 1H), 2.86 (dt, $J = 17.4$, 11.3 Hz, 1H), 2.46 (s, 3H), 2.14 (m, 1H), 2.06 – 1.92 (m, 3H), 1.64 (m, 4H), 1.47 (s, 9H), 1.15 (m, 2H), 1.05 (m, 4H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 210.1, 167.8, 159.3, 143.8, 137.6, 136.9, 129.9, 129.7, 128.6, 128.0, 126.9, 82.2, 77.7, 77.40, 77.2, 68.3, 51.8, 45.1, 37.9, 35.2, 30.0, 29.9, 28.5, 26.3, 26.0, 21.9. IR (liquid film, cm$^{-1}$): 1739.8 (s, carbonyl C=O), 1716.0 (s, carbonyl C=O). HPLC: Chiralcel AD-H (hexane/i-PrOH 80/20, flow rate 0.5 mL/min, $\lambda = 230.4$ nm), retention times $t_R$ (minor) = 10.5 min, $t_R$ (major) = 12.0 min; 90.5% ee (>99.5% ee after recrystallization). $[\alpha]_{20}^D = -197.6$ (c = 1, CHCl$_3$). HRMS (ESI): Calcd. for C$_{32}$H$_{43}$N$_2$O$_5$S $m/z$ 567.2887, found $m/z$ 567.2895. EA: Calcd. for C$_{32}$H$_{39}$NO$_5$S (549.72): C, 69.92; H, 7.15; N, 2.55; O, 14.55; found: C, 69.94; H, 7.18; N, 2.57; O, 14.46.

The absolute configuration of the major enantiomer is $1R,5S$, as indicated by the Flack value of the crystal structure and as determined by reduction of the keto group and esterification with ($1S,4R$)-camphanic acid chloride to give the camphanic ester derivative 19c. An X-ray study indicated that the absolute configuration of 19c is $1S$,$4R$,$1'R$,$2'S$,$5'R$ (pages xxx and xxxiii).

**tert-Butyl-6-cyclohexyl-7-[N-methyl-4-methylphenylsulfonamido]-2-oxobicyclo[3.2.0]hept-6-ene-1-carboxylate (17b):** The reaction of 6a and 16b gave 17b as a colorless oil. Yield: 50.4 mg, 0.106 mmol, 88%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 3.36 – 3.28 (m, 1H), 3.14 (dt, $J = 17.6$, 11.0 Hz, 1H), 2.98 (s, 3H), 2.42 (s, 3H), 2.40 – 2.48 (m, 1H), 2.28 (m, 1H), 2.05 (m, 2H), 1.91 (m, 2H), 1.74 (m, 4H), 1.41 (s, 9H), 1.28 (s, 4H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 209.8, 168.2, 155.2, 143.9, 136.3, 129.9, 128.5, 82.1, 67.5, 45.7, 38.1, 36.6, 35.6, 30.3, 30.2, 28.4, 26.4, 26.2, 21.8. IR (liquid film, cm$^{-1}$): 1740.5 (s, carbonyl C=O), 1716.1 (s, carbonyl C=O). HPLC: Chiralcel AD-H (hexane/i-PrOH 80/20, flow rate 0.5 mL/min, $\lambda = 230.4$ nm), retention times $t_R$ (minor) = 11.6 min, $t_R$ (major) = 12.9 min; 92% ee. $[\alpha]_{20}^D = -141.1$ (c = 1, CHCl$_3$). HRMS (ESI): Calcd. for C$_{26}$H$_{39}$N$_2$O$_5$S $m/z$ 491.2574, found $m/z$ 491.2558.

**tert-Butyl-7-[N-benzyl-4-methylphenylsulfonamido]-2-oxo-6-phenylbicyclo[3.2.0]hept-6-ene-1-carboxylate (17c):** The reaction of 17a and 16c gave 17c as a colorless oil. Yield: 47.0 mg, 0.086 mmol, 72%. The same reaction at room temperature gave 66% yield after 5 days. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.86 (d, $J = 8.1$ Hz, 2H), 7.40 (m, 2H), 7.33 – 7.22 (m, 7H), 7.11 (m, 3H),
4.70 (d, $J = 14.9$ Hz, 1H), 4.49 (d, $J = 14.9$ Hz, 1H), 3.78 (d, $J = 6.9$ Hz, 1H), 2.89 – 2.73 (m, 1H), 2.46 (s, 3H), 2.20 (dd, $J = 17.4$, 8.0 Hz, 1H), 1.95 – 2.1 (m, 2H), 1.49 (s, 9H). 

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 209.4, 167.3, 149.0, 144.1, 137.2, 136.0, 131.1, 129.9, 129.6, 128.8, 128.6, 128.4, 128.0, 127.9, 82.5, 68.1, 52.3, 44.6, 35.3, 28.5, 21.9, 20.6. IR (liquid film, cm$^{-1}$): 1740.1 (s, carbonyl C-O), 1716.1 (s, carbonyl C-O). HPLC: Chiralcel AD-H (hexane/i-PrOH 90/10, flow rate 0.6 mL/min, $\lambda = 210.8$ nm), retention times $t_R$ (minor) = 25.3 min, $t_R$ (major) = 30.2 min; 90% ee (92% for reaction at room temperature). 

$[\alpha]^{20}_D = -237.9$ (c = 1, CHCl$_3$). HRMS (ESI): Calcd. for C$_{32}$H$_{37}$N$_2$O$_5$S m/z 561.2418, found m/z 561.2436.

tert-Butyl-7-[N-methyl-4-methylphenylsulfonamido]-2-oxo-6-phenylbicyclo[3.2.0]hept-6-ene-1-carboxylate (17d): The reaction of 6a and 16d gave 17d as a colorless oil. Yield: 36.0 mg, 0.077 mmol, 64%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.88 (d, $J = 8.2$ Hz, 2H), 7.62 (d, $J = 7.2$ Hz, 2H), 7.46 (t, $J = 7.4$ Hz, 2H), 7.38 (m, 3H), 3.79 – 3.72 (m, 1H), 3.29 – 3.14 (m, 1H), 3.04 (s, 3H), 2.46 (s, 3H), 2.40 – 2.32 (m, 1H), 2.21 – 2.12 (m, 2H), 1.41 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 209.0, 168.0, 146.3, 144.1, 136.1, 130.3, 130.0, 129.9, 129.3, 127.7, 82.4, 67.6, 45.0, 35.7, 35.6, 28.4, 21.9, 21.1. IR (liquid film, cm$^{-1}$): 1741.5 (s, carbonyl C-O), 1714.1 (s, carbonyl C-O). HPLC: Chiralcel AD-H (hexane/i-PrOH 70/30, flow rate 0.5 mL/min, $\lambda = 254.8$ nm), retention times $t_R$ (major) = 14.4 min, $t_R$ (minor) = 17.8 min; 87% ee. $[\alpha]^{20}_D = -171.1$ (c = 1, CHCl$_3$). HRMS (ESI): Calcd. for C$_{26}$H$_{33}$N$_2$O$_5$S m/z 485.2105, found m/z 485.2108.

tert-Butyl-7-[N-methyl-methylsulfonamido]-2-oxo-6-phenylbicyclo[3.2.0]hept-6-ene-1-carboxylate (17e): The reaction of 6a and 16e gave 17e as a colorless oil. Yield: 32.6 mg, 0.083 mmol, 69%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.62 (d, $J = 7.2$ Hz, 2H), 7.48 – 7.35 (m, 3H), 3.80 (s, 1H), 3.22 (s, 3H), 3.18 – 3.12 (m, 1H), 3.11 (s, 3H), 2.41 – 2.29 (m, 1H), 2.13 – 2.20 (m, 2H), 1.53 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 210.0, 167.9, 145.7, 131.0, 130.0, 129.9, 129.3, 127.7, 82.8, 67.9, 44.9, 39.5, 36.4, 35.5, 28.5, 21.1. IR (liquid film, cm$^{-1}$): 1739.0 (s, carbonyl C-O), 1715.7 (s, carbonyl C-O). HPLC: Chiralcel AD-H (hexane/i-PrOH 70/30, flow rate 0.5 mL/min, $\lambda = 254.8$ nm), retention times $t_R$ (minor) = 9.8 min, $t_R$ (major) = 18.6 min; 83% ee. $[\alpha]^{20}_D = -345.0$ (c = 1, CHCl$_3$). HRMS (ESI): Calcd. for C$_{20}$H$_{29}$N$_2$O$_5$S m/z 409.1793, found m/z 409.1792.
** tert-Butyl-7-[N-methyl-4-methoxyphenylsulfonamido]-2-oxo-6-phenylbicyclo[3.2.0]hept-6-ene-1-carboxylate (17f): ** The reaction of 6a and 16f gave 17f as a colorless oil. Yield: 43.8 mg, 0.091 mmol, 75%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.94 (d, $J = 8.9$ Hz, 2H), 7.63 (d, $J = 7.2$ Hz, 2H), 7.43 (m, 3H), 7.03 (d, $J = 8.9$ Hz, 2H), 3.90 (s, 3H), 3.77 (m, 1H), 3.28 – 3.17 (m, 1H), 3.03 (s, 3H), 2.42 – 2.32 (m, 1H), 2.18 (m, 2H), 1.42 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 209.1, 168.0, 163.5, 146.3, 131.0, 129.9, 129.3, 127.7, 114.5, 82.3, 77.7, 77.4, 77.2, 67.6, 56.0, 45.0, 35.7, 28.4, 21.1. IR (liquid film, cm$^{-1}$): 1740.8 (s, carbonyl C-O), 1713.5 (s, carbonyl C-O). HPLC: Chiralcel AD-H (hexane/i-PrOH 70/30, flow rate 0.5 mL/min, $\lambda$ = 230.4 nm), retention times $t_R$ (major) = 18.0 min, $t_R$ (minor) = 21.3 min; 61% ee. [$\alpha$]$^\text{20}_D$ = –250.1 (c = 1, CHCl$_3$). HRMS (ESI): Calcd. for C$_{20}$H$_{29}$N$_2$O$_6$S m/z 501.2054, found m/z 501.2064.

** tert-Butyl-7-[N-benzyl-4-methylphenylsulfonamido]-6-hexyl-2-oxobicyclo[3.2.0]hept-6-ene-1-carboxylate (17g): ** The reaction of 6a and 16g gave 17g as a colorless oil. Yield: 65.8 mg, 0.119 mmol, 99%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.82 (d, $J = 8.2$ Hz, 2H), 7.42 – 7.13 (m, 7H), 4.63 (d, $J = 15.4$ Hz, 1H), 4.45 (d, $J = 15.4$ Hz, 1H), 3.28 (d, $J = 7.0$ Hz, 1H), 2.78 – 2.52 (m, 1H), 2.45 (m, 2H), 2.00 – 1.88 (m, 2H), 1.83 (m, 1H), 1.44 (s, 9H), 1.36 – 1.15 (m, 8H), 0.91 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 210.0, 167.6, 154.5, 143.9, 129.9, 129.1, 128.6, 128.5, 127.9, 82.2, 77.7, 77.4, 77.2, 68.4, 51.6, 45.8, 35.2, 32.0, 29.8, 28.4, 27.5, 26.5, 22.9, 21.9, 20.1, 14.4. IR (liquid film, cm$^{-1}$): 1740.1 (s, carbonyl C-O), 1718.1 (s, carbonyl C-O). HPLC: Chiralcel OD-H (hexane/i-PrOH 95/5, flow rate 0.6 mL/min, $\lambda$ = 254.8 nm), retention times $t_R$ (major) = 10.5 min, $t_R$ (minor) = 12.0 min; 78% ee. [$\alpha$]$^\text{20}_D$ = –159.8 (c = 1, CHCl$_3$). HRMS (ESI): Calcd. for C$_{32}$H$_{45}$N$_2$O$_5$S m/z 569.3044, found m/z 569.3045.

** tert-Butyl-6-hexyl-7-[N-methyl-methylsulfonamido]-2-oxobicyclo[3.2.0]hept-6-ene-1-carboxylate (17h): ** The reaction of 6a and 16h gave 17h as a colorless oil. Yield: 45.3 mg, 0.113 mmol, 94%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.32 (d, $J = 6.9$ Hz, 1H), 3.11 (s, 3H), 3.05 – 2.96 (m, 1H), 2.98 (s, 3H), 2.42 – 2.29 (m, 2H), 2.18 (m, 1H), 2.09 – 2.01 (m, 1H), 1.98 (m, 1H), 1.54 (m, 1H), 1.48 (s, 9H), 1.35 – 1.25 (m, 7H), 0.92 – 0.88 (m, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 211.0, 168.1, 150.1, 130.5, 82.4, 67.6, 46.7, 39.1, 36.4, 35.7, 31.9, 29.8, 28.4, 27.4, 26.6, 23.0, 20.5, 14.4. IR (liquid film, cm$^{-1}$): 1738.5 (s, carbonyl C-O), 1718.5 (s, carbonyl C-O). HPLC: Chiralcel AD-H (hexane/i-PrOH 95/5, flow rate 0.6 mL/min, $\lambda$ = 210.8 nm),
retention times $t_R$ (minor) = 11.2 min, $t_R$ (major) = 12.4 min; 70% ee. $[\alpha]_D^{20} = -278.7$ (c = 1, CHCl$_3$). HRMS (ESI): Calcd. for C$_{20}$H$_{37}$N$_2$O$_5$S m/z 417.2418, found m/z 417.2421.

**tert-Butyl-6-hexyl-7-[N-methyl-4-methoxyphenylsulfonamido]-2-oxobicyclo[3.2.0]hept-6-ene-1-carboxylate (17i):** The reaction of 6a and 16i gave 17i as a colorless oil. Yield: 58.5 mg, 0.119 mmol, 99%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.79 (d, $J = 8.9$ Hz, 2H), 6.98 (d, $J = 8.9$ Hz, 2H), 3.88 (s, 3H), 3.28 (d, $J = 7.0$ Hz, 1H), 2.99 (s, 3H), 3.04 – 2.97 (m, 1H), 2.41 (m, 1H), 2.30 (m, 1H), 2.17 (m, 1H), 2.05 – 1.99 (m, 1H), 1.94 (m, 1H), 1.42 (s, 9H), 1.35 – 1.26 (m, 7H), 0.91 (t, $J = 5.7$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 209.8, 168.0, 163.5, 149.1, 130.6, 114.5, 82.1, 67.6, 56.0, 46.5, 35.9, 35.8, 31.9, 29.7, 28.4, 27.7, 26.6, 23.0, 20.4, 14.4. IR (liquid film, cm$^{-1}$): 1739.9 (s, carbonyl C-O), 1719.6 (s, carbonyl C-O). HPLC: Chiralcel AD-H (hexane/i-PrOH 90/10, flow rate 0.5 mL/min, $\lambda$ = 230.4 nm), retention times $t_R$ (major) = 17.5 min, $t_R$ (minor) = 20.7 min; 78% ee. $[\alpha]_D^{20} = -167.8$ (c = 1, CHCl$_3$). HRMS (ESI): Calcd. for C$_{26}$H$_{41}$N$_2$O$_6$S m/z 509.2680, found m/z 509.2680.

**tert-Butyl-6-((benzyloxy)methyl)-7-[N-methyl-4-methylphenylsulfonamido]-2-oxobicyclo[3.2.0]hept-6-ene-1-carboxylate (17j):** The reaction of 6a and 16j gave 17j as a colorless oil. Yield: 37.0 mg, 0.072 mmol, 60%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.69 (d, $J = 8.2$ Hz, 2H), 7.42 – 7.27 (m, 7H), 4.61 (d, $J = 11.8$ Hz, 1H), 4.55 (d, $J = 11.8$ Hz, 1H), 4.39 (d, $J = 14.2$ Hz, 1H), 4.31 (d, $J = 14.1$ Hz, 1H), 3.43 (d, $J = 6.6$ Hz, 1H), 3.08 (s, 3H), 2.91 – 2.76 (m, 1H), 2.44 (s, 3H), 2.32 (dd, $J = 18.2$, 8.3 Hz, 1H), 2.13 – 1.97 (m, 2H), 1.40 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 209.7, 167.5, 144.4, 138.5, 137.2, 135.7, 131.0, 130.0, 128.8, 128.2, 128.1, 82.4, 73.4, 66.7, 65.7, 46.6, 46.1, 35.3, 36.1, 28.3, 22.0, 20.8. IR (liquid film, cm$^{-1}$): 1740.2 (s, carbonyl C-O), 1720.2 (s, carbonyl C-O). HPLC: Chiralcel AD-H (hexane/i-PrOH 97/3, flow rate 0.7 mL/min, $\lambda$ = 254.8 nm), retention times $t_R$ (minor) = 46.1 min, $t_R$ (major) = 51.7 min; 70% ee. $[\alpha]_D^{20} = -177.3$ (c = 1, CHCl$_3$). HRMS (ESI): Calcd. for C$_{28}$H$_{41}$N$_2$O$_6$S m/z 529.2367, found m/z 529.2363.

**tert-Butyl-7-[N-benzyl-4-methylphenylsulfonamido]-6-(2-((tert-butylidimethylsilyl)oxy)ethyl)-2-oxobicyclo[3.2.0]hept-6-ene-1-carboxylate (17k):** The reaction of 6a and 16k gave 17k as a colorless oil. Yield: 64.5 mg, 0.103 mmol, 86%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.81 (d, $J = 8.2$ Hz, 2H), 7.42 – 7.27 (m, 7H), 4.61 (d, $J = 11.8$ Hz, 1H), 4.55 (d, $J = 11.8$ Hz, 1H), 4.39 (d, $J = 15.5$ Hz, 1H), 4.45 (d, $J = 15.5$ Hz, 1H), 3.63 – 3.53 (m, 1H), 3.46 – 3.39 (m, 1H), 3.36 (d, $J = 6.6$ Hz, 1H), 2.68 – 2.53 (m, 1H), 2.44 (s, 3H), 2.36 (m, 1H), 2.23 (m, 1H), 2.14 – 2.05 (m, 1H), 1.98 – 1.83 (m, 2H), 1.42 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 210.3,
7 Experimental

167.3, 151.3, 144.0, 130.0, 129.0, 128.7, 128.5, 127.9, 82.1, 68.6, 61.0, 51.5, 47.1, 35.1, 30.9, 28.4, 26.3, 21.9, 20.1. IR (liquid film, cm$^{-1}$): 1741.4 (s, carbonyl C-O), 1718.9 (s, carbonyl C-O). HPLC: Chiralcel AD-H (hexane/i-PrOH 95/5, flow rate 0.6 mL/min, $\lambda$ = 254.8 nm), retention times $t_R$ (major) = 10.7 min, $t_R$ (minor) = 13.1 min; 76% ee. $[\alpha]_{D}^{20}$ = −117.5 (c = 1, CHCl$_3$). HRMS (ESI): Calcd. for C$_{34}$H$_{51}$N$_2$O$_6$SSi m/z 643.3238, found m/z 643.3238.

Ethyl-7-[N-benzyl-4-methylphenylsulfonamido]-6-cyclohexyl-2-oxobicyclo[3.2.0]hept-6-ene-1-carboxylate (17l): The reaction of 6b and 16a gave 17l as a colorless oil. Yield: 61.1 mg, 0.117 mmol, 97%.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.83 (d, $J$ = 8.3 Hz, 2H), 7.46 – 7.15 (m, 7H), 4.59 (d, $J$ = 15.0 Hz, 1H), 4.42 (d, $J$ = 15.0 Hz, 1H), 4.15 (dq, $J$ = 10.8, 7.1 Hz, 1H), 4.07 (dq, $J$ = 10.8, 7.1 Hz, 1H), 3.42 – 3.29 (m, 1H), 2.96 – 2.73 (m, 1H), 2.45 (s, 3H), 2.21 – 2.05 (m, 2H), 2.03 – 1.94 (m, 2H), 1.72 – 1.59 (m, 4H), 1.24 (t, $J$ = 7.1 Hz, 3H), 1.21 – 0.99 (m, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 209.9, 168.4, 159.4, 144.0, 137.5, 136.7, 130.0, 129.6, 128.6, 128.5, 128.1, 126.8, 67.4, 61.5, 51.7, 45.0, 38.0, 35.2, 30.0, 29.9, 26.4, 26.3, 26.0, 22.0, 14.5. IR (liquid film, cm$^{-1}$): 1741.3 (s, carbonyl C-O), 1721.8 (s, carbonyl C-O). HPLC: Chiralcel AD-H (hexane/i-PrOH 95/5, flow rate 0.6 mL/min, $\lambda$ = 254.4 nm), retention times $t_R$ (minor) = 28.3 min, $t_R$ (major) = 34.8 min; 53% ee. $[\alpha]_{D}^{20}$ = −177.0 (c = 1, CHCl$_3$). HRMS (ESI): Calcd. for C$_{30}$H$_{39}$N$_2$O$_5$S m/z 539.2574, found m/z 539.2557.

Ethyl-8-[N-benzyl-4-methylphenylsulfonamido]-7-cyclohexyl-2-oxobicyclo[4.2.0]oct-7-ene-1-carboxylate (17m): The reaction of 6d and 16a gave 17m as a colorless oil. Yield: 54.0 mg, 0.101 mmol, 84%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.81 (d, $J$ = 8.3 Hz, 2H), 7.45 (d, $J$ = 6.9 Hz, 2H), 7.36 – 7.22 (m, 5H), 4.67 (d, $J$ = 15.3 Hz, 1H), 4.53 (d, $J$ = 15.3 Hz, 1H), 4.19 – 4.03 (m, 2H), 3.13 – 2.99 (m, 1H), 2.54 – 2.47 (m, 1H), 2.45 (s, 3H), 2.27 – 2.14 (m, 1H), 2.05 – 1.95 (m, 2H), 1.95 – 1.52 (m, 8H), 1.19 (t, $J$ = 7.1 Hz, 3H), 1.16 – 0.95 (m, 5H). $^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ 206.2, 170.9, 160.0, 143.9, 137.5, 137.3, 129.9, 129.6, 128.7, 128.5, 127.9, 125.2, 66.9, 61.5, 51.8, 44.0, 40.7, 38.1, 30.3, 30.0, 26.4, 26.3, 26.0, 25.9, 22.0, 18.7, 14.4. IR (liquid film, cm$^{-1}$): 1731.5 (s, carbonyl C-O), 1696.6 (s, carbonyl C-O). HPLC: Chiralcel AD-H (hexane/i-PrOH 80/20, flow rate 0.5 mL/min, $\lambda$ = 254.4 nm), retention times $t_R$ (minor) = 12.4 min, $t_R$ (major) = 14.5 min; 57% ee. $[\alpha]_{D}^{20}$ = −114.1 (c = 1, CHCl$_3$). HRMS (ESI): Calcd. for C$_{31}$H$_{41}$N$_2$O$_5$S m/z 553.2731, found m/z 553.2744.
**7.4 Catalytic Reactions**

**tert-Butyl-8-[[N-benzyl-4-methylphenylsulfonamido]-7-cyclohexyl-2-oxobicyclo[4.2.0]oct-7-ene-1-carboxylate** (17n):

The reaction of 6e and 16a gave 17n as a colorless oil. Yield: 29.0 mg, 0.051 mmol, 43%. \(^1\)H NMR (700 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 7.80 (d, \(J = 7.6\) Hz, 2H), 7.44 (d, \(J = 7.2\) Hz, 2H), 7.33 - 7.20 (m, 5H), 4.69 (d, \(J = 15.4\) Hz, 1H), 4.55 (d, \(J = 15.4\) Hz, 1H), 3.01 (s, 1H), 2.44 (s, 3H), 2.43 - 2.36 (m, 1H), 2.22 - 2.11 (m, 1H), 2.07 (s, 3H), 1.97 (d, \(J = 13.0\) Hz, 1H), 1.89 - 1.57 (m, 7H), 1.39 (s, 9H), 1.19 - 1.00 (m, 4H). \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 169.5, 158.6, 143.4, 137.2, 129.4, 129.1, 128.3, 128.1, 127.4, 125.2, 81.5, 67.1, 60.4, 51.5, 43.7, 40.3, 37.7, 29.9, 29.7, 27.9, 26.0, 26.0, 25.7, 25.7, 21.6, 18.4, 14.2. IR (liquid film, cm\(^{-1}\)): 1734.6 (s, carbonyl C-O), 1697.3 (s, carbonyl (C-O). HPLC: Chiralcel AD-H (hexane/i-PrOH 80/20, flow rate 0.5 mL/min, \(\lambda = 214.4\) nm), retention times \(t_R\) (minor) = 9.5 min, \(t_R\) (major) = 11.9 min; 75% ee. \([\alpha]^{20}_D = -80.3\) (c = 1, CHCl\(_3\)). HRMS (ESI): Calcd. for C\(_{33}\)H\(_{45}\)N\(_2\)O\(_5\)S m/z 581.3044, found m/z 581.3053.

**Methyl-7-[[N-benzyl-4-methylphenylsulfonamido]-6-cyclohexyl-2-oxobicyclo[3.2.0]hept-6-ene-1-carboxylate** (17o): In order to obtain an authentic sample for the assignment of the \(^{31}\)P signals of [Ru(17o)(PNNP)]\(^{2+}\), 17o was prepared in the following way: A solution of complex 5b (13 mg, 0.012 mmol, 0.1 equiv) in CH\(_2\)Cl\(_2\) (1 mL) was added to tritylium hexafluorophosphate (Ph\(_3\)C)PF\(_6\) (4.8 mg, 0.013 mmol, 0.105 equiv) in a Young schlenk tube. The color of the solution immediately changed from orange to yellow. 6c (16.5 mg, 0.108 mmol, 0.9 equiv) was added in 1 mL of CH\(_2\)Cl\(_2\), followed by N-benzyl-N-(cyclohexylethynyl)-4-methylbenzenesulfonamide (16a) (50.2 mg, 0.137 mmol, 1.1 equiv) after 10 minutes. The Schlenk tube was closed and the mixture was heated to 55 °C. After 24 h, the solvent was evaporated under reduced pressure, and the oily residue was subjected to flash chromatography on silica to give 17o as a white solid. Yield: 55.0 mg, 0.108 mmol, 87%. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.82 (d, \(J = 8.3\) Hz, 2H), 7.62 - 7.09 (m, 7H), 4.62 (d, \(J = 15.1\) Hz, 1H), 4.42 (d, \(J = 15.1\) Hz, 1H), 3.62 (s, 3H), 3.38 (dd, \(J = 4.8, 2.4\) Hz, 1H), 2.77 (dt, \(J = 17.6, 11.3\) Hz, 1H), 2.46 (s, 3H), 2.22 - 2.11 (m, 2H), 1.98 (dt, \(J = 10.5, 5.2\) Hz, 2H), 1.73 – 1.58 (m, 4H), 1.33 – 1.05 (m, 6H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 210.0, 168.8, 159.2, 144.0, 137.5, 136.7, 130.0, 129.5, 128.7, 128.4, 128.1, 126.8, 67.2, 52.5, 51.7, 45.0, 38.1, 35.2, 30.0, 29.9, 26.4, 26.3, 26.1, 22.0, 21.9. IR (liquid film, cm\(^{-1}\)): 1742.8 (s, carbonyl C-O), 1724.5 (s, carbonyl C-O). HRMS (ESI): Calcd. for C\(_{32}\)H\(_{43}\)N\(_2\)O\(_5\)S m/z 525.2418, found m/z 525.2417.
7.4.3 Cu(I) and Cu(II)-Catalyzed Reactions

General Procedure for Catalytic Reactions. A CH$_2$Cl$_2$ solution (1.5 mL) of the unsaturated β-ketoester 6b or 6f (0.15 mmol, 1 equiv), the appropriate reagent 8, 16a, 23 or 25 (1.1 equiv, 5 equiv for 2,3-dimethylbutadiene 8), and copper(I) triflate benzene complex (24) or copper(II) triflate (28) (0.015 or 0.03 mmol, 0.01 or 0.02 equiv) was stirred at room temperature for 0.5 to 3 h, until TLC analysis showed that the unsaturated β-ketoester was fully converted. The solvent was removed under reduced pressure, and the oily residue was subjected to flash column chromatography on silica.

1-Ethoxycarbonyl-3,4-dimethyl-9-oxobicyclo[4.3.0]oct-3-ene (11b): The reaction of 6b and 2,3-dimethylbutadiene (8) with copper(I) triflate benzene complex (24) (0.02 equiv) gave 11b as a colorless oil after 3 h. Yield: 33.7 mg, 0.143 mmol, 95%. This material was identical with the product from the ruthenium-catalyzed reaction based on $^1$H NMR spectra data (see page 126).

Ethyl-7-[N-benzyl-4-methylphenylsulfonamido]-6-cyclohexyl-2-oxobicyclo[4.2.0]oct-7-ene-1-carboxylate (17l): The reaction of 6b and N-benzyl-N-(cyclohexylethynyl)-4-methylbenzenesulfonamide (16a) with 24 (0.01 equiv) as catalyst gave (17l) as a colorless oil after 30 min. Yield: 78.0 mg, 0.15 mmol, >99%. This material was identical with the product from the ruthenium-catalyzed reaction based on $^1$H NMR spectra data (see page 136).

Ethyl 2-oxo-7-(phenylthio)bicyclo[3.2.0]hept-6-ene-1-carboxylate (26a): The reaction of 6b and ethynyl(phenyl)sulfane (23) with 24 (0.01 equiv) as catalyst gave 26a as a colorless oil after 30 min. Yield: 32.0 mg, 0.111 mmol, 74%. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.64 – 7.47 (m, 2H), 7.45 – 7.30 (m, 3H), 5.88 (s, 1H), 4.23 (q, $J = 7.1$ Hz, 2H), 3.68 (d, $J = 6.9$ Hz, 1H), 3.03 (ddd, $J = 18.4$, 11.9, 9.2 Hz, 1H), 2.40 (dd, $J = 18.3$, 8.5 Hz, 1H), 2.26 – 2.06 (m, 1H), 1.90 (dd, $J = 13.4$, 9.1 Hz, 1H), 1.30 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 208.9, 167.7, 141.0, 134.1, 133.2, 130.3, 129.8, 129.1, 66.7, 61.8, 48.7, 35.3, 22.8, 14.6. IR (liquid film, cm$^{-1}$): 1719.7 (s, carbonyl C=O), 1736.7 (s, carbonyl C=O). HRMS (ESI): Calcd. for C$_{16}$H$_{17}$O$_3$S m/z 289.0893, found m/z 289.0889.
7.4 Catalytic Reactions

**Ethyl 2-oxo-5-(1,2,5-trimethyl-1H-pyrrol-3-yl)cyclopentanecarboxylate (27a):** The reaction of 6b and 1,2,5-trimethyl-1H-pyrrole (25) in the presence of 24 (0.01 equiv) gave 25a as a slightly red oil after 30 min. Yield: 39.0 mg, 0.148 mmol, 99%. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.74 (s, 1H), 4.30 – 4.07 (m, 2H), 3.71 (td, $J = 11.6$, 6.4 Hz, 1H), 3.38 (s, 3H), 3.21 (d, $J = 11.5$ Hz, 1H), 2.64 – 2.36 (m, 2H), 2.35 – 2.25 (m, 1H), 2.21 (s, 3H), 2.19 (s, 3H), 2.02 – 1.81 (m, 1H), 1.28 (t, $J = 7.1$ Hz, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 212.5, 169.6, 128.0, 124.9, 118.5, 102.6, 63.7, 61.6, 39.4, 38.8, 30.6, 29.9, 14.6, 12.9, 10.5. Chiral GC: $\alpha$-DEX column, 135°C isotherm, retention times $t_R = 133.2$ min, $t_R = 136.9$ min. IR (liquid film, cm$^{-1}$): 1720.5 (s, carbonyl C-O), 1750.1 (s, carbonyl C-O). HRMS (ESI): Calcd. for C$_{15}$H$_{22}$NO$_3$ m/z 264.1594, found m/z 264.1588.

**Ethyl 1-benzoyl-3,4-dimethylcyclohex-3-enecarboxylate (11d):** The reaction of 6f and 2,3-dimethylbutadiene (8) with 24 (0.02 equiv) as catalyst gave 11d as a colorless oil after 3 h. Yield: 41.4 mg, 0.145 mmol, 96%. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.84 (d, $J = 7.9$ Hz, 2H), 7.53 (t, $J = 7.2$ Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 2H), 4.15 (q, $J = 7.1$ Hz, 2H), 2.53 (s, 2H), 2.38 – 2.18 (m, 2H), 2.00 – 1.79 (m, 2H), 1.66 (s, 3H), 1.61 (s, 3H), 1.11 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 197.5, 174.0, 136.3, 132.9, 128.8, 124.9, 118.5, 102.6, 63.7, 61.6, 39.4, 38.0, 30.4, 29.7, 19.2, 14.3, 14.3. IR (liquid film, cm$^{-1}$): 1681.2 (s, carbonyl C-O), 1731.4 (s, carbonyl C-O). HRMS (ESI): Calcd. for C$_{18}$H$_{23}$O$_3$ m/z 287.1642, found m/z 287.1634.

**Ethyl 1-benzoyl-2-(N-benzyl-4-methylphenylsulfonamido)-3-cyclohexylcyclobut-2-enecarboxylate (17p):** The reaction of 6f and N-benzyl-N-(cyclohexylethynyl)-4-methylbenzenesulfonamide (16a) with 24 (0.02 equiv) as catalyst gave 17p as a colorless oil after 3 h. Yield: 85.0 mg, 0.149 mmol, 99%. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.85 (d, $J = 7.6$ Hz, 2H), 7.77 (d, $J = 8.1$ Hz, 2H), 7.54 (t, $J = 7.3$ Hz, 1H), 7.48 – 7.37 (m, 4H), 7.31 – 7.21 (m, 5H), 4.98 (d, $J = 14.9$ Hz, 1H), 4.81 (d, $J = 14.9$ Hz, 1H), 4.17 – 4.05 (m, 1H), 4.04 – 3.91 (m, 1H), 3.02 (d, $J = 12.7$ Hz, 1H), 2.43 (s, 3H), 2.48 – 2.36 (m, 1H), 1.63 – 1.32 (m, 5H), 0.99 (t, $J = 7.1$ Hz, 3H), 1.03 – 0.73 (m, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 195.2, 170.5, 158.3, 143.7, 138.2, 137.9, 136.0, 135.5, 129.8, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 127.9, 127.1, 67.7, 62.1, 52.8, 52.8, 37.2, 32.7, 30.1, 29.9, 26.1, 25.9, 21.9, 21.9, 14.0. IR (liquid film, cm$^{-1}$): 1680.6 (s, carbonyl C-O), 1734.0 (s, carbonyl C-O). HRMS (ESI): Calcd. for C$_{34}$H$_{38}$NO$_5$S m/z 572.2465, found m/z 572.2472.
Experimental

Ethyl 1-benzoyl-3-(phenylthio)cyclobut-2-enecarboxylate (26b') and Ethyl 1-benzoyl-2-(phenylthio)cyclobut-2-enecarboxylate (26b): The reaction of 6f and ethynyl(phenyl)sulfane (23) in the presence of 24 (0.02 equiv) as catalyst gave a mixture of the two regioisomers 26b':26b (4:1) as a slightly yellow oil after 3 h. Yield: 24.4 mg, 0.072 mmol, 48%. 1H NMR (700 MHz, CDCl$_3$) δ 8.10 – 8.05 (m, 2H, 26b'), 7.93 – 7.87 (m, 2H, 26b'), 7.65 – 7.61 (m, 1H, 26b'), 7.60 – 7.55 (m, 3H, 26b'), 7.54 – 7.50 (m, 2H, 26b'), 7.49 – 7.45 (m, 2H, 26b'), 7.38 – 7.29 (m, 7H, 3H from 26b' and 4H from 26b), 7.23 – 7.19 (m, 1H, 26b), 6.03 (t, J = 1.0 Hz, 1H, 26b'), 4.68 (t, J = 7.4 Hz, 1H, 26b), 4.41 – 4.07 (m, 2H, 26b'), 3.41 (dd, J = 12.8, 1.1 Hz, 1H, 26b'), 3.23 (dd, J = 17.2, 7.6 Hz, 1H, 26b), 3.15 (dd, J = 17.2, 7.2 Hz, 1H, 26b), 2.95 (dd, J = 12.8, 1.1 Hz, 1H, 26b'), 1.20 (t, J = 7.1 Hz, 3H, 26b), 1.08 (t, J = 7.1 Hz, 3H, 26b'). 13C NMR (126 MHz, CD$_2$Cl$_2$) δ 193.9, 193.7, 170.0, 140.1, 136.3, 135.5, 134.2, 133.7, 133.1, 133.1, 131.8, 129.6, 129.5, 129.3, 129.2, 128.9, 128.5, 126.7, 126.4, 96.1, 68.2, 66.7, 62.3, 53.8, 37.2, 30.1, 20.7, 14.4, 14.3. IR (liquid film, cm$^{-1}$): 1680.8 (s, carbonyl C-O), 1731.7 (s, carbonyl C-O). HRMS (ESI): Calcd. for C$_{20}$H$_{19}$O$_3$S m/z 339.1049, found m/z 339.1050.

Ethyl 3-oxo-3-phenyl-2-((1,2,5-trimethyl-1H-pyrrol-3-yl)methyl)propanoate (27b): The reaction of 6f and 1,2,5-trimethyl-1H-pyrrole (25) with 24 (0.01 equiv) as catalyst gave 27b as a slightly yellow oil after 30 min. Yield: 30.0 mg, 0.096 mmol, 64%. 1H NMR (700 MHz, CD$_2$Cl$_2$) δ 8.07 – 7.92 (m, 2H), 7.63 – 7.54 (m, 1H), 7.48 (t, J = 7.8 Hz, 2H), 5.71 (s, 1H), 4.54 (t, J = 7.1 Hz, 1H), 4.28 – 4.04 (m, 2H), 3.32 (s, 3H), 3.15 (dd, J = 14.6, 7.6 Hz, 1H), 3.10 (dd, J = 14.6, 6.7 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H). 13C NMR (176 MHz, CDCl$_3$) δ 193.9, 193.7, 170.0, 168.7, 140.1, 136.3, 135.5, 134.2, 133.7, 133.1, 133.1, 129.6, 129.5, 129.3, 129.2, 129.1, 128.9, 128.5, 126.7, 126.4, 96.1, 68.2, 66.7, 62.3, 53.8, 37.2, 30.1, 20.7, 14.4. IR (liquid film, cm$^{-1}$): 1682.2 (s, carbonyl C-O), 1731.8 (s, carbonyl C-O). HRMS (ESI): Calcd. for C$_{19}$H$_{24}$NO$_3$ m/z 314.1751, found m/z 314.1746.

Cu(I) and Cu(II) Ph-BOX Catalysts. The reactions were performed in close analogy to a procedure published by Aggarwal. The catalyst was prepared by stirring copper(I) triflate benzene complex (24) or copper (II) triflate (28) (0.03 mmol, 0.2 equiv) and Ph-BOX (11.5 mg, 0.033 mmol, 0.22 equiv) in freshly distilled CH$_2$Cl$_2$ (0.5 mL) for 3 h. After cooling the solution down to –78 °C, substrate 6b (23.1 mg, 0.15 mmol, 1 equiv) in CH$_2$Cl$_2$ (1 mL) was added thereto. After 5 minutes, 2,3-dimethylbutadiene (8) (25.5 µL, 0.225 mmol, 1.5 equiv) was slowly added to
the reaction solution, and the stirring was continued for 2 h at –78 °C, after which neither catalyst gave detectable conversion (by TLC analysis). Cu(II) triflate (28) gave about 20% conversion after 1 h at 0 °C, and the conversion was quantitative after 1 h at room temperature. With Cu(I) triflate (24), no conversion was observed after 1 h at 0 °C, and the reaction required 24 h at room temperature to achieve completion. In both reactions, the solvent was removed under reduced pressure and the oily residue was subjected to flash column chromatography on silica. Compound 11b was obtained in 47% yield with 24, and in 65% yield with copper(II) triflate (28). Chiral GC: β-DEX column, 120 °C isotherm, retention times $t_R$ (major) = 164.1 min, $t_R$ (minor) = 167.3 min; 19% ee for copper(I) triflate (24) and 23% ee for copper(II) triflate (28).

**SnCl₄-Catalyzed Diels-Alder Reactions.** Following the procedure published by Browne, the reaction of 6b (23.1 mg, 0.15 mmol, 1 equiv) and 2,3-dimethylbutadiene (8) (85 µL, 0.750 mmol, 5 equiv) with SnCl₄ (9 µL, 0.075 mmol, 0.5 equiv) gave 1-ethoxycarbonyl-3,4-dimethyl-9-oxobicyclo[4.3.0]oct-3-ene (11b) as a colorless oil. Yield: 19.4 mg, 0.082 mmol, 55%.

### 7.5 Derivatisation for the Determination of the Absolute Configuration

**9-Hydroxy-1-methoxycarbonyl-3,4-dimethyl bicyclo[4.3.0]oct-3-ene (18a):** A solution of 8c (@ 58% ee) (210 mg, 0.945 mmol, 1 equiv) in freshly distilled methanol (4 mL) was added dropwise to a solution of NaBH₄ (50 mg, 1.32 mmol, 1.4 equiv) in 6 mL of the same solvent. The reaction mixture was quenched with water and extracted three times with CH₂Cl₂. The combined organic layers were washed with saturated NaHCO₃ solution, water, and brine. Each of the aqueous phases was extracted once with CH₂Cl₂. The combined organic layers were dried with MgSO₄, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica to give diastereomerically pure 18a as a colorless oil. Yield: 195 mg, 0.896 mmol, 92%. ^1^H NMR (300 MHz, CDCl₃) δ 1.44 – 1.60 (m, 3H, aliph. H, 1.63 (s, 3H, CCH₃), 1.68 (s, 3H, CCH₃), 1.71 – 1.81 (m, 1H, aliph. H, 2.05 – 2.50 (m, 4H, aliph. H, 3.71 (s, 3H, OCH₃), 4.38 (m, 1H, CHOH).
Camphanic acid 1′-methoxycarbonyl-3′,4′-dimethyl bicyclo[4.3.0]oct-3′-en-9′-yl ester (19a): A solution of 9-hydroxy-1-methoxycarbonyl-3,4-dimethyl bicyclo[4.3.0]oct-3-ene (18a) (53.7 mg, 0.239 mmol, 1 equiv) (@ 58% ee) and of (1S,4R)-camphanic acid chloride (104 mg, 0.479 mmol, 2 equiv) in pyridine (1.5 mL) was stirred overnight at room temperature. Aqueous HCl (10%, 10 mL) was added and the mixture was extracted 3 times with dichloromethane (12 mL). The combined organic layers were washed twice with 0.1 M HCl (20 mL), and once with water (20 mL). After drying over MgSO$_4$ the solvent was removed under reduced pressure. Flash chromatography on silica gave 19a as a colorless oil. Yield: 97.5 mg, 99%. The 1S,4R,1′S,6′S,9′S (19a, major) and 1S,4R,1′R,6′R,9′R (19a′, minor) diastereoisomers were separated via preparative HPLC (Chiralcel OJ, hexane/i-PrOH 99/1, flow rate 0.5 mL/min). The minor 1S,4R,1′R,6′R,9′R diastereoisomer (19a′) gave crystals suitable for X-ray analysis by slow evaporation from diethyl ether. $^1$H NMR (500 MHz, CDCl$_3$) δ 0.96 (s, 3H), 1.06 (s, 3H), 1.11 (s, 3H), 1.26 – 1.63 (m, 1H, aliph. H, 1.60 (s, 3H), 1.66 (s, 3H), 1.48 - 1.81 (m, 4H, aliph. H, 1.91 (ddd, J = 13.2, 10.8, 4.6 Hz, 1H), 2.02 (ddd, J = 13.6, 9.4, 4.6 Hz, 1H), 2.06 - 2.22 (m, 2H, aliph. H, 2.26 - 2.44 (m, 3H, aliph. H, 2.56 (m, 1H), 3.56 (s, 3H), 5.48 (m, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 178.4, 175.7, 167.2, 123.0, 122.4, 91.4, 82.0, 55.2, 54.3, 53.3, 52.5, 39.2, 32.6, 31.1, 29.6, 29.4, 28.6, 27.5, 19.5, 19.4, 17.0, 17.00, 10.0.

(1S,4R,8′R,13′S,14′S,17′S)-Camphanic acid 13′-tert-butoxycarbonyl-3-methoxy-7′,8′,12′,13′,14′,15′,16′,17′-octahydro-6′H-cyclopenta[a]phenanthren-17′-yl ester (19b). 15a (88.6 mg, 0.24 mmol, 1 equiv) and NaBH$_4$ (12.7 mg, 0.34 mmol, 1.4 equiv) were suspended in freshly distilled methanol (2.5 mL). After stirring for 30 min, the reaction mixture was quenched with water and extracted three times with CH$_2$Cl$_2$. The combined organic layers were washed with saturated NaHCO$_3$ solution, water, and brine. Each of the aqueous phases was extracted once with CH$_2$Cl$_2$. The combined organic layers were dried with MgSO$_4$, and the solvent was removed under reduced pressure yielding 43.4 mg (49%) of crude 13′-tert-butoxycarbonyl-17′-hydroxy-3-methoxy-7′,8′,12′,13′,14′,15′,16′,17′-octahydro-6′H-cyclopenta[a]phenanthrene (18b). Pyridine (0.7 mL) and (1S,4R)-camphanic acid chloride (50.6 mg, 0.234 mmol, 2 equiv) were added, and the reaction mixture was stirred overnight. Aqueous HCl (10%, 5 mL) was added, and the mixture was extracted 3 times with dichloromethane (6 mL). The combined organic layers were washed twice with 0.1 M HCl (10 mL) and once with water (10 mL). After drying over MgSO$_4$, the solvent was removed.
under reduced pressure. The residue was purified by flash column chromatography on silica to give \(19b\) as a yellowish oil. Yield: 55.7 mg, 0.101 mmol, 87%. The NMR spectrum shows a diastereomeric ratio of 9:1. Colorless crystals were obtained after recrystallization from ethanol. M.p. (recryst): 160.2 °C. ¹H NMR (500 MHz, CDCl₃) δ 0.98 (s, 3H), 1.11 (s, 3H), 1.15 (s, 3H), 1.44 (s, 9H), 1.48 – 1.59 (m, 1H, aliph. H), 1.59 – 1.82 (m, 4H, aliph. H), 1.83 – 1.92 (m, 1H, aliph. H), 1.92 – 2.00 (m, 1H, aliph. H), 2.02 – 2.12 (m, 1H, aliph. H), 2.30 – 2.52 (m, 4H, aliph. H), 2.58 – 2.67 (m, 1H, aliph. H), 2.70 – 2.78 (m, 1H, aliph. H), 2.78 – 2.99 (m, 2H, aliph. H), 3.87 (s, 3H, H₄₁). 13C NMR (CDCl₃, 125.8 MHz): δ 10.1, 17.1, 17.2, 23.4, 24.9, 28.4, 28.5, 29.4, 30.9, 31.0, 35.0, 45.1, 53.8, 54.4, 55.2, 55.6, 81.4, 81.7, 91.5, 113.1, 113.7, 115.1, 125.1, 127.5, 132.0, 138.2, 158.8, 167.0, 174.0, 178.6. HRMS (EI): Calcd. for C₃₃H₄₂NaO₇ m/z 573.2823, found m/z 573.2808. EA: Calcd. for C₃₃H₄₂O₇ (550.69): C, 71.98; H, 7.69; O, 20.34; found: C, 71.95; H, 7.69; O, 20.19.

\((1S,4R,1'R,2'S,5'S)\) - Camphanic acid 7’-[N-benzyl-4-methylphenylsulfonamido]-1’-tert-butoxycarbonyl-6’-cyclohexylbicyclo[3.2.0]hept-6’-ene-2’-yl ester (19c): Product 17a (139.3 mg, 0.253 mmol, 1 equiv, @ 90% ee) and NaBH₄ (13.7 mg, 0.355 mmol, 1.4 equiv) were suspended in freshly distilled methanol (2.5 mL). After stirring for 30 min, the reaction mixture was quenched with water and extracted three times with CH₂Cl₂. The combined organic layers were washed with saturated NaHCO₃ solution, water, and brine. Each of the aqueous phases was extracted once with CH₂Cl₂. The combined organic layers were dried with MgSO₄, and the solvent was removed under reduced pressure yielding 134.2 mg (96%) of the crude 2-hydroxy-product 18c. 80.5 mg (0.292 mmol, 1 equiv) of this product were added to pyridine (0.9 mL) and (1S,4R)-camphamic acid chloride (63.2 mg, 0.292 mmol, 2 equiv), and the reaction mixture was stirred overnight. Aqueous HCl (10%, 6 mL) was added, and the mixture was extracted 3 times with dichloromethane (9 mL). The combined organic layers were washed twice with 0.1 M HCl (15 mL) and once with water (15 mL). After drying over MgSO₄, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica to give 19c as a white foam. Yield: 66 mg, 0.09 mmol, 62%. Colorless crystals were obtained by slow evaporation of diethyl ether. M.p.: 127.6 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, J = 8.2 Hz, 2H), 7.33 (m, 2H), 7.30 – 7.20 (m, 5H), 5.41 (dd, J = 10.7, 6.3 Hz, 1H), 4.82 (d, J = 15.9 Hz, 1H), 4.45 (d, J = 15.9 Hz, 1H), 2.87 (m, 1H), 2.81 – 2.68 (m, 1H), 2.42 (s, 3H), 2.15 – 1.90 (m, 5H), 1.75 – 1.45 (m, 8H), 1.41 (s, 9H), 1.18 (s, 3H), 1.13 (s, 3H), 1.12 – 1.06 (m, 2H), 1.05 (s, 2H), 0.98 (s, 3H), 0.93 (s, 3H).
3H), 1.04 – 0.86 (m, 3H). 13C NMR (126 MHz, CDCl3) δ 178.4, 171.0, 167.5, 147.3, 143.4, 137.8, 136.9, 129.5, 128.4, 128.4, 127.9, 127.8, 125.9, 91.5, 81.4, 74.8, 63.2, 54.9, 54.5, 51.8, 45.3, 38.4, 31.4, 30.6, 29.9, 29.3, 28.1, 27.6, 26.06, 26.05, 26.0, 22.8, 21.6, 17.1, 17.1, 9.9. IR (ATR, cm⁻¹): 1788.2 (s, carbonyl C-O), 1740.0 (s, carbonyl C-O), 1720.5 (s, carbonyl C-O). HRMS (ESI): Calcd. for C43H57N2O8S m/z 749.3830, found m/z 749.3838. EA: Due to the strong tendency of the crystals to build in solvent molecules in a non-coordinated manner, no clean elemental analysis was obtained. However, the recorded NMR spectra of the crystals show no contaminations except for diethyl ether (also present in crystal structure) and traces of dichloromethane.

7.6 Stoichiometric Reactions and NMR Experiments

Stoichiometric Diels-Alder Reactions of 7a-c. To the solution of complex 7a, 7b or 7c prepared as described above in a Young NMR tube, Dane’s diene (14) (5.1 µL, 0.032 mmol, 1.1 equiv) were added and the reaction mixture was shaken for 30 minutes. Then, an excess of tetrabutylammonium chloride was added to release the entire coordinated product 15a or 15b from the complex for isolation. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography on silica. The analytical data of the products matched the values obtained from the catalytic reactions (see above).

Stoichiometric Diels Alder Reaction of 6a or 6c and Dane’s Diene (14) Catalyzed by Complex 2. A solution of dichloro complex 1 (20 mg, 0.024 mmol, 1 equiv) in CD2Cl2 (0.5 mL) was added to (Et3O)PF6 (13.3 mg, 0.048 mmol, 2 equiv) in a Young NMR tube and shaken overnight. 6a or 6c (0.025 mmol, 1.05 equiv) was added as a solution in CD2Cl2 (0.2 mL), followed by Dane’s diene (14) (4.3 µL, 0.026 mmol, 1.1 equiv) after 10 min. The reaction mixture was shaken for 30 minutes at room temperature. Then, an excess of tetrabutylammonium chloride was added to release the entire coordinated product 15a or 15b from the complex. The reaction mixture was filtered through a small plug of silica and the solvent was evaporated under reduced pressure. Chiral HPLC chromatography showed an enantioselectivity of 90% ee for 15a and 56% ee for 15b.

One Pot Procedure for the Stoichiometric Diels-Alder Reaction via in situ Generation of 7b and 7c from 1. A solution of dichloro complex 1 (20 mg, 0.024 mmol, 1 equiv) in CD2Cl2 (0.5 mL) was added to (Et3O)PF6 (13.3 mg, 0.048 mmol, 2 equiv) in a Young NMR tube and shaken overnight. Saturated β-ketoester 3c (3.3 µL, 0.026 mmol, 1.1 equiv) was added and the mixture was shaken for 3 h. 31P NMR spectroscopy showed a mixture of diastereoisomers with a d.r. of 70:30 (δ 63.1 + 50.4, 2J P,P' = 29.4
Hz and δ 62.4 + 48.3, $^2J_{P,P'} = 29.1$ Hz). Triethylamine (4.0 µL, 0.029 mmol, 1.2 equiv) was added, which lead to the formation of complexes 5b and 5c. The ratio between the major (δ 63.7 + 52.3, $^2J_{P,P} = 30.8$ Hz) and the minor (δ 60.7 + 52.3, $^2J_{P,P} = 28.8$ Hz) diastereoisomer remained constant within experimental error. (Ph$_3$C)PF$_6$ (11.4 mg, 0.029 mmol, 1.2 equiv) was added, which resulted in a color change from red-orange to yellow. 31P NMR spectroscopy showed the formation of complexes 7b and 7c in a maintained ratio of 70:30 (δ 64.3 + 50.5, $^2J_{P,P} = 29.4$ Hz and δ 62.6 + 49.8, $^2J_{P,P} = 29.0$ Hz). Dane’s diene (14) (4.7 µL, 0.029 mmol, 1.2 equiv) was added and after 15 min. The 31P NMR spectrum showed full conversion of 7b and 7c to two diastereomeric forms of [Ru(15b)(PNNP)]$^{2+}$ (δ 62.8 + 49.1, $^2J_{P,P} = 29.7$ Hz and δ 61.8 + 47.1, $^2J_{P,P} = 30.3$ Hz) in a 65:35 ratio. Then, an excess of tetrabutylammonium chloride was added to release the entire coordinated product 15b from the complex. The solvent was evaporated under reduced pressure and the residue was subjected to flash column chromatography on silica, yielding 7.3 mg (0.022 mmol, 78%) of 15b with an enantioselectivity of 34% ee. This value is reasonably close to the theoretical value (30%) derived from the diastereomeric ratio of the two complexes [Ru(15b)(PNNP)]$^{2+}$ (65:35). It is also close to the theoretical value obtained, starting from the initial d.r. in [Ru(3c)(PNNP)]$^{2+}$ (70:30), when the different enantioselectivities of activated complexes 7b (87% ee) and 7c (97% ee) are taken into account [(70%–30%)-87%/97%] = 36%].

**General Procedure for the Observation of Cycloaddition and Product Release-Exchange of 15b for 6c.** To the solution of complex 7b, prepared as described above in a Young NMR tube, Dane’s diene (14) (5.1 µL, 0.032 mmol, 1.1 equiv) was added. After 15 min, 31P NMR spectroscopy showed complete conversion of complex 7b and two new pairs of doublets (δ 62.8 + 49.1, $^2J_{P,P'} = 29.7$ Hz and δ 61.8 + 47.1, $^2J_{P,P'} = 30.3$ Hz) had appeared, which were assigned to two diastereoisomers of [Ru(15b)(PNNP)]$^{2+}$. The assignment was confirmed by comparison with an authentic sample, formed from 2 and isolated 15b (see below). A solution of 6c (4.2 mg, 0.03 mmol, 1.05 equiv) in CD$_2$Cl$_2$ (0.2 mL) was added and the regeneration of complex 7b and 7c was monitored by 31P NMR spectroscopy.

**Procedure to Verify the 31P NMR Signals of Complexes [Ru(15b)(PNNP)]$^{2+}$ and [Ru(17o)(PNNP)]$^{2+}$.** A solution of dichloro complex 1 (20 mg, 0.024 mmol, 1 equiv) in CD$_2$Cl$_2$ (0.7 mL) was added to (Et$_3$O)PF$_6$ (13.3 mg, 0.048 mmol, 2 equiv) in a Young NMR tube and shaken overnight. The methyl ester estrone derivative 15b (10.22 mg, 0.031 mmol, 1.3 equiv) or the Ficini product 17o (15.9 mg, 0.031 mmol, 1.3 equiv) was added and the mixture was shaken for another 3 h. 31P NMR spectroscopy showed the formation of the signals previously assigned to [Ru(15b)(PNNP)]$^{2+}$ (δ 49.1 + 62.9 (major) and δ 47.1 +61.8 (minor)) and [Ru(17o)(PNNP)]$^{2+}$ (δ 43.9 + 59.7 (major) and δ 45.2 + 61.5 (minor)) along
with minor unidentified species. In case of [Ru(15b)(PNNP)]^{2+}, an additional major species \((\delta 62.2 + 49.1)\) was present in solution that might be assigned to a diaqua complex (usually around \(\delta 63 + 48\)).

### Table 10: \(^{31}\)P NMR data of catalytically relevant complexes.

<table>
<thead>
<tr>
<th>entry</th>
<th>complex</th>
<th>(\delta_A)</th>
<th>(\delta_X)</th>
<th>({^2}J_{P,P'}) (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><a href="PF(_6)">Ru(3a)(PNNP)</a>(_2) (4a)</td>
<td>61.2</td>
<td>51.3</td>
<td>29.1</td>
</tr>
<tr>
<td>2</td>
<td><a href="PF(_6)">Ru(3c)(PNNP)</a>(_2) major (4b)</td>
<td>63.1</td>
<td>50.4</td>
<td>29.4</td>
</tr>
<tr>
<td>3</td>
<td><a href="PF(_6)">Ru(3c)(PNNP)</a>(_2) minor (4c)</td>
<td>62.4</td>
<td>48.3</td>
<td>29.1</td>
</tr>
<tr>
<td>4</td>
<td><a href="PF(_6)">Ru(3a-H)(PNNP)</a> (5a)</td>
<td>63.4</td>
<td>53.5</td>
<td>31.2</td>
</tr>
<tr>
<td>5</td>
<td><a href="PF(_6)">Ru(3c-H)(PNNP)</a>(_2) major (5b)</td>
<td>63.7</td>
<td>52.3</td>
<td>30.8</td>
</tr>
<tr>
<td>6</td>
<td><a href="PF(_6)">Ru(3c-H)(PNNP)</a>(_2) minor (5c)</td>
<td>60.7</td>
<td>52.3</td>
<td>28.8</td>
</tr>
<tr>
<td>7</td>
<td><a href="PF(_6)">Ru(6a)(PNNP)</a>(_2) (7a)</td>
<td>63.2</td>
<td>50.4</td>
<td>29.3</td>
</tr>
<tr>
<td>8</td>
<td><a href="PF(_6)">Ru(6c)(PNNP)</a>(_2) major (7b)</td>
<td>64.3</td>
<td>50.5</td>
<td>29.4</td>
</tr>
<tr>
<td>9</td>
<td><a href="PF(_6)">Ru(6c)(PNNP)</a>(_2) minor (7c)</td>
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<td>49.8</td>
<td>29.0</td>
</tr>
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<td>10</td>
<td><a href="PF(_6)">Ru(15c)(PNNP)</a>(_2) major</td>
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<td>49.1</td>
<td>29.7</td>
</tr>
<tr>
<td>11</td>
<td><a href="PF(_6)">Ru(15c)(PNNP)</a>(_2) minor</td>
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<td>47.1</td>
<td>30.3</td>
</tr>
<tr>
<td>12</td>
<td><a href="PF(_6)">Ru(15a)(PNNP)</a>(_2)</td>
<td>61.1</td>
<td>49.2</td>
<td>29.4</td>
</tr>
<tr>
<td>13</td>
<td><a href="PF(_6)">Ru(17o)(PNNP)</a>(_2) major</td>
<td>59.7</td>
<td>43.9</td>
<td>27.8</td>
</tr>
<tr>
<td>14</td>
<td><a href="PF(_6)">Ru(17o)(PNNP)</a>(_2) minor</td>
<td>61.5</td>
<td>45.2</td>
<td>29.8</td>
</tr>
</tbody>
</table>

#### 7.6.1 NMR Experiments on Monocationic Ru / PNNP Complexes

Experimental procedures not performed by the author are reported in reference 237.

[RuCl(PNNP)]PF\(_6\) (29) + H\(_2\)O. TIPF\(_6\) (8.4 mg, 0.024 mmol) was given into a NMR tube under an argon atmosphere. A CD\(_2\)Cl\(_2\) solution (0.5 mL) of [RuCl\(_2\)(PNNP)] (20 mg, 0.024 mmol, 1 equiv) was added thereto, and the slurry was shaken at room temperature overnight. Water was added in portions (0.43, 2.2, and 8.7 µL; 1, 5, and 20 equiv, respectively) with a microsyringe, and the solution was shaken for 10 min before analyzing it by NMR spectroscopy. \(^1\)H NMR (500 MHz, CD\(_2\)Cl\(_2\), 20 equiv H\(_2\)O, 298 K) \(\delta 9.26\) (d, \(^4\)J\(_{P,H}\) = 9.0 Hz, 1H, HC=N, 31), 8.98 (d, \(^4\)J\(_{P,H}\) = 9.4 Hz, 1H, HC=N, 31), 8.85 (d, \(^4\)J\(_{P,H}\) = 9.6 Hz, 1H, HC=N, 30), 8.73 (br s, 1H, HC=N, 30), 7.96 - 6.52 (m, 54H, arom. H, 30 + 31), 6.07 (t, \(J = 8.9\) Hz, 1H, arom. H, 30), 5.86 (t, \(J = 8.5\) Hz, 1H, arom. H, 31), 4.80 (br, 1H, 30), 4.43 (t, \(J = 9.1\) Hz, 1H, 30), 3.99 (t, \(J = 10.2\) Hz, 1H, 31), 3.58 (t, \(J = 11.2\) Hz, 1H, 31),
2.94 (d, $J = 10.0$ Hz, 1H, 31), 2.67 (d, $J = 11.0$ Hz, 1H, 31), 2.64 - 2.04 (m, 2H, 30), 2.01 - 0.86 (m, 12H, 30 + 31 + H$_2$O). $^{31}$P NMR (202 MHz, CD$_2$Cl$_2$, 20 equiv H$_2$O, 298 K) $\delta$ 62.8 (d, $2J_{P,P'} = 32.0$ Hz, 1P, 30), 50.6 (d, $2J_{P,P'} = 27.1$ Hz, 1P, 31), 45.4 (d, $2J_{P,P'} = 27.0$ Hz, 1P, 30), 44.1 (d, $2J_{P,P'} = 27.1$ Hz, 1P, 31), $-144.4$ (sept, $J_{P,F} = 707$ Hz, PF$_6$).

**Determination of $k$ for the Chemical Exchange between 29 and 30.** The chemical exchange between the unsymmetrically populated sites, that is, complexes 29 and 30, was treated according to a literature method by Perrin and Dwyer. The exchange rate constant was calculated with Equation 29 from this reference.

$$k = \frac{1}{t_m} \ln \frac{r + 1}{r - 1}$$

where $r$ is $4X_AX_B(I_{AA} + I_{BB})/(I_{AB} + I_{BA}) - (X_A - X_B)^2$ and accounts for the unsymmetrical exchange. The integrated intensities of the diagonal and cross peaks for each mixing time, $I_{AA}$, $I_{BB}$, $I_{AB}$, $I_{BA}$, were obtained from a series of 2D ($^{31}$P,$^{31}$P)-EXSY spectra measured at room temperature with various mixing times (Table 11). The exchange occurs between the signals at $\delta$ 64 and 60, and between those at $\delta$ 45 and 51 of the two AX spins systems (see Figure 35), which gives rise to two data sets, 1 and 2. The $k$ values were calculated for both data sets, and the average value and standard deviation was calculated using all data points to give $k$(average) = 47(9) s$^{-1}$. The molar fractions of 29 and 30, $X_a$ (30) = 0.685 and $X_b$ (29) = 0.315, were calculated from the corresponding 1D $^{31}$P spectrum. Mixing times of 1 and 5 ms gave no exchange under these conditions and were not used in the calculation.

**Table 11: Integrated intensities (with $\delta$ values) and calculated rate constants $k$ for different mixing times.**

<table>
<thead>
<tr>
<th>mixing time (s)</th>
<th>$I_{AA}(1)$</th>
<th>$I_{BB}(1)$</th>
<th>$I_{AB}(1)$</th>
<th>$I_{BA}(1)$</th>
<th>$I_{AA}(2)$</th>
<th>$I_{BB}(2)$</th>
<th>$I_{BA}(2)$</th>
<th>$I_{AB}(2)$</th>
<th>$\delta$ 60-64</th>
<th>$\delta$ 45-51</th>
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<tr>
<td>0.1</td>
<td>1201</td>
<td>235</td>
<td>478</td>
<td>523</td>
<td>353</td>
<td>1028</td>
<td>535</td>
<td>483</td>
<td>1.1</td>
<td>30.3</td>
</tr>
<tr>
<td>0.05</td>
<td>2005</td>
<td>575</td>
<td>808</td>
<td>948</td>
<td>579</td>
<td>1863</td>
<td>740</td>
<td>816</td>
<td>1.1</td>
<td>55.8</td>
</tr>
<tr>
<td>0.04</td>
<td>989</td>
<td>240</td>
<td>383</td>
<td>343</td>
<td>318</td>
<td>865</td>
<td>331</td>
<td>441</td>
<td>1.3</td>
<td>49.4</td>
</tr>
<tr>
<td>0.03</td>
<td>890</td>
<td>363</td>
<td>273</td>
<td>312</td>
<td>365</td>
<td>717</td>
<td>279</td>
<td>346</td>
<td>1.7</td>
<td>44.6</td>
</tr>
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<td>0.02</td>
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<td>221</td>
<td>186</td>
<td>450</td>
<td>757</td>
<td>202</td>
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<td>2.5</td>
<td>41.5</td>
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<tr>
<td>0.01</td>
<td>879</td>
<td>383</td>
<td>114</td>
<td>118</td>
<td>484</td>
<td>834</td>
<td>144</td>
<td>88</td>
<td>4.6</td>
<td>44.3</td>
</tr>
</tbody>
</table>

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7.7 Molecular Modeling

The approach of ynamide 16a to the unsaturated β-keto ester 6a in complex 7a has been modeled by MM calculations with Cerius² with standard UFF settings. The transition state (TS) has been calculated starting from the X-ray coordinates of 7a. The conformation of ynamide 16a was refined to fit into the chiral space above the free enantioface of the coordinated substrate 6a with the required regiochemistry. The only restrain applied was the distance of 2.00 Å, which was chosen arbitrarily, between the C²-atom of the ynamide and the C³-atom of the β-keto ester. The coordinates of 7a were kept frozen during all refinement. The orientation of the C¹–C² triple bond was corrected after the first refinement cycles until the C¹'–C²'–C³–C² dihedral angle stabilized to a value close to 0°. After reaching convergence, the main structural parameters were: C(2')–C(3), 2.00 Å; C(2)–C(1'), 2.91 Å; C(1')–C(2')–C(3)–C(2), 0°. The transition state is shown in Figure 19. The space-filling model shows that there are no major steric interactions between complex 7a and the incoming ynamide 16a.

Then, the C¹'–C² and C²'–C³ bonds were generated, and the structure of the putative complex containing product 17a was refined keeping the coordinates of the Ru / PNNP fragment frozen. The coordinated product 17a fits into the available space without major interactions with the PNNP ligand. Thereafter, a new refinement was started, in which only the coordination sphere of the ruthenium atom (Ru, P, N, and O atoms) was kept frozen. Figure 19 shows the optimized structure of the putative complex [Ru(17a)(PNNP)]²⁺ containing the coordinated amidocyclobutene 17a.
References


References


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[250] Ranocchiari, M.; Ph.D. thesis; ETH Zürich; Wolfgang-Pauli-Str. 10, 8093 Zürich; 2009.


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8 Appendix

8.1 Abbreviations

acac acetylacetonato
BINAP 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
BINOL 1,1’-bi-2-naphthol
Bn benzyl
BOX bisoxazoline
BSA N,O-bis(trimethylsilyl)acetamide
coe cyclooctene
DMEDA N,N’-dimethylethylenediamine
equiv equivalent
ee enantiomeric excess
Et ethyl-
h hour
Hz Hertz
IR infrared
J coupling constant
KHMD KHMDS potassium bis(trimethylsilyl)amide
Mbs 4-methoxyphenylsulfonamido
Me methyl
MeOH methanol
min minute
NMR nuclear magnetic resonance
nbd norbornadiene
NFSI N-fluorobenzenesulfonamide
Ph phenyl
Ph-Box 2,2’-isopropylidenebis(4-phenyl-2-oxazoline)
PNNP (1S,2S)-N,N’-bis[o-(diphenylphosphino)benzylidene)cyclohexane-1,2-diamine
ppm parts per million
p-TsOH p-toluenesulfonic acid
PyBOX pyridyl bis(oxazoline)
rt room temperature
TADDOL tetraaryl-1,3-dioxolane-4,5-dimethanol
Ts tosyl
8.2 List of Numbered Compounds

1  \([\text{RuCl}_2(\text{PNNP})]\)
2  \([\text{Ru}((\text{OE})_2)(\text{PNNP})]\)(\text{PF}_6)_2
3  saturated \(\beta\)-ketoesters
   3a \(2-\text{tert}-\text{butoxycarbonylcyclopentanone}\)
   3b \(2\text{-ethoxycarbonylcyclopentanone}\)
   3c \(2\text{-methoxycarbonylcyclopentanone}\)
4  \(2\text{-dicarbonyl complexes }[\text{Ru}(\text{3})(\text{PNNP})](\text{PF}_6)_2\)
   4a \([\text{Ru}(\text{3a})(\text{PNNP})](\text{PF}_6)_2\)
   4b \([\text{Ru}(\text{3c})(\text{PNNP})](\text{PF}_6)_2\text{ major}\)
   4c \([\text{Ru}(\text{3c})(\text{PNNP})](\text{PF}_6)_2\text{ minor}\)
5  \(2\text{-enolato complexes }[\text{Ru}(\text{3}-\text{H})(\text{PNNP})](\text{PF}_6)\)
   5a \([\text{Ru}(\text{3a}-\text{H})(\text{PNNP})](\text{PF}_6)\)
   5b \([\text{Ru}(\text{3c}-\text{H})(\text{PNNP})](\text{PF}_6)\text{ major}\)
   5c \([\text{Ru}(\text{3c}-\text{H})(\text{PNNP})](\text{PF}_6)\text{ minor}\)
6  unsaturated \(\beta\)-ketoesters
   6a \(2-\text{tert}-\text{butoxycarbonyl-2-cyclopenten-1-one}\)
   6b \(2\text{-ethoxycarbonyl-2-cyclopenten-1-one}\)
   6c \(2\text{-methoxycarbonyl-2-cyclopenten-1-one}\)
   6d \(2\text{-ethoxycarbonyl-2-cyclohexen-1-one}\)
   6e \(2-\text{tert}-\text{butoxycarbonyl-2-cyclohexen-1-one}\)
   6f \(\text{ethyl 2-benzoylacrylate}\)
7  \(\text{alkylidene }\beta\)-ketoester complexes \([\text{Ru}(\text{6})(\text{PNNP})](\text{PF}_6)_2\)
   7a \([\text{Ru}(\text{6a})(\text{PNNP})](\text{PF}_6)_2\)
   7b \([\text{Ru}(\text{6c})(\text{PNNP})](\text{PF}_6)_2\text{ major}\)
   7c \([\text{Ru}(\text{6c})(\text{PNNP})](\text{PF}_6)_2\text{ minor}\)
8  \(2,3\text{-dimethylbutadiene}\)
9  \(2,3\text{-dimethoxybutadiene}\)
10  \(2,3\text{-(dibenzzyloxy)butadiene}\)
11a-c Diels-Alder products with 2,3-dimethylbutadiene (8)
12a-c Diels-Alder products with 2,3-dimethoxybutadiene (9)
13a-c Diels-Alder products with 2,3-(dibenzzyloxy)butadiene (10)
14  Dane’s diene
15a-b Diels-Alder products with Dane’s Diene (14)
16a-k ynamides
<table>
<thead>
<tr>
<th>Appendix</th>
</tr>
</thead>
</table>

17a-p  
[2+2] Ficini cycloaddition products

18a-d  
reduced cycloaddition products

19a-c  
camphanic acid derivatives

20a-d  
diene ligands derived from [2+2] Ficini cycloaddition products

21a-d  
phosphite-alkene ligands derived from [2+2] Ficini cycloaddition products

22a-b  
diphosphite ligands derived from [2+2] Ficini cycloaddition products

23  
ethynyl(phenyl)sulfane

24  
copper(I) triflate benzene complex

25  
1,2,5-trimethyl-1H-pyrrole

26a-b'  
[2+2] cycloaddition products with ethynyl(phenyl)sulfane (23)

27a-b  
Michael addition products with 1,2,5-trimethyl-1H-pyrrole (25)

28  
copper(II) triflate

29  
[RuCl(PNNP)]^+

30  
cis-β-[RuCl(OH₂)(PNNP)]PF₆

31  
trans-[RuCl(OH₂)(PNNP)]PF₆

32  
[RuCl(OEt₂)(PNNP)]PF₆
Appendix

8.3 Crystallographic Data

8.3.1 Methylester Enolato Complex - Major Isomer (5b)

Dark red crystals of the major diastereoisomer 5b were obtained by slow diffusion of n-pentane into a CH2Cl2 solution of the racemic complex (prepared with (R,R+S,S)-PNNP). Crystal data for C53H51Cl4F6N2O3P3Ru: prism (0.37 x 0.27 x 0.11 mm), triclinic, P–1, cell dimensions (100 K) a = 13.3663(9), b = 14.6427(10), c = 14.7977(10) Å, α = 79.809(1), β = 70.191(1), γ = 73.345(1)°, and V = 2600.3(3) Å³ with Z = 2, Dc = 1.550 Mg/m³, μ = 0.667 mm⁻¹ (Mo Kα, graphite monochromated), λ = 0.71073 Å, F(000) = 1 236. The data were collected at 100 K on a Bruker AXS SMART APEX platform in the θ range 1.46 – 28.27°. The structure was solved with SHELXTL using direct methods. Of the 26 980 measured reflections with index ranges −17 ≤ h ≤ 17, −19 ≤ k ≤ 19, −19 ≤ l ≤ 19, 12 775 independent reflections (Rint = 0.0334) were used in the refinement (full-matrix least squares on F²) with anisotropic displacement parameters for all non-H atoms. Hydrogen atoms at calculated positions and refined with the riding model and individual isotropic thermal parameters for each group. Final residuals were R₁ = 0.0437 (for 10 837 reflections with I>2σ(I)) and wR₂ = 0.1037 (all data), GOF = 1.026. Max. and min. difference peaks were +1.02 and −1.02 eÅ⁻³, the largest and mean Δ/σ = −0.345 and 0.008.
### Table 12: Bond lengths (Å). Calculated distances to hydrogen atoms and disordered CH₂Cl₂ molecules are omitted:

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<th>Bond</th>
<th>Å</th>
<th>Bond</th>
<th>Å</th>
<th>Bond</th>
<th>Å</th>
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<td>C(37)–C(38)</td>
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### Table 13: Bond angles (°). Angles involving hydrogen atoms and disordered CH₂Cl₂ molecules are omitted:

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### 8.3.2 Methylester Enolato Complex - Minor Isomer (5c)

\((OC-6-43-A-(S,S)+OC-6-43-C-(R,R))-\text{[Ru}(3c–H)\text{(PNNP)}]\text{PF}_6\): Red orange crystals of the minor diastereoisomer 5c were obtained by slow diffusion of \(n\)-pentane into a dilute CHCl\(_3\) solution of the complex. Crystal data for C\(_{52}\)H\(_{50}\)Cl\(_3\)F\(_6\)N\(_2\)O\(_3\)P\(_3\)Ru: prism (0.30 x 0.19 x 0.14 mm), monoclinic, \(P2_1/c\), cell dimensions (100 K) \(a = 10.4554(14)\), \(b = 14.350(2)\), \(c = 35.366(5)\) Å, \(\beta = 95.133(3)^\circ\), and \(V = 5284.9(13)\) Å\(^3\) with \(Z = 4\), \(D_c = 1.465\) Mg/m\(^3\), \(\mu = 0.6045\) mm\(^{-1}\) (Mo K\(\alpha\), graphite monochromated), \(\lambda = 0.71073\) Å, \(F(000) = 2\) 376. The data were collected at 100 K on a Bruker AXS SMART APEX platform in the \(\theta\) range 1.16 – 25.05\(^\circ\). The structure was solved with SHELXTL using direct methods. Of the 41 090 measured reflections with index ranges \(-12 \leq h \leq 12\), \(-17 \leq k \leq 17\), \(-42 \leq l \leq 42\), 9 340 independent reflections (R\(_{int} = 0.0804\)) were used in the refinement (full-matrix least squares on \(F^2\)) with anisotropic displacement parameters for all non-H atoms. Hydrogen atoms at calculated positions and refined with the riding model and individual isotropic thermal parameters for each group. Final residuals were R\(_1\) = 0.0864 (for 7 501 reflections)
with $I>2\sigma(I)$ and $wR_2 = 0.1835$ (all data), GOF = 1.154. Max. and min. difference peaks were +1.29 and −1.04 eÅ$^{-3}$, the largest and mean $\Delta/\sigma = 0.001$ and 0.000.

**Table 14**: Bond lengths (Å). Calculated distances to hydrogen atoms and disordered CHCl$_3$ molecules are omitted:

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### 8.3.3 Campanic Acid Tetrahydro-1-indanone Derivative ent-19a

(1S,4R,1’R,6’R,9’R)-Campanic acid 1’-methoxycarbonyl-3’,4’-dimethylbicyclo[4.3.0]oct-3’-en-9’-yl ester: Colorless plates of ent-19a were obtained by slow evaporation of a diethyl ether solution. Crystal data for $\text{C}_{23}\text{H}_{32}\text{O}_{6}$: prism (0.39 ×0.18 ×0.06 mm), monoclinic, $\text{P2}_1$, cell dimensions (200 K) $a = 12.2734(15)$, $b = 7.0211(9)$, $c = 13.0651(17)$ Å, $\beta = 108.615(3)^\circ$, and $V = 1067.0(3)$ Å³ with $Z = 2$, $D_c = 1.259$ Mg/m³, $\mu$ xxiv
= 0.090 mm\(^{-1}\) (Mo K\(_\alpha\), graphite monochromated), \(\lambda = 0.71073 \text{ Å}\), \(F(000) = 436\). The data were collected at 200 K on a Bruker AXS SMART APEX platform in the \(\theta\) range 1.64 – 28.35\(^\circ\). The structure was solved with SHELXTL using direct methods. Of the 11210 measured reflections with index ranges \(-16 \leq h \leq 16, -9 \leq k \leq 9, -17 \leq l \leq 17\), 2 880 independent reflections \((R\text{int} = 0.0523)\) were used in the refinement (full-matrix least squares on \(F^2\)) with anisotropic displacement parameters for all non-H atoms. Hydrogen atoms at calculated positions and refined with the riding model and individual isotropic thermal parameters for each group. Final residuals were \(R_1 = 0.0461\) (for 2111 reflections with \(I > 2\sigma(I)\)) and \(wR_2 = 0.1203\) (all data), GOF = 0.943. Max. and min. difference peaks were +0.25 and −0.16 eÅ\(^{-3}\), the largest and mean \(\Delta/\sigma = 0.000\) and 0.000.

**Table 16**: Bond lengths (Å). Calculated distances to hydrogen atoms are omitted:

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**Table 17**: Bond angles (°). Angles involving hydrogen atoms are omitted:

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### Estrone Derivative 15a

**13-tert-Butoxycarbonyl-3-methoxy-7,8,12,13,15,16-hexahydro-6H-cyclopenta[a]phenanthren-17(14H)-one:** Colorless plates of 15a were obtained by slow evaporation of a diethyl ether solution. Crystal data for C\textsubscript{23}H\textsubscript{32}O\textsubscript{6}: prism (0.35 × 0.28 × 0.11 mm), orthorhombic, P\textsubscript{2}1\textsubscript{2}1\textsubscript{2}1, cell dimensions (100 K) \(a = 8.8778(15)\), \(b = 11.951(2)\), \(c = 18.680(3)\) Å, and \(V = 1981.8(6)\) Å\textsuperscript{3} with \(Z = 4\), \(D_c = 1.235\) Mg/m\textsuperscript{3}, \(\mu = 0.083\) mm\textsuperscript{-1} (Mo K\(_\alpha\), graphite monochromated), \(\lambda = 0.71073\) Å, \(F(000) = 792\). The data were collected at 100 K on a Bruker AXS SMART APEX platform in the \(\theta\) range 2.02 – 28.53°. The structure was solved with SHELXTL using direct methods. Of the 20956 measured reflections with index ranges \(-11 \leq h \leq 11\), \(-16 \leq k \leq 15\), \(-25 \leq l \leq 25\), 5002 independent reflections (\(R_{int} = 0.0822\)) were used in the refinement (full-matrix least squares on \(F^2\)) with anisotropic displacement parameters for all non-H atoms. Hydrogen atoms at calculated positions and refined with the riding model and individual isotropic thermal parameters for each group. Final residuals were \(R_1 = 0.0457\) (for 3433 reflections with \(I > 2\sigma(I)\)) and \(wR_2 = 0.078\) (all

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data), GOF = 0.819. Max. and min. difference peaks were +0.23 and −0.19 eÅ⁻³, the largest and mean $\Delta/\sigma = 0.001$ and 0.000.

**Table 18**: Bond lengths (Å). Calculated distances to hydrogen atoms are omitted:

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<th>Bond</th>
<th>Å</th>
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**Table 19**: Bond angles (°). Angles involving hydrogen atoms are omitted:

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<tr>
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</table>
8.3.5 Camphanic Acid Estrone Derivative 19b

(1S,4R,8'R,13'S,14'S,17'S)-Camphanic Acid 13'-tert- butoxycarbonyl-3-methoxy-7',8',12',13',14',15',16',17'-octahydro-6'H-cyclopenta[a] phenanthren-17'-yl ester: Colorless crystals of 19b were obtained by slow evaporation of an ethanol solution. Crystal data for C_{33}H_{42}O_{7}: prism (0.65 × 0.50 × 0.45 mm), triclinic, P1, cell dimensions (100 K) \( a = 7.6079(14) \) Å, \( b = 10.0378(18) \) Å, \( c = 10.3899(19) \) Å, \( \alpha = 68.164(3) \) °, \( \beta = 83.564(3) \) °, \( \gamma = 83.013(3) \) °, and \( V = 729.1(2) \) Å\(^3\) with \( Z = 1 \), \( D_c = 1.254 \) Mg/m\(^3\), \( \mu = 0.087 \) mm\(^{-1}\) (Mo K\(_\alpha\), graphite monochromated), \( \lambda = 0.71073 \) Å, \( F(000) = 296 \). The data were collected at 100 K on a Bruker AXS SMART APEX platform in the \( \theta \) range 2.12 – 28.34°. The structure was solved with SHELXTL using direct methods. Of the 7541 measured reflections with index ranges \(-10 \leq h \leq 10, -13 \leq k \leq 13, -13 \leq l \leq 13\), 6590 independent reflections \( (R_{int} = 0.0143) \) were used in the refinement (full-matrix least squares on \( F^2 \)) with anisotropic displacement parameters for all non-H atoms. Hydrogen atoms at calculated positions and refined with the riding model and individual isotropic thermal parameters for each group. Final residuals were \( R_1 = 0.0384 \) (for 6380 reflections with \( I > 2\sigma(I) \)) and \( wR_2 = 0.1002 \) (all data), GOF = 1.052. Max. and min. difference peaks were +0.31 and –0.20 eÅ\(^{-3}\), the largest and mean \( \Delta/\sigma = 0.000 \) and 0.000.
### Table 20: Bond lengths (Å). Calculated distances to hydrogen atoms are omitted:

<table>
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<th>Bond</th>
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### Table 21: Bond angles (°). Angles involving hydrogen atoms are omitted:

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</table>
### 8.3.6 Ficini Product 17a

(1\(R\),5\(S\))-tert-Butyl-7-\([\text{N}-\text{benzyl-4-methylphenylsulfonamido}]\)-6-cyclohexyl-2-oxobicyclo[3.2.0]hept-6-ene-1-carboxylate: CCDC Deposition number: 802191. Colorless crystals of 17a were obtained by slow evaporation of a hexane solution. Crystal data for C\(_{32}\)H\(_{39}\)NO\(_5\)S: plate (0.59 × 0.58 × 0.26 mm), orthorhombic, \(P2_1\)\(2_1\)\(2_1\), cell dimensions (100 K) \(a = 11.1461(9)\), \(b = 12.7847(10)\), \(c = 20.6887(17)\) Å, and \(V = 2948.1(4)\) Å\(^3\) with \(Z = 4\), \(D_c = 1.238\) Mg/m\(^3\), \(\mu = 0.150\) mm\(^{-1}\) (Mo K\(_\alpha\), graphite monochromated), \(\lambda d = 0.71073\) Å, \(F(000) = 1176\). The data were

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**Table:**

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collected at 100 K on a Bruker AXS SMART APEX platform in the θ range 1.87–28.34°. The structure was solved with SHELXTL using direct methods. Of the 30691 measured reflections with index ranges -14 ≤ h ≤ 14, -17 ≤ k ≤ 17, -27 ≤ l ≤ 27, 7329 independent reflections (Rint = 0.0757) were used in the refinement (full-matrix least squares on F²) with anisotropic displacement parameters for all non-H atoms. Hydrogen atoms at calculated positions and refined with the riding model and individual isotropic thermal parameters for each group. Final residuals were R1 = 0.0403 (for 6179 reflections with I>2σ(I)) and wR2 = 0.0776 (all data), GOF = 0.931. Max. and min. difference peaks were +0.38 and -0.30 eÅ⁻³, the largest and mean Δ/σ = -0.002 and 0.000. The molecule is the 1R,5S enantiomer, as indicated by the value of the Flack x parameter 0.04(5) for this absolute configuration. This assignment was confirmed by reduction of the keto group and esterification with (1S,4R)-camphanic acid chloride to give camphanic ester 19c.

Table 22: Bond lengths (Å). Calculated distances to hydrogen atoms are omitted:

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Table 23: Bond angles (°). Angles involving hydrogen atoms are omitted:

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8.3.7 Camphanic Acid Ficini Derivative 19c

(1S,4R,1’R,2’S,5’S) - Camphanic acid 7’-[N-benzyl-4-methylphenylsulfonamido]-1’-tert-butoxycarbonyl-6’-cyclohexylbicyclo[3.2.0]hept-6'-ene-2'-yl ester: CCDC Deposition number: 802192. Colorless crystals of 19c were obtained by slow evaporation of a diethyl ether solution. Crystal data for C_{42}H_{53}NO_{8}S·Et_{2}O: prism (0.48×0.46×0.36 mm), triclinic, P1, cell dimensions (95 K) \(a = 8.1799(10)\), \(b = 10.5342(12)\), \(c = 14.7885(18)\) Å, \(\alpha = 107.165(3)\)°, \(\beta = 105.421(3)\)°, \(\gamma = 92.189(3)\)°, and \(V = 1164.3(2)\) Å³ with \(Z = 1\), \(D_c = 1.135\) Mg/m³, \(\mu = 0.121\) mm⁻¹ (Mo K\(\alpha\), graphite monochromated), \(\lambda = 0.71073\) Å, \(F(000) = 424\). The data were collected at 95 K on a Bruker AXS SMART APEX platform in the \(\theta\) range 2.04–28.35°. The structure was solved with SHELXTL using direct methods. Besides 19c, the asymmetric unit contains one Et₂O molecule disordered over two sites. Of the 12179 measured reflections with index ranges \(-10 \leq h \leq 10\), \(-14 \leq k \leq 14\), \(-19 \leq l \leq 19\), 10604 independent reflections (\(R_{int} = 0.0317\)) were used in the refinement (full-matrix least squares on \(F^2\)) with anisotropic displacement parameters for all non-H atoms. Hydrogen atoms were introduced at calculated positions (except for the disordered Et₂O molecules) and refined with the riding model and individual isotropic thermal parameters for each group. Final residuals were \(R_1 = 0.0582\) (for 8159 reflections with \(I > 2\sigma(I)\)) and \(wR_2 = 0.1316\) (all data), GOF = 0.930. The Flack \(x\) parameter was -0.02(7). Max. and min. difference peaks were +0.52 and -0.39 eÅ⁻³, the largest and mean \(\Delta/\sigma = -0.028\) and 0.001.
Table 24: Bond lengths (Å). Calculated distances to hydrogen atoms and disordered Et$_2$O molecules are omitted:

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Table 25: Bond angles (°). Angles involving hydrogen atoms and disordered Et$_2$O molecules are omitted:

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</table>
Appendix

8.4 Curriculum Vitae

Name          Schotes
First Name    Christoph
Date of Birth 31st of August 1982
Citizenship  German

Education
03.2008 - 09.2011 Ph.D. in Chemistry, Laboratory of Inorganic Chemistry, ETH Zurich
Title of the thesis: "Ru / PNNP-Catalyzed Asymmetric Diels-Alder and Ficini Reactions on Alkylidene β-Ketoesters"
Supervisor: Prof. Dr. Antonio Mezzetti
Co-examiners: Prof. Dr. Antonio Togni, Prof. Dr. Eric Carreira
10.2006 - 02.2008 M.Sc. in Chemistry at ETH Zurich
Master Thesis with Prof. Dr. Antonio Mezzetti and Prof. Dr. Antonio Togni on “Enantioselective Metal Catalyzed Aziridination of Imines”
10.2003 - 08.2006 B.Sc. in Chemistry at the Technical University of Munich
Bachelor Thesis with Prof. Dr. Dr. h.c. mult. Wolfgang A. Herrmann on “Carbocyclic Carbenes as Directing Ligands in Homogenous Catalysis”
08.1993 - 06.2002 Abitur (A-Levels) at the Bischöfliche Marienschule Mönchengladbach

Work Experience
09.2008 - 01.2011 Teacher in the “Inorganic and Organic Chemistry 2” lab course
01.2009 - 06.2011 Supervising three semester students during their research projects and one graduate student during his Master thesis
02.2005 - 03.2005 Internship at Bayer AG in Leverkusen, Germany
06.2003 - 07.2003 Internship at NGK Spark Plug Europe GmbH in Ratingen, Germany
07.2002 - 04.2003 Civil Service at the Arbeiterwohlfahrt in Mönchengladbach, Germany