Topics in Organometallic Chemistry 74

Marko Hapke
Martin Kotora *Editors*

Metallocenes in Regio- and Stereoselective Synthesis

Springer

74
Topics in Organometallic Chemistry

Aims and Scope

The series *Topics in Organometallic Chemistry* presents critical overviews of research results in organometallic chemistry. As our understanding of organometallic structure, properties and mechanisms increases, new ways are opened for the design of organometallic compounds and reactions tailored to the needs of such diverse areas as organic synthesis, medical research, biology and materials science. Thus the scope of coverage includes a broad range of topics of pure and applied organometallic chemistry, where new breakthroughs are being achieved that are of significance to a larger scientific audience.

The individual volumes of *Topics in Organometallic Chemistry* are thematic. Review articles are generally invited by the volume editors. All chapters from Topics in Organometallic Chemistry are published Online First with an individual DOI. In references, *Topics in Organometallic Chemistry* is abbreviated as Top Organomet Chem and cited as a journal.

Marko Hapke • Martin Kotora
Editors

Metallocenes in Regio- and Stereoselective Synthesis

With contributions by

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Preface

In the intricate landscape of organic synthesis, the fusion of metallocenes and regio- and stereoselective strategies has emerged as a transformative alliance, empowering chemists to shape molecular architectures with meticulous precision. Although the application of metallocenes as catalysts started shortly after their discovery in the 1950s, they are still a rich source for discovering novel and often unusual transformations of organic molecules as well as a tool for induction of stereochemical control in asymmetric synthesis. A first volume on metallocene chemistry was edited for *Topics in Organometallic Chemistry* by Prof. T. Takahashi in 2005. The presented edited volume "Metallocenes in Regio- and Stereoselective Synthesis" is a dedicated exploration of the synergistic interplay between metallocene catalysts and the pursuit of precise control over both regio- and stereoisomeric outcomes in organic transformations.

This volume comprises cyclopentadienyl complexes from the early to the late transition metals, describing actual synthetic methodology for the preparation of highly substituted as well as chiral cyclopentadienes and novel methodologies for their installation on the different transition metals. The synthesis and application of highly substituted cyclopentadienes (chapter "Synthesis and Application of Highly Substituted Cyclopentadienes") and more specifically 1,2-substituted cyclopentadienes (chapter "Synthesis of 1,2-Disubstituted Cyclopentadienes and Their Application") is complemented by a compilation of various synthetic approaches towards novel chiral cyclopentadienes, which recently found application in a variety of chiral transformations, including C–H functionalization reactions (chapter "Synthesis and Application of Novel Chiral Cp Ligands in Transition Metal Catalysis"). The chemistry of ferrocenes including novel syntheses of chiral ferrocenes and examples of new applications is presented (chapter "Planar Chiral Ferrocenes: A Concise Introduction"), as well as the use of cyclopentadienes as functional ligand class such as the Knölker-type complexes and their function in hydrogen transfer reactions (chapter "Knölker-Type Catalysts for (Asymmetric) Hydrogenation Reactions"). A separate chapter is devoted to recent developments in the preparation of early transition metal (half-)sandwich metallocenes and their

synthetic application (chapter "Selective Transformations Mediated by Group 4 Metal Cyclopentadienyl Complexes"). In addition, two contributions focus on the less-known chemistry of naturally occurring cyclopentadienes, cyclopentadienyl anions and diazafluorenes (chapters "Naturally Occurring Cyclopentadienes and Cyclopentadienyl Anions" and "Naturally Occurring Diazofluorenes").

A single volume can hardly cover the broad field and synthetic application of metallocenes. Therefore, we hope that the chapters herein will allow to embrace the dynamic development and potential possibilities of metallocenes, contributing to a general understanding of their role in shaping regio- and stereoselective synthetic pathways. From fundamental concepts to modern applications, the content shall cater to a broader audience, encompassing active researchers and synthetic chemists alike. Metallocenes are a vibrant field of research even after decades, therefore, this volume covers state-of-the-art knowledge and sheds light on future developments and applications. The book is aimed at researchers, graduate students, and synthetic chemists at all levels in academia and industry.

Our sincere gratitude goes out to the contributors whose commitment and scholarly rigor have enriched this volume. We also extend our appreciation to the publishers, Charlotte Hollingworth and Alamelu Damodharan, for their patience through the pandemic times and their dedication to the publication of this volume.

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Synthesis and Application of Highly Substituted Cyclopentadienes

Ken Tanaka

Contents

Abstract Densely substituted cyclopentadienes and pentafulvenes are important compounds because these compounds serve as versatile precursors of metallocenes that show high activity in valuable catalytic transformations. For example, half-sandwich metallocenes of late transition metals, such as rhodium, iridium, and cobalt, are highly active catalysts for the C–H bond functionalization. As the structural modification of cyclopentadienyl ligands on the metallocenes improves catalytic efficiency and selectivity, the development of new methods for the synthesis of substituted cyclopentadienes and pentafulvenes is highly important. In this chapter, the synthesis of highly substituted cyclopentadienes and pentafulvenes and their application to the synthesis of half-sandwich metallocenes of late transition metals are described.

Keywords Annulation · C–H bond functionalization · Cyclopentadienes · Half-sandwich metallocenes · Late transition metals · Palladium · Pentafulvenes · Reductive complexation · Rhodium

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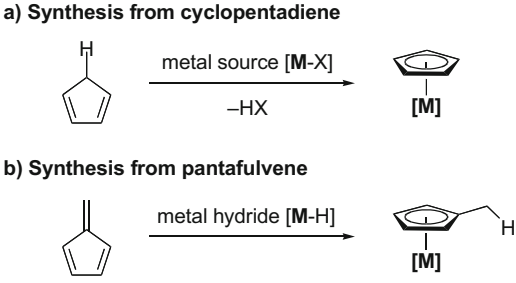
1 Introduction

Cyclopentadienes and pentafulvenes have been widely used as versatile precursors of metallocenes [1, 2]. Recently, half-sandwiches of late transition metals, such as rhodium, iridium, and cobalt, attract much attention as highly active catalysts for the C–H bond functionalization [3–8]. The half-sandwich metallocenes of the late transition metals can be readily synthesized by deprotonative complexation of cyclopentadiene with metal halide [M-X] through the elimination of HX (Scheme 1a) [1], and reductive complexation of pentafulvene with metal hydride [M-H] (Scheme 1b) [2].

Recent interests in the half-sandwich metallocene-catalyzed C–H bond functionalization reactions focus on the modification of cyclopentadienyl (Cp) ligands in order to improve catalytic efficiency and selectivity [9]. Thus, the development of new methods for the synthesis of substituted cyclopentadienes and pentafulvenes is highly important [1, 2]. As the other chapter covers the synthesis and application of disubstituted cyclopentadienes, this chapter focuses on recent progress in the synthesis of highly substituted cyclopentadienes and pentafulvenes. The complexation of these cyclopentadienes and pentafulvenes with late transition metals, and the applications of the thus synthesized late transition metal half-sandwich metallocenes to catalytic reactions are also disclosed.

2 Synthesis of Highly Substituted Cyclopentadienes and Pentafulvenes

This section covers the synthesis of tri-, tetra-, and penta-substituted cyclopentadienes and pentafulvenes. In the synthesis of the highly substituted cyclopentadienes, the synthetic methods are further classified into those for (1) alkyl- and aryl-substituted cyclopentadienes, and (2) functionalized cyclopentadienes. The common methods for the synthesis of cyclopentadienes are classified into two categories: (1) five-membered ring constructing annulation reactions (e.g., [2 + 2 + 1] and [3 + 2] annulation reactions) and (2) electrocyclization reactions (e.g., Nazarov Cyclization). *On the other hand,* the common methods for



Scheme 1 Cyclopentadiene (**a**) and pentafulvene (**b**) as precursors for half-sandwich metallocenes of late transition metals

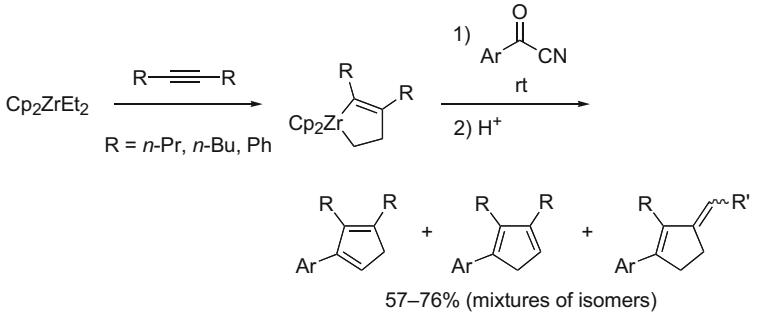
the synthesis of pentafulvenes are also classified into two categories: (1) condensation of carbonyl compounds and substituted cyclopentadienes, and (2) stoichiometric and catalytic [2 + 2 + 1] annulations. Recent progress as well as classical common methods is disclosed.

2.1 Alkyl- and Aryl-Substituted Cyclopentadienes

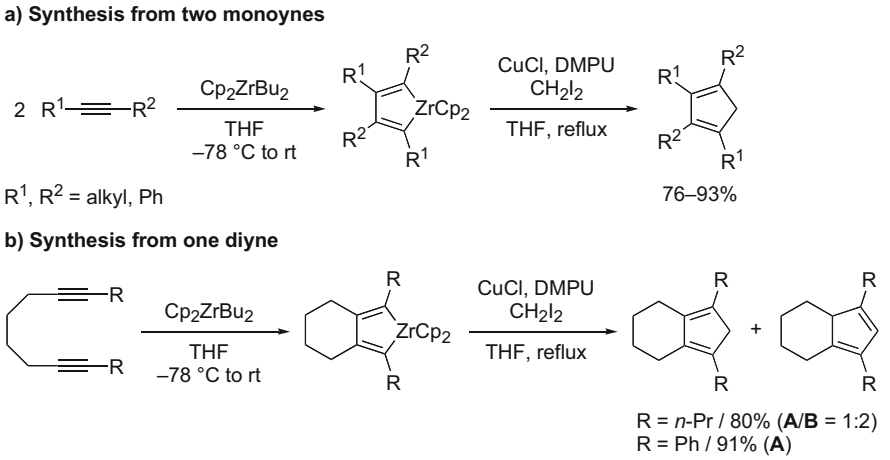
The [2 + 2 + 1] annulation reactions of zirconacyclopentenes and C1 sources are useful methods for the synthesis of tri-, tetra-, and penta-substituted cyclopentadienes. For example, zirconacyclopentenes, generated by the reactions of Cp_2ZrEt_2 (Cp = η^5-C_5H_5) and internal alkynes, reacted directly with acyl cyanides at room temperature to give 1,2,3-trisubstituted cyclopentadienes in high yields, although products were isolated as mixtures of positional double-bond isomers (Scheme 2) [10].

Tetrasubstituted cyclopentadieness with identical or different substituents could be synthesized in good to excellent yields through a zirconium- and copper-mediated intermolecular coupling process. This synthetic procedure involved three organic partners, including one CH_2I_2 and two different or identical internal alkynes. Two internal monoynes reacted with Cp_2ZrBu_2 regioselectively to afford the corresponding zirconacyclopentadienes. These zirconacycles reacted with CH_2I_2 in the presence of CuCl and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) to afford the tetrasubstituted cyclopentadienes in good yields (Scheme 3a) [11]. One internal diyne instead of two internal monoynes also reacted with Cp_2ZrBu_2 to afford the corresponding bicyclic zirconacyclopentadienes. These zirconacycles reacted with CH_2I_2 to afford the bicyclic cyclopentadienes in high yields, although the use of a dialkyl-substituted 1,7-diyne afforded a mixture of positional double-bond isomers (Scheme 3b) [11].

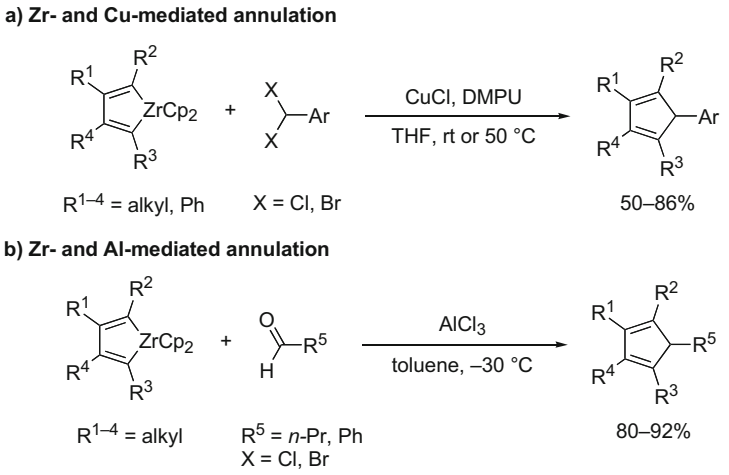
Pentasubstituted cyclopentadienes with identical or different substituents could be synthesized in moderate to good yields through the zirconium- and copper-



Scheme 2 Synthesis of 1,2,3-trisubstituted cyclopentadienes by zirconium-mediated [2 + 2 + 1] annulation



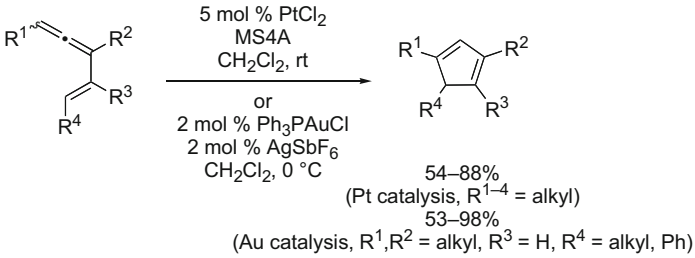
Scheme 3 Synthesis of tetrasubstituted cyclopentadienes from two monotones (**a**) and one diyne (**b**) by zirconium- and copper-mediated [2 + 2 + 1] annulation



Scheme 4 Synthesis of pentasubstituted cyclopentadienes by zirconium- and copper (**a**)- or aluminum (**b**)-mediated [2 + 2 + 1] annulation

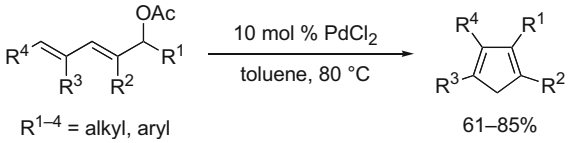
mediated intermolecular coupling reaction using benzal halides instead of CH_2I_2 (Scheme 4a) [12]. Additionally, pentasubstituted cyclopentadienes could also be synthesized in good yields through the zirconium- and aluminum-mediated intermolecular coupling reaction of two molecules of an alkyne with an aldehyde (Scheme 4b) [13]. Importantly, only one of the possible positional double-bond isomers was formed.

The $PtCl_2$-catalyzed cycloisomerization of 1,2,4-trienes proceeded at room temperature in the presence of MS4A to give the corresponding tri- and tetrasubstituted



Scheme 5 Synthesis of tri- and tetrasubstituted cyclopentadienes by platinum- or gold-catalyzed cycloisomerization

Scheme 6 Synthesis of tetrasubstituted cyclopentadienes by intramolecular alder–ene reaction



cyclopentadienes in moderate to good yields (Scheme 5) [14]. This cycloisomerization reaction was also catalyzed by a cationic gold(I)/PPh_3 complex (Scheme 5) [15].

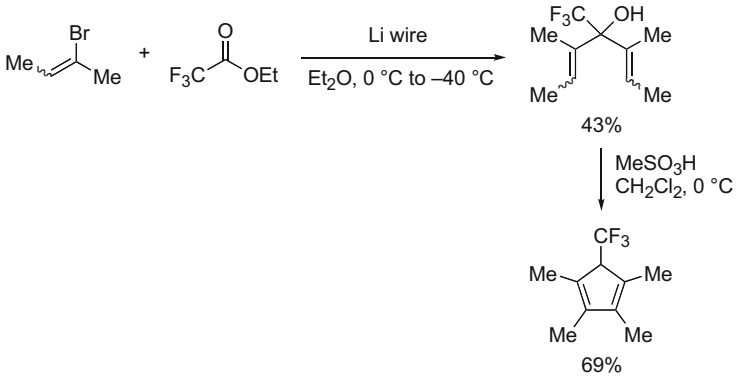
The intramolecular Alder–ene reaction was also applied to the synthesis of densely substituted cyclopentadienes. The $PdCl_2$-catalyzed intramolecular Alder–ene-type reaction of 2,4-pentadienyl acetates afforded the corresponding tetrasubstituted cyclopentadienes in moderate to good yields (Scheme 6) [16].

The Nazarov cyclization is a useful and general method for the synthesis of pentasubstituted cyclopentadienes, although strong acids are necessary. For example, trifluoromethyl-substituted electron-deficient cyclopentadiene was successfully synthesized in good yield via the double Grignard reactions giving dienyl *tert*-alcohol followed by the Nazarov cyclization using $MeSO_3H$ (Scheme 7) [17, 18].

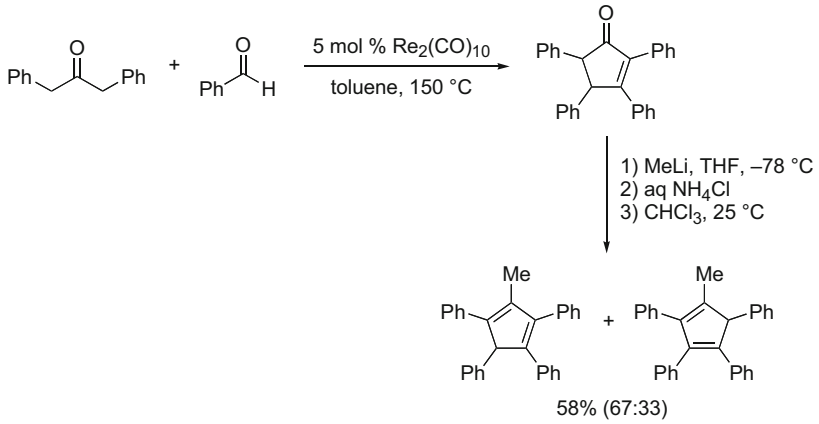
The rhenium-catalyzed double aldol condensation and the successive Nazarov cyclization afforded a tetrasubstituted cyclopentenone. This cyclopentenone was converted to a pentasubstituted cyclopentadiene as a mixture of positional double-bond isomers through methylation with methyllithium followed by dehydration (Scheme 8) [19].

2.2 *Functionalized Cyclopentadienes*

The nickel-catalyzed [3 + 2] annulation of 2-trifluoromethyl-1-alkenes with internal alkynes via sequential β-fluorine elimination afforded fluorine-substituted cyclopentadienes in moderate to good yields (Scheme 9) [20, 21]. The nickel (II) difluoride species formed in this reaction was reduced by a diboron compound $[B_2(nep)_2]$, regenerating the catalytically active nickel(0) species.

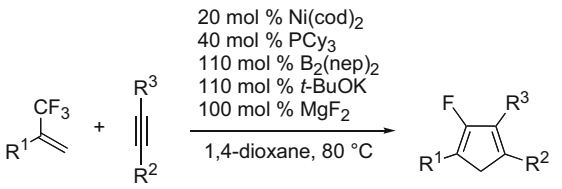


Scheme 7 Synthesis of pentasubstituted cyclopentadiene via double grignard reactions followed by Nazarov cyclization



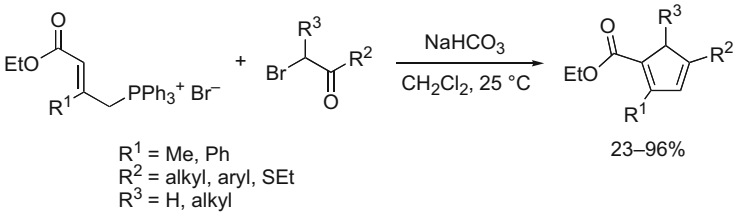
Scheme 8 Synthesis of pentasubstituted cyclopentadienes via rhenium-catalyzed double aldol condensation, Nazarov cyclization, and methylation/dehydration

Scheme 9 Synthesis of fluorine-substituted cyclopentadienes by nickel-catalyzed [3 + 2] annulation

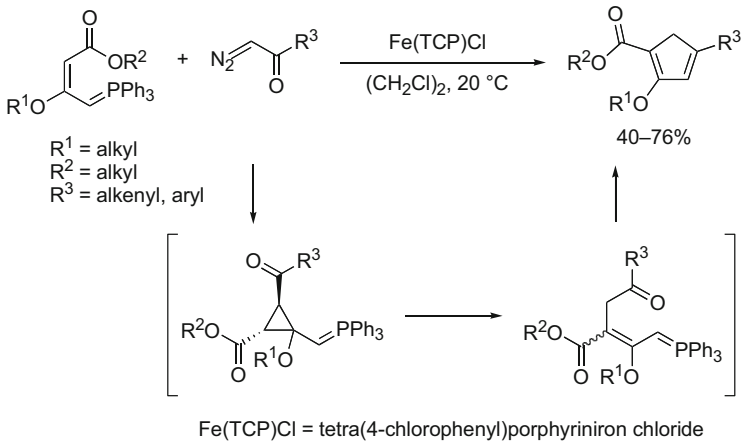


R^1 = aryl, CO_2t-Bu
R^2, R^3 = alkyl

nep = neopentylglycolato



Scheme 10 Synthesis of alkoxycarbonyl-substituted cyclopentadienes by [3 + 2] annulation

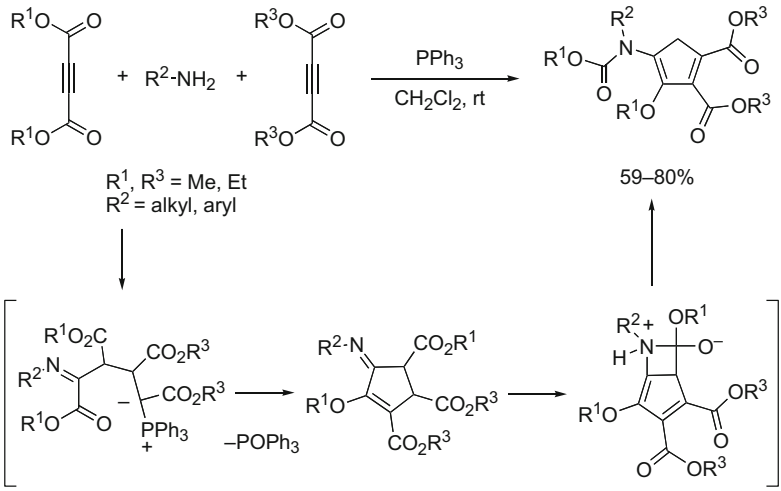


Scheme 11 Synthesis of alkoxycarbonyl-substituted cyclopentadienes by iron-catalyzed [3 + 2] annulation

The [3 + 2] annulation of (3-ethoxycarbonyl-2-substituted-2-propenylidene)-triphenylphosphoranes regioselectively reacted with α-bromoketones at room temperature to give tri- or tetrasubstituted cyclopentadienes bearing the alkoxycarbonyl group in good to excellent yields (Scheme 10) [22, 23]. *S*-Ethyl bromoethanethioafote could be employed for this reaction to yield 4-ethylthiocyclopentadienes (R^2 = SEt, Scheme 10) [22, 23].

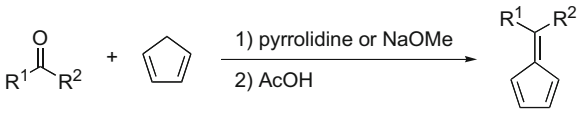
A range of ester-containing cyclopentadienes was obtained in moderate to good yields by the sp^2 C-H insertion reaction and the Wittig reaction between ylide-activated and trisubstituted alkenes, and substituted diazo carbonyls in the presence of catalytic amounts of tetra(4-chlorophenyl)porphyrin iron chloride [Fe(TCP)Cl] at room temperature (Scheme 11) [24].

Highly functionalized cyclopentadienes, dialkyl 4-[alkyl(alkoxycarbonyl)-amino]-3-alkoxy-1,3-cyclopentadiene-1,2-dicarboxylates, were obtained in good yields at room temperature via a three-component tandem reaction between primary alkylamines and two acetylenic esters in the presence of triphenylphosphine at room temperature (Scheme 12) [25].



Scheme 12 Synthesis of highly functionalized cyclopentadienes by three-component tandem reaction

Scheme 13 Synthesis of substituted pentafulvenes by condensation of cyclopentadiene with carbonyl compounds

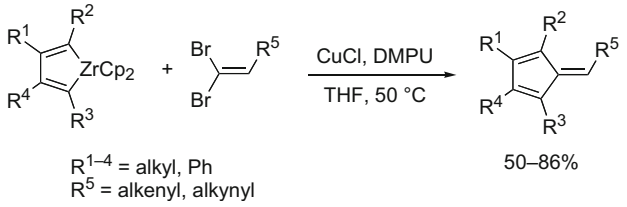


2.3 *Pentafulvenes*

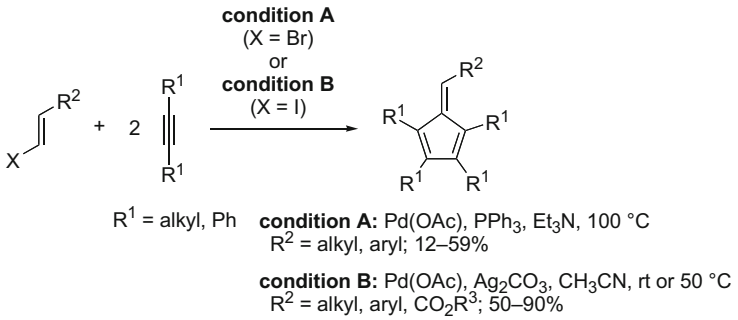
Substituted pentafulvenes were readily prepared by the condensation reactions. The reaction of freshly distilled cyclopentadiene and aldehydes or ketones in the presence of pyrrolidine or NaOMe as a base, and the successive treatment with AcOH afforded the corresponding substituted pentafulvenes in moderate to high yields (Scheme 13) [26].

As described in the previous section, the zirconium- and copper-mediated intermolecular coupling reaction of zirconacyclopentadienes, derived from two internal alkynes, and benzal halides affords pentasubstituted cyclopentadienes (Scheme 4a) [12]. In this transformation, the use of 1,1-dibromo-1-alken-3-ynes and 1,1-dibromo-1,3-alkadienes in place of benzal halides afforded the corresponding pentasubstituted pentafulvenes in moderate to good yields (Scheme 14) [12].

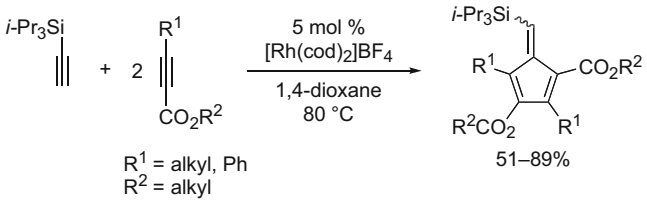
$Pd(OAc)_2$ was able to catalyze the [2 + 2 + 1] annulation of one alkenyl bromide and two alkynes at 100°C to give the corresponding densely substituted pentafulvenes (Scheme 15) [27, 28]. Although the product yields were low to moderate, this reaction is very useful and practical because this method enables the one-step catalytic synthesis of pentasubstituted pentafulvenes from readily



Scheme 14 Synthesis of pentasubstituted pentafulvenes by zirconium- and copper-mediated [2 + 2 + 1] annulation



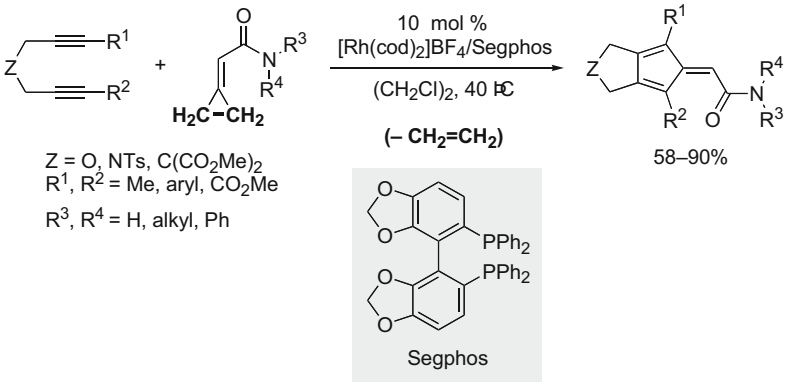
Scheme 15 Synthesis of pentasubstituted pentafulvenes by palladium-catalyzed [2 + 2 + 1] annulation



Scheme 16 Synthesis of 1,3-dialkoxycarbonyl-6-triisoprpylsilylpentafulvenes by rhodium-catalyzed [2 + 2 + 1] annulation

available starting materials. It is interesting to note that, in addition to the palladium catalyst, the silver salt and carbonate ions significantly affect this reaction. Thus, the reactions of two alkynes and an alkenyl iodide proceeded at lower temperature of 50°C in the presence of Ag_2CO_3 to give the corresponding pentasubstituted pentafulvenes in improved yields of 50–90% (Scheme 15) [27, 28].

A rhodium(I) complex is able to catalyze the [2 + 2 + 1] annulation of one terminal alkyne and two internal alkynes, leading to pentasubstituted pentafulvenes. The cationic rhodium(I)/cod complex-catalyzed [2 + 2 + 1] annulation of one triisopropylsilylacetylene and two alkynyl esters produced 1,3-dialkoxycarbonyl-6-triisoprpylsilylpentafulvenes in moderate to good yields (Scheme 16) [29].



Scheme 17 Synthesis of 6-carbamoylpentafulvenes by rhodium-catalyzed [2 + 2 + 1] annulation

A cationic rhodium(I)/Segphos complex catalyzed the [2 + 2 + 1] cycloaddition of internal 1,6-diynes with cyclopropylideneacetamides giving pentasubstituted pentafulvenes bearing a pendant amide moiety in good yields (Scheme 17) [30]. In this reaction, cyclopropylideneacetamides act as a C1 source by the conversion into rhodium vinylidenes through liberation of ethylene.

3 Application to Synthesis of Half-Sandwich Metallocenes of Late Transition Metals

The highly substituted cyclopentadienes and pentafulvenes serve as versatile precursors for the synthesis of metallocenes [3–9]. As the other chapter covers the synthesis of metallocenes of early transition metals, this section focuses on the synthesis of metallocenes of late transition metals, especially half-sandwich ones that are useful for the catalytic reactions.

As mentioned in the introduction, half-sandwich metallocenes of late transition metals can be readily synthesized by deprotonative complexation of cyclopentadiene with a metal halide (Scheme 1a) [3–8] and reductive complexation of pentafulvene with a metal hydride (Scheme 1b) [9]. The most simple complexation method of substituted cyclopentadienes with late transition metals is the deprotonative complexation using metal halides [M-X] through liberation of HX. However, this method suffers from low reactivity toward sterically demanding and/or less acidic cyclopentadienes. The deprotonative complexation using $Tl(OEt)_2$ as a base is highly reliable, while the use of $Tl(OEt)_2$ is not practical due to its high toxicity [31].

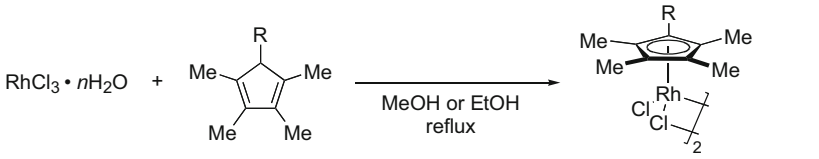
In addition to classical methods, recently developed highly efficient and practical methods that allow complexation of highly substituted cyclopentadienes with transition metals are disclosed. Additionally, newly developed reductive complexation methods of highly substituted pentafulvenes with metal hydrides are disclosed. The

thus synthesized highly substituted and functionalized cyclopentadienyl late transition metal complexes were successfully employed in the catalytic transformations.

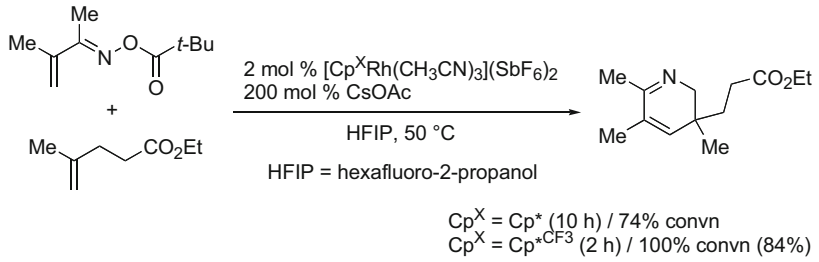
3.1 From Highly Substituted Cyclopentadienes

The reaction of the electronically and sterically tuned cyclopentadienes with $RhCl_3$ in an alcohol solvent furnished the corresponding dinuclear cyclopentadienyl rhodium(III) complexes through liberation of HCl. For example, trifluoromethyl- [32] or *tert*-butyl- [33] substituted cyclopentadiene reacted with $RhCl_3$ in MeOH or EtOH, respectively, to give the corresponding dinuclear pentasubstituted cyclopentadienyl (Cp^{*CF3} and $Cp^{*t\text{-}Bu}$) rhodium(III) complexes (Scheme 18). The complexation yield using the sterically less demanding and highly acidic trifluoromethyl-substituted cyclopentadiene was high (72%), however, that using the sterically demanding and less acidic *tert*-butyl-substituted cyclopentadiene was low (20%).

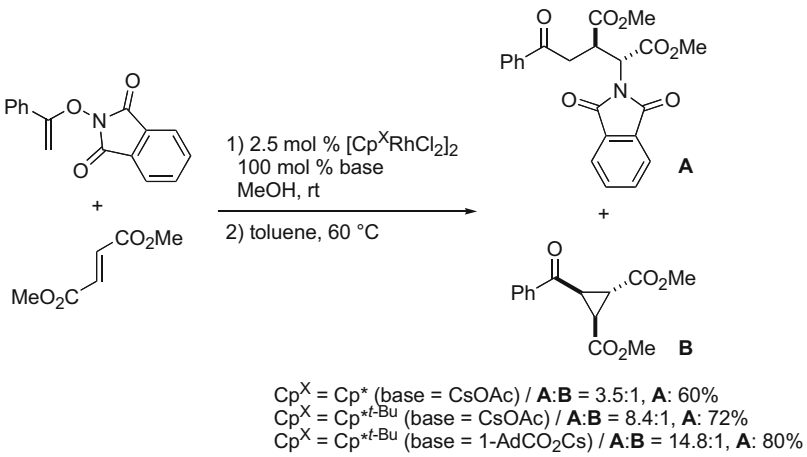
The thus obtained electron-deficient trifluoromethyl-tetramethylcyclopentadienyl (Cp^{*CF3}) rhodium(III) complex showed significantly higher catalytic activity and selectivity than a commercially available pentamethylcyclopentadienyl (Cp*) rhodium(III) complex in the [4 + 2] annulation of *O*-pivaloylalkenyloxime and 1,1-disubstituted alkene, leading to substituted 2,3-dihydropyridine, through the sp^2 C–H bond activation (Scheme 19) [34].



Scheme 18 Synthesis of Cp^{*CF3}Rh(III) and $Cp^{*t\text{-}Bu}$Rh(III) complexes by deprotonative complexation of pentasubstituted cyclopentadienes with $RhCl_3$

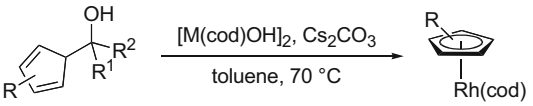


Scheme 19 Application of Cp^{*CF3}Rh(III) complex to sp^2 C–H bond functionalization



Scheme 20 Application of $Cp^{*t\text{-}Bu}Rh(III)$ complex to sp^2 C–H bond functionalization

Scheme 21 Synthesis of substituted cyclopentadienyl transition metal complexes from substituted cyclopentadienyl carbinols and transition metal hydroxides through β-carbon elimination



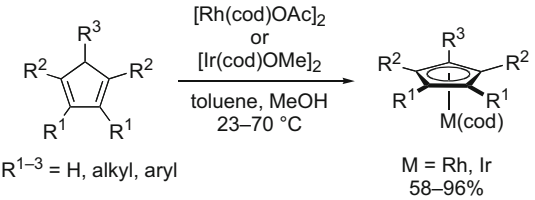
$R^1 = R^2 = Me$
$R^1 = Ph$, $R^2 = Me$
$R^1 = Ph$, $R^2 = CO_2Me$

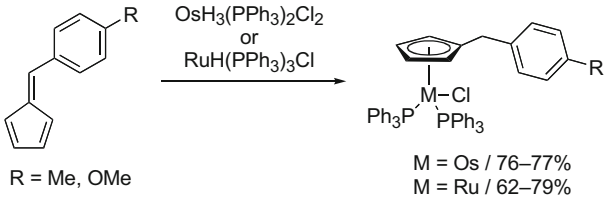
M = Rh, Ir, Co

In the rhodium-catalyzed carboamination reaction of dimethylfumarate with 2-phenyl-*O*-phthalimidylvinylether giving amino compound **A**, the cyclopropanation reaction giving cyclopropane **B** was competitive process. The screening of the cyclopentadienyl ligands revealed that the chemoselectivity depends on the size of the cyclopentadienyl ligand used. Thus, the use of *tert*-butyl-tetramethyl-cyclopentadienyl ligand ($Cp^{*t\text{-}Bu}$) delivered the best selectivity (**A/B** = 8.4:1). Replacing the cesium acetate base with cesium adamantylcarboxylate further improved the selectivity (**A/B** = 14.8:1) to give the desired carboamination product **A** in high yield of 80% (Scheme 20) [33].

As mentioned above, the use of $Tl(OEt)_2$ as a base is highly reliable method for the complexation of the sterically demanding and/or less acidic cyclopentadienes with $RhCl_3$ [31]. However, the use of $Tl(OEt)_2$ suffers from its high toxicity. Recently, new approach to access cyclopentadienyl late transition metal complexes has been reported. Rhodium, iridium, and cobalt hydroxides rapidly reacted with a wide variety of cyclopentadienyl carbinols in the presence of non-toxic base (Cs_2CO_3) via β-carbon eliminations to give directly the corresponding cyclopentadienyl-metal complexes (Scheme 21) [35]. An advantage of this method is the direct and flexible use of storable preligands (cyclopentadienyl carbinols).

Scheme 22 Synthesis of substituted cyclopentadienyl rhodium(I) and iridium (I) complexes from substituted cyclopentadienes, and RhOAc and IrOMe through C-H activation





Scheme 23 Reductive complexation of pentafulvenes with osmium and ruthenium hydrides

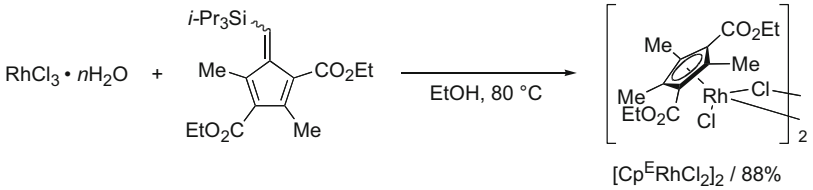
A more direct and highly practical complexation method for substituted cyclopentadienyl rhodium and iridium complexes was reported recently. $[Rh(cod)OAc]_2$ and $[Ir(cod)OMe]_2$ complexes reacted with substituted cyclopentadienes to give the corresponding cyclopentadienyl rhodium(I) and iridium(I) complexes in good yields, through an intramolecular proton abstraction by the acetate or methoxide ligand (Scheme 22) [36]. This procedure employs the free Cp^xH with stable and commercially available rhodium(I) and iridium(I) complexes without using base or additive. Furthermore, the reaction conditions are mild and do not require the exclusion of air and moisture.

3.2 *From Highly Substituted Pentafulvenes*

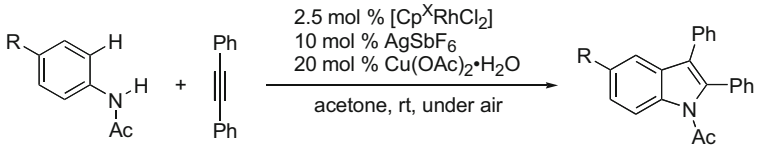
Reductive complexation of osmium and ruthenium hydrides with 6-substituted pentafulvenes afforded the corresponding substituted cyclopentadienyl osmium (II) [37] and ruthenium(II) [38] complexes in good yields (Scheme 23).

Desilylative reductive complexation of 1,3-dimethyl-2,4-di(ethoxycarbonyl)-6-triisopropyl-pentafulvene with rhodium(III) hydride, generated in situ from $RhCl_3$ and EtOH through liberation of HCl, proceeded smoothly in EtOH at 80°C to furnish the corresponding dinuclear electron-deficient cyclopentadienyl rhodium(III) complex, $[Cp^ERhCl_2]_2$, in quantitative yield (88% isolated yield) (Scheme 24) [29]. In this reaction, protodesilylation proceeded by liberated HCl.

The thus obtained electron-deficient cyclopentadienyl rhodium(III) complex, $[Cp^ERhCl_2]_2$, is a highly active and selective pre-catalyst for C–H bond functionalization. For example, a cationic $Cp^ERh(III)$ complex showed significantly higher catalytic activity than a cationic Cp*Rh(III) complex in the oxidative [3 + 2] annulation of acetanilides and an alkyne. The reactions proceeded at room

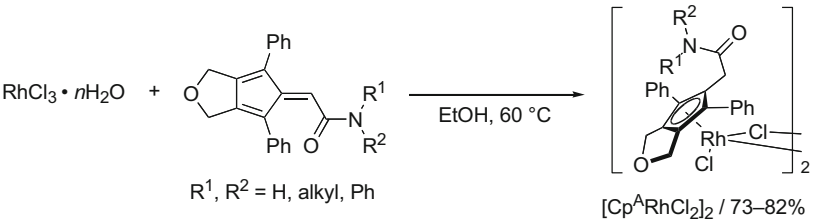


Scheme 24 Synthesis of $Cp^{E}Rh(III)$ complex by desilylative reductive complexation of 1,3-dimethoxycarbonyl-6-trimethylsilylpentafulvene with $RhCl_3$



	[Cp*RhCl$_2$]$_2$	[Cp^{E}RhCl$_2$]
R = H	28%	>99%
R = F	25%	>99%

Scheme 25 Application of $Cp^{E}Rh(III)$ complex to sp^2 C–H bond functionalization

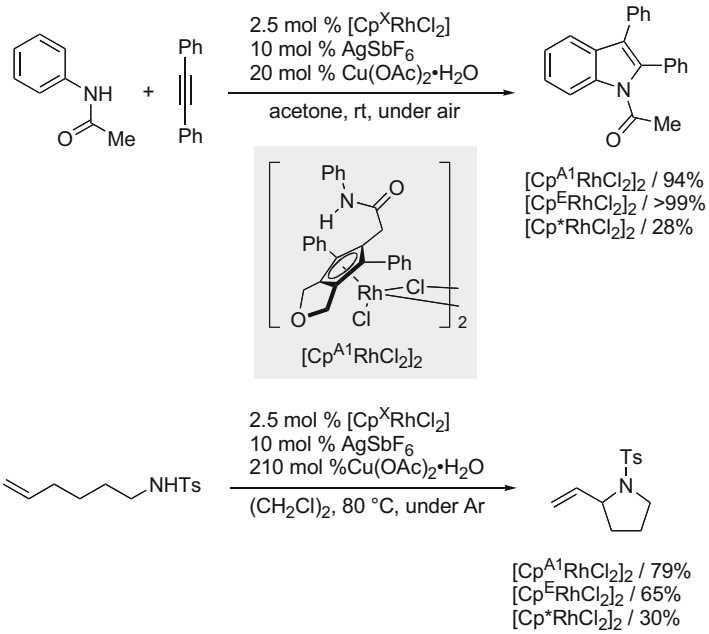


Scheme 26 Synthesis of Cp^{A}-rhodium(III) complex by reductive complexation of 6-carbamoylpentafulvenes with $RhCl_3$

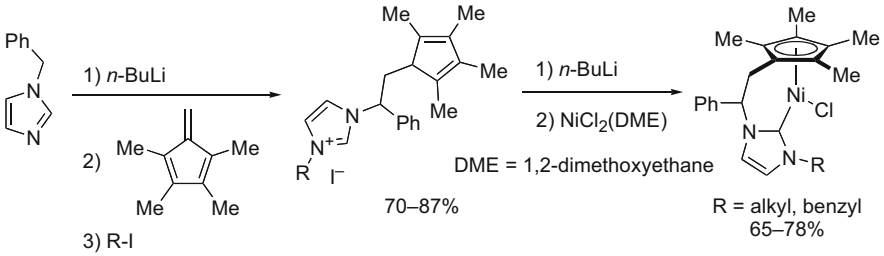
temperature under air to give the desired [3 + 2] annulation products (substituted indoles) in quantitative yields (Scheme 25) [29].

Similarly, the reductive complexation of 6-carbamoyl-pentafulvenes with $RhCl_3$ proceeded smoothly in EtOH at 60°C to furnish the corresponding dinuclear cyclopentadienyl rhodium(III) complexes bearing a pendant amide moiety, $[Cp^{A}RhCl_2]_2$, in quantitative yields (73–82% isolated yields) (Scheme 26) [30].

The thus obtained secondary NH-amide-pendant cyclopentadienyl rhodium(III) complex, $[Cp^{A}RhCl_2]_2$, is a highly active and selective pre-catalyst for C–H bond functionalization. For example, a cationic $Cp^{A1}Rh(III)$ complex showed significantly higher catalytic activity than a cationic Cp*Rh(III) complex in the oxidative [3 + 2] annulation of acetanilides and an alkyne through sp^2 C-H activation (Scheme 27, top) [30]. This catalytic activity is comparable to that of the cationic $Cp^{E}Rh(III)$ complex. This cationic $Cp^{A1}Rh(III)$ complex showed high catalytic activity in not



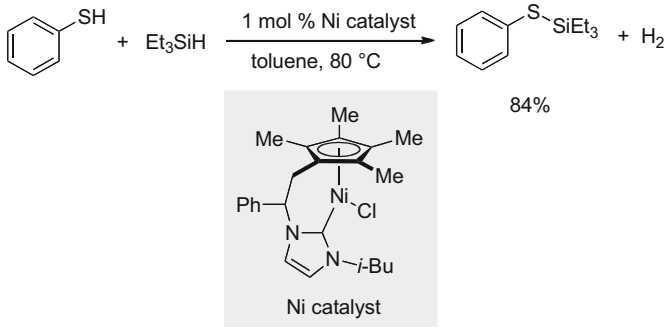
Scheme 27 Application of $Cp^{A}Rh(III)$ complexes to sp^2 and sp^3 C–H bond functionalizations



Scheme 28 Synthesis of NHC-coordinated Cp*Ni(II) complexes from pentafulvenes via carbometalation followed by deprotonative complexation

only sp^2 C-H functionalization but also sp^3 C-H functionalization (Scheme 27, bottom) [30]. The cationic $Cp^{A1}Rh(III)$ complex-catalyzed oxidative cyclization of an alkenyl-tosylamide proceeded in higher yield than those using the cationic Cp* and $Cp^{E}Rh(III)$ complexes.

The reaction of 1,2,3,4-tetramethylpentafulvene, *N*-benzyl imidazole, and alkyl or benzyl iodide afforded NHC-pendant Cp* ligand precursors in good yields. These ligand precursors reacted with $NiCl_2(DME)$ to give the corresponding NHC-pendant Cp*Ni(II) complexes in good yields (Scheme 28) [39].



Scheme 29 Application of NHC-coordinated Cp*Ni(II) complex to dehydrogenative coupling of thiols with Et_3SiH

The thus obtained NHC-pendant Cp*Ni(II) complex was a highly active catalyst for the dehydrogenative coupling reaction of benzene thiol with Et_3SiH (Scheme 29) [39, 40].

4 Summary and Outlook

This chapter disclosed the methods for the synthesis of tri-, tetra-, and pentasubstituted cyclopentadienes and pentafulvenes. The application of these compounds to the synthesis of half-sandwich metallocenes of late transition metals is also described. The development of new methods for the introduction of sterically demanding substituents and functional groups to cyclopentadienes and pentafulvenes enabled the syntheses of sterically and electronically tuned metallocenes. The development of new methods for complexation of the sterically demanding and functionalized cyclopentadienes and pentafulvenes with late transition metals also significantly expands the accessible metallocenes. For example, the thus synthesized new half-sandwich metallocenes of late transition metals significantly improved the catalytic efficiency and selectivity in the C–H bond functionalization. Further development of more facile and diverse synthesis of densely substituted cyclopentadienes and pentafulvenes is still waiting for the synthesis of structurally and functionally diverse metallocenes.

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Synthesis of 1,2-Disubstituted Cyclopentadienes and Their Application

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Abstract Cyclopentadiene and its substituted congeners have played an important role in organic chemistry since their discovery. Cyclopentadienyl and substituted cyclopentadienyl anions constitute currently a very important class of ligands for transition metal compounds. Cyclopentadienyl ligands in the respective metallocene complexes show usually high chemical inertness and stability. This property makes the metallocenes popular and indispensable catalysts in a plethora of organic transformations. This review focuses on development of synthetic pathways for preparation of selectively 1,2-disubstituted cyclopentadienes and their conversion to a wide variety of metallocenes. Application of 1,2-disubstituted metallocenes in catalytic processes is mentioned as well.

Keywords Cyclopentadiene · Metallocene · Regioselectivity · Synthesis

1 Introduction

Although the first synthesis of 1,3-cyclopentadiene had been reported shortly before the end of the nineteenth century by Kraemer and Spilker [1], it took more than 50 years before cyclopentadiene and its substituted congeners found its way into the realm of transition metal and organometallic chemistry. After the ground-breaking discovery of ferrocene by Pauson and Kealy in 1951 [2], cyclopentadienyl (Cp) or pentamethylcyclopentadienyl (Cp*) anions opened a pathway to a new class of anionic ancillary ligands for a broad range of various transition metals [3]. There have been several reasons for such a situation. First, the robust nature of the metal complexes expressed by oxidation stability, ligand non-transferability, and chemical inertness stimulated their application in the field of catalysis. Second, development of basic synthetic routes toward chiral cyclopentadienes, their transition metal complexes, and their exploitation in enantioselective synthesis have attracted interest for a long period of time. This is supported by two reviews on this topic published in the early 1990s [4, 5]. Given the long history of cyclopentadienyl complexes (or cyclopentadienyl salts) that has been spanning already for more than 70 years, these compounds have been always considered as typical examples of truly man-made molecules, albeit it has been shown in the last 20 years that the cyclopentadienyl anion can be an important fragment of several complex natural compounds such as juglorubine, daphnicyclidin, kinamycines, etc. (see chapters entitled Naturally Occurring Cyclopentadienes and Cyclopentadienyl Anions and Naturally Occurring Diazofluorenes). In addition, substituted cyclopentadienes obtained from a biosource can serve as advanced building blocks for synthesis of more complex molecules [6].

Attaching substituents to the cyclopentadiene's framework has a profound effect on properties of their respective transition metal complexes. In this respect both electronic and steric effects exerted by specific substituents affect the overall chemical and physical behavior of the respective Cp-metal complexes. These can be

varied over a wide range by the specific choice of the substituents on the cyclopentadiene ring. Such effects have been studied in detail for monosubstituted cyclopentadienes and their corresponding Ti, Zr, Hf complexes as part of development of new efficient polymerization catalysts [7–9]. Dehydrogenative arylation of electron-rich alkenes catalyzed by monosubstituted cyclopentadienyl rhodium complexes may serve as another example [10]. Attaching alkyl groups to the cyclopentadiene rings also increases solubility of the respective cyclopentadienyl complexes in non-polar solvents, comparison of Cp_2ZrHCl (Schwartz reagent) with that of $(MeC_6H_4)_2ZrHCl$ clearly demonstrates such an effect. The former is due to its polymeric nature almost insoluble in any solvent, whereas the latter is fairly soluble in toluene [11, 12].

Although the general trends are known and predictable, it should be emphasized that no predictions can be made concerning the overall effect to be expected of specific substituents. Depending on the metal, its valency state, and the cyclopentadienyl ligand used, the complexes proved to be of varying suitability for various applications.

Unlike application of unsubstituted or pentasubstituted cyclopentadienes in the form of their complexes with transition metals in organic synthesis, the use of 1,2-disubstituted cyclopentadienes as ligands for transition metals has not been pursued extensively. The situation has, however, changed in the last decade since it has been shown that transition metal complexes with 1,2-disubstituted cyclopentadienyl anions bearing a chiral scaffold based on the binaphthyl or spiranyl frameworks can be used as catalyst for a number of enantioselective reactions involving C–C, C–heteroatom, etc. bond formation processes [13]. Interestingly, other types of 1,2-disubstituted cyclopentadienyl complexes have not received such an attention. Their synthesis and application have been rather limited to a handful of cases, albeit a few noteworthy examples do exist. Hence, we intend to fill this gap and to cover synthetic approaches to their preparation and application. It should be also mentioned that a review dealing with synthesis of variously substituted cyclopentadienes has been recently published [14–17]; however, it does not cover specifically synthesis of 1,2-disubstituted cyclopentadienes.

2 1,2-Disubstituted Cyclopentadienes

There are three regioisomers for homo 1,2-disubstituted cyclopentadienes: 1,2-disubstituted cyclopenta-1,3-diene (**a**), 2,3-disubstituted cyclopenta-1,3-diene (**b**), and 1,5-disubstituted cyclopenta-1,3-diene (**c**) (Fig. 1, a). As for hetero (non-homosubstituted) 1,2-disubstituted ones the number of regioisomers increases to 5. For the sake of simplicity cyclopentadienes **a-c** will be referred to as 1,2-disubstituted cyclopentadienes and where the exact structure of the cyclopentadiene, i.e., positions of the double bonds relative to the substituents, is known or is assumed to be known the respective letters (a-c) will be added to the compound number. Where such an information is missing, only the respective

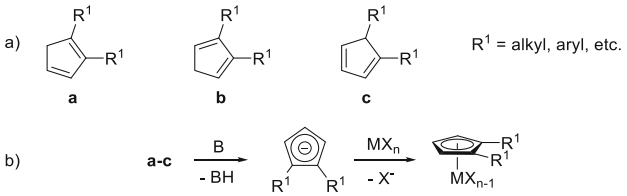


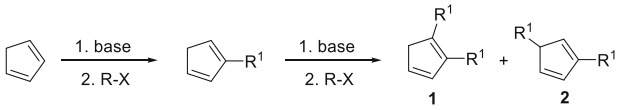
Fig. 1 Regioisomeric 1,2-disubstituted cyclopentadienes and their conversion to cyclopentadienyl anion and complexes

compound number will be used. Likelihood to form double bond regioisomers (in most cases very difficult to separate one from another), at the end of the day, makes analyses of such mixtures a bit complicated. On the other hand, after being converted to the respective anions and/or a metal η^5-Cp-complex such problem disappears due to the aromatic character of the Cp-anion (Fig. 1, b).

3 General Synthetic Approaches to 1,2-Dihomo and 1,2-Diheterosubstituted Cyclopentadienes

A regioselective preparation of 1,2-disubstituted cyclopentadienes **1** constitutes a challenging synthetic problem. From a general point of view, a sequential bisalkylation via intermediate monosubstituted cyclopentadienes commonly results in the formation of a mixture of 1,2- **1** and 1,3-substituted cyclopentadienes **2** that are as a rule difficult to separate because of their similar physical properties (Scheme 1). From mechanistic point of view, regioselectivity of the bisalkylation is uncontrollable leading always to mixtures of 1,2- and 1,3-disubstituted products. Overalkylation to multi-substituted cyclopentadienes could be an issue as well. The direct functionalization of cyclopentadiene is not feasible for preparation of arylated cyclopentadienes and other methods must be applied that, eventually, could result in regioselective synthesis of 1,2-disubstituted cyclopentadienes. Optionally, substituted cyclopentadienyl complexes could be prepared by direct functionalization of paternal unsubstituted cyclopentadienyl complexes. These methods usually rely on electrophilic aromatic substitution.

The lack of a unifying synthetic approach to 1,2-disubstituted cyclopentadienes **1** and derivatives thereof, several semi-general approaches have emerged over the last decades to prepare small libraries of such compounds. However, it should be taken into the account that 1,2-disubstituted cyclopentadienes **1** or the respective cyclopentadienyl complexes have not always been the final desired products, instead, in some cases they have been used as synthetic building blocks for preparation of more complex organic compounds.



Scheme 1 Two-fold alkylation of cyclopentadiene forming regioisomeric 1,2- and 1,3-disubstituted cyclopentadienes **1** and **2**

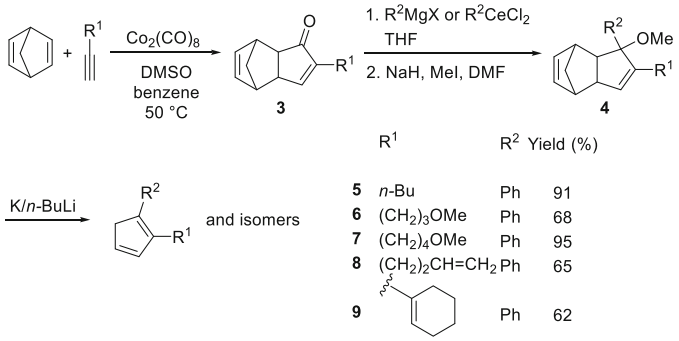
3.1 Regioselective Synthesis Based on Pauson–Khand Reaction

Chung et al. used the Pauson–Khand reaction as the crucial step in synthesis of several polysubstituted cyclopentadienes. The set of prepared substances included five examples of 1,2-disubstituted cyclopentadienes (Scheme 2) [18]. The approach was based on reactions of norbornadiene with terminal alkynes in the presence of a stoichiometric amount of $Co_2(CO)_8$ giving rise to tricyclic ketones **3**. Addition of Grignard or organocerium compounds to the carbonyl groups of the formed cyclopentenones **3** provided alcohols that were converted to methyl ethers **4**. Methyl ethers **4** underwent, upon treatment with a mixture of K/*n*-BuLi, retro-Diels-Alder reaction at room temperature forming the desired 1,2-disubstituted cyclopentadienes **5–9**. Five products bearing phenyl and various alkyl groups were synthesized. Internal alkynes could be used as well and 1,2,3-trisubstituted cyclopentadienes were obtained with a similar efficacy (not shown).

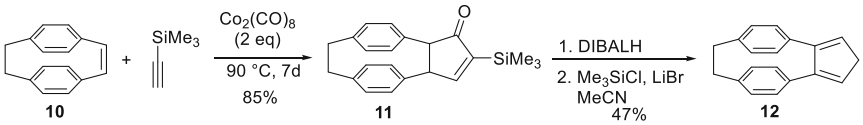
The Pauson–Khand strategy was also applied in a synthesis of 1,2-disubstituted cyclopentadienes bridged by the [2.2]paracyclophane scaffold. These compounds, from structural point of view, constitute an interesting class of substances with the defined rigid 3D framework. Their preparation was described by de Meijere et al. [19] and it started with [2.2]paracyclophan-1-ene **10** (Scheme 3) or [2.2] paracyclophanediene **13** (Scheme 4) furnishing ketones **11** and **14**, respectively. Ketones **11** and **14** were reduced to alcohols with DIBALH and after the subsequent treatment with Me_3SiCl/LiBr in MeCN yielded the corresponding cyclopentadienes **12** and **15** in 47 and 79% yields, respectively.

3.2 Regioselective Synthesis Based on Retro-Diels-Alder Reaction

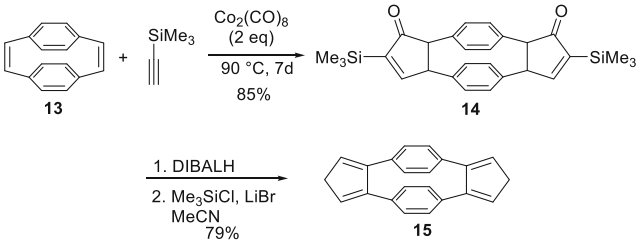
This method for preparation of 1,2-disubstituted cyclopentadienes is based on observation that norbornadiene reacts with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (DET) or 1,2,4,5-tetrazine-3,6- di(pyrid-2-yl) (DPT) giving rise to cyclopentadienes **16** (Scheme 5). An early report of Fabris et al. demonstrated that this methodology could be used for preparation of 2-bromo-1-trimethylstannylcyclopentadiene [20]. Later, Dastan et al. expanded the scope of the reaction preparing **16** and other 1,2-disubstituted cyclopentadienes **17–21** as well



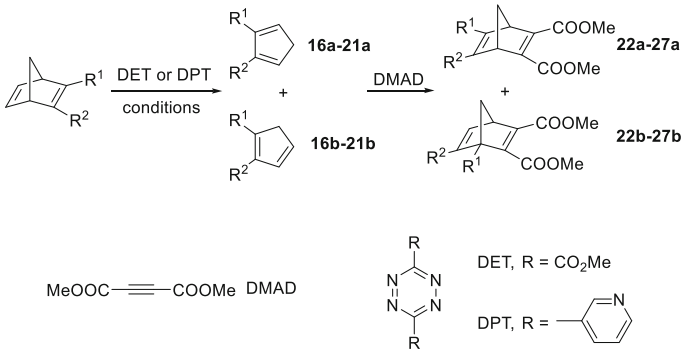
Scheme 2 Synthesis of 1,2-disubstituted cyclopentadienes **5–9** via the Pauson–Khand reaction



Scheme 3 Synthesis of **12** utilizing Pauson–Khand reaction



Scheme 4 Synthesis of **15** utilizing two-fold Pauson–Khand reaction



Scheme 5 Synthesis of 1,2-disubstituted cyclopentadienes **10–15** via *retro*-Diels-Alder reaction

Table 1 Yields of norbornadienes **22–27**

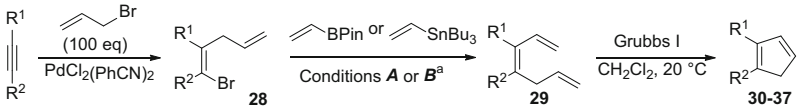
R^1	R^2	Conditions[a]	**a**:**b**[b]	Norbornadienes	Yield (%)[c]
Br	Br	iii	6:4	**22a** + **22b**	38 + 25
Br	$SnMe_3$	ii		**23a**	98
Ph-≡	Ph-≡	i	2:1	**24a** + **24b**	54 + 27
Br	$SiMe_3$	ii		**25a**	95
$SiMe_3$	$SiMe_3$	ii		**25a**	97
Ph	Ph	i		**27a**	96

[a] Conditions: i: DET, toluene, reflux overnight; ii: DET, CH_2Cl_2, rt, 5 min; iii: DPT, MeCN, sealed tube, 130°C, 2 d
[b] Isolated yields
[c] Determined as ratio of **22a**:**22b** and **24a**:**24b**, respectively

[21]; however, the formed cyclopentadienes **16–21** were not isolated as individual compounds but were trapped in the subsequent Diels-Alder reaction with dimethyl acetylene dicarboxylate as substituted norbornadienes **22–27** (Table 1).

3.3 Regioselective Synthesis Based on Haloallylation of Alkynes

A more general approach toward homo and hetero 1,2-disubstituted cyclopentadienes starting from alkynes was designed by Kotora et al. The reaction pathway starts from symmetrical or unsymmetrical alkynes and is based on sequence of three reactions: a) Pd-catalyzed haloallylation of alkynes, b) Pd-catalyzed cross-coupling, and, finally, c) Ru-catalyzed ring-closing metathesis (Scheme 6) [22]. Various starting alkynes bearing different functionalities such as alkyl, aryl, metallocenyl, and 2-hydroxyalkyl groups were successfully used. The crucial step of the sequence is regio- and stereoselective bromoallylation of alkynes that provides the corresponding *cis*-1-bromo-1,4-dienes **28** (*cis* with respect to relative position of bromine atom and allyl group). Haloallylation reaction was explored in the seminal work of Kaneda et al. who demonstrated its synthetic utility applicability [23]. The second step consisted of Stille or Suzuki-Miyaura cross-coupling of **28** with vinylstannane or vinylboronic acid pinacol ester to give trienes **29** that were in the third step subjected to ring-closing metathesis with the Grubbs I type catalyst giving the desired 1,2-disubstituted cyclopentadiene **30–37**. In general, various combinations of substituents in the starting alkyne were tolerated and all steps proceeded in good yields. The obtained cyclopentadienes were usually stable and did not succumb to Diels-Alder reaction. The only exceptions were cyclopentadienes bearing ester group. Although they could be detected in the reaction mixture, their isolation was



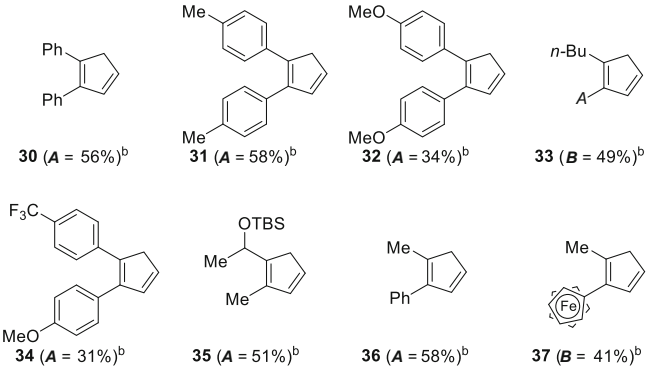
Scheme 6 Synthesis 1,2-disubstituted cyclopentadienes via bromoallylation

not successful resulting in the formation of intractable mixtures. Typical examples are displayed in Fig. 2.

3.4 Regioselective Synthesis Based on Alkylation of 2-Substituted 2-Cyclopentenones

1,2-Disubstituted cyclopentadienes were prepared from 2-methyl-2-cyclopentenone as it was demonstrated by Okawa et al. (Scheme 7). Nucleophilic addition of various alkyl Grignard reagents to the carbonyl group of 2-methyl-2-cyclopentenones **38** provided allyl alcohols **39** that were subsequently dehydrated to the corresponding homo and hetero 1,2-disubstituted cyclopentadienes **40–43** [24]. Exact yields of individual cyclopentadienes were not given, but they were claimed to be in the range of 36–45% yields. The prepared cyclopentadienes served as intermediates for preparation of 1,4-diacetoxycyclopent-2-enes via anodic oxidation.

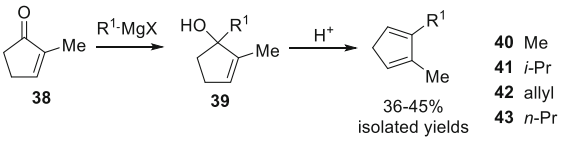
Nucleophilic addition to the carbonyl group followed by elimination was also exploited in other syntheses of 1,2-disubstituted cyclopentadienes, albeit this approach was used for preparation of individual substances. Elizarova et al. reported dehydration of unstable 1,2-dimethylcyclopent-2-en-1-ol **44**, which was prepared by addition of MeMgI to 2-methyl-2-cyclopentenone **38**, with PTSA, that provided a mixture of cyclopentadienes and other products in 41% yield (Scheme 8) [25]. It should be emphasized that the mixture contained 90% of 2,3-dimethylcyclopentadiene **40b**. During distillation equilibration took place and the ratio of isomers of **40a** and **40b** shifted to 3:2. A synthesis of a mixture of **40a** and **40b** (14:86) under similar conditions was also reported by Haynes [26]. The cyclopentadiene isomer ratio is close to the one reported by Elizarova et al. who described dehydration of 1,2-dimethylcyclopent-2-en-l-o1 **44** with NH_4Cl that yielded a mixture of **40a** and **40b**. However, details regarding yields of products were not given [27]. Dehydration of 2,3-dimethylcyclopent-2-en-1-ol with 15% HCl yielding 2,3-dimethylcyclopentadiene **40b** in 55% yield was reported by Schmitt et al. [28]. Later modification designed by Britzinger et al. relied on I_2 induced dehydration that provided the desired cyclopentadiene **40** as a mixture of double bond isomers (ratio of isomers was not specified) in even higher yield (cca. 30% overall yield starting from crotonic acid isopropyl ester) [29].

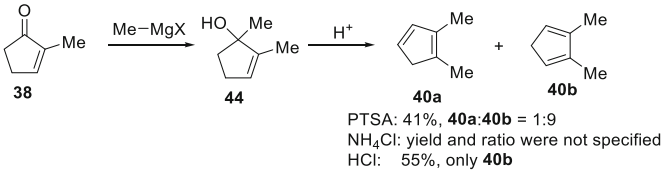


[a] ***A*** (Suzuki coupling): PEPPSI-i-Pr (5 mol %), Cs_2CO_3, THF/H_2O (9/1), 50 °C;
B (Stille coupling): PEPPSI-i-Pr (5 mol %), CsF, THF, MS 4 Å, 50 °C.
[b] Overall yields after three steps starting from alkynes.

Fig. 2 Synthesis of 1,2-disubstituted cyclopentadienes **30–37** via bromoallylation of alkynes

Scheme 7 Synthesis of 1,2-disubstituted cyclopentadienes **40–43** from 2-methyl-2-cyclopentenones **38**

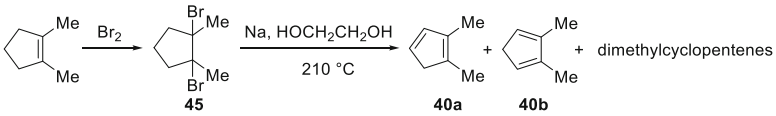




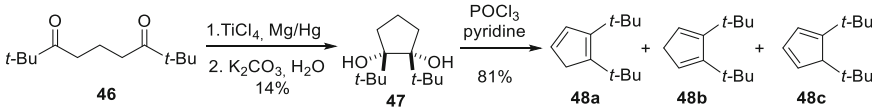
Scheme 8 Dehydration of 1,2-dimethylcyclopent-2-en-1-ol **44** to a mixture of 1,2-dimethylcyclopentadienes **40a** and **40b**

Elizarova et al. reported debromination of 1,2-dibromo-1,2-dimethylcyclopentane **45** with sodium in ethylene glycol providing a mixture of **40a** and **40b** in 3:2 ratio and 40% yield (Scheme 9) [25, 30].

Synthesis of 1,2-di(*t*-butyl)cyclopentadienes **48** constitutes a special case, because they cannot be prepared by an alkylation method, hence a different approach had to be developed. A method introduced by Hughes et al. relied on intramolecular coupling of 2,2,8,8-tetramethylnonane-3,7-dione **46** by using a mixture of $TiCl_4$ and Mg/Hg to *cis*-1,2-di(*t*-butyl)cyclopentane-1,2-diol **47** followed by dehydration. It resulted in the formation of a mixture of regioisomeric 1,2-di-*t*-butylcyclopentadienes **48** (Scheme 10) [31]. An optional method was developed as well and it was based on McMurry coupling of 2,2,8,8-tetramethylnonane-3,7-



Scheme 9 Debromination route to a mixture of **40a** and **40b**

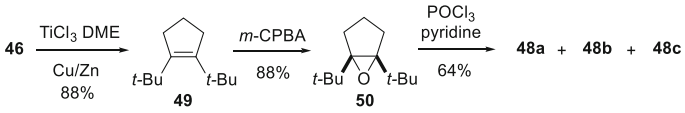


Scheme 10 Dehydration of pinacol **47** to regioisomeric 1,2-di(*t*-butyl)cyclopentadienes **48**

dione **46** to 1,2-di(*t*-butyl)cyclopent-1-ene **49** followed by epoxidation with *m*-CPBA to **50** and concluded by dehydration of the formed epoxide. The overall yield of the former approach after two steps starting from **46** was 33%, whereas the latter route gave the final compound **48** in 48% yield after three steps (Scheme 11) [32]. In addition, the latter route avoided the use of magnesium amalgam. 1,2-Di(*t*-butyl)cyclopentadiene **48** was converted to Sn and Tl cyclopentadienides that served as intermediates for preparation of the respective Re and Ru cyclopentadienyl complexes [33, 34]. Cyclopentadiene **48** was also used as a precursor for a preparation of an *ansa*-zirconocene as a catalyst for high pressure polymerization of 1-hexene [35].

4 Specific Synthetic Approaches to 1,2-Dialkylatedcyclopentadienes

For preparation of 1,2-dialkylcyclopentadienes several synthetic strategies were used based on different starting material. The most exploited method is based on non-regioselective two-fold alkylation of cyclopentadienes under basic conditions via cyclopentadienyl anions. On the other hand, regioselective approaches usually utilize elimination reactions to build the unsaturated system. In addition, it was demonstrated that skeletal rearrangements can also furnish 1,2-disubstituted cyclopentadienes, albeit this approach is not synthetically applicable. A rare example of a 1,2-disubstituted cyclopentadiene synthesis, but mechanistically interesting one, utilizes CO insertion into a diene-metal complex.



Scheme 11 An improved synthetic method for preparation of **48**

4.1 Alkylation of Cyclopentadiene

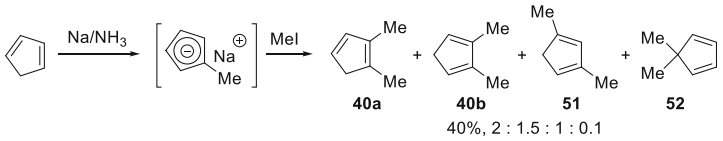
Although double alkylation of the maternal cyclopentadiene seems to be the simplest method to synthesize 1,2-disubstituted cyclopentadienes, it is plagued by formation of 1,2- and 1,3-disubstituted cyclopentadienes. Nonetheless, there have been several reports based on this approach.

An early example of double alkylation of cyclopentadiene was reported by Alder et al. [36]. Thus, a sequential alkylation of cyclopentadiene in Na/NH_3 with MeBr, EtBr, or *i*-PrBr provided mixtures of the corresponding dialkylated cyclopentadienes in high isolated yields of 90, 85, and 85%. However, regioisomeric composition of the obtained products was not specified, although it is obvious that mixtures of 1,2- and 1,3-disubstituted cyclopentadienes must have been obtained.

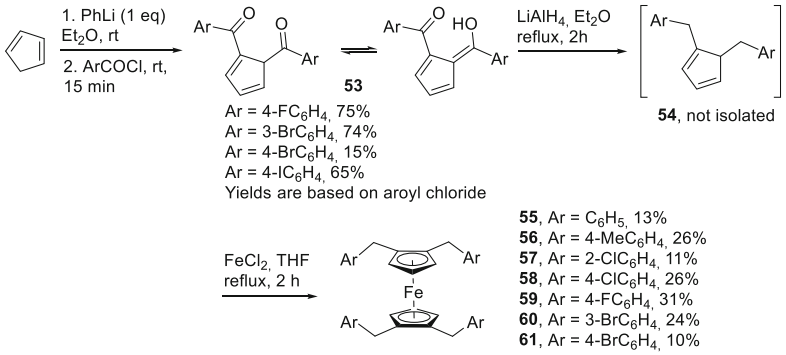
Similar reaction conditions as above were used by Haynes et al. who reacted sodium methylcyclopentadienide in liquid ammonia with CH_3I. The reaction provided a mixture of 1,2-dimethyl- **40a** and **40b**, 1,3-dimethyl- **51**, and 1,1-dimethylcyclopentadiene **52** in 40% combined yield and ratio of 2:1.5:1:0.1, respectively (Scheme 12). The yields and distribution of isomers slightly varied upon different reaction conditions (solvents, etc.) [26].

Comparable results were also obtained by alkylation with dimethyl sulfate (Me_2SO_4) [37, 38]. A large-scale preparation of various dialkylated and polyalkylated cyclopentadienes was reported via alkylation of cyclopentadiene under phase-transfer conditions (KOH or NaOH, ammonium salts, water) with alkyl bromides. In this respect, formation of dipropyl, dicyclohexyl, di(3-hexyl), di (2-pentyl), and di(2-butyl)cyclopentadienes was described. Although it was not specifically mentioned, the corresponding dialkylated cyclopentadienes must have been obtained as mixtures of 1,2- and 1,3-disubstituted cyclopentadienes [39, 40]. Interestingly, it was also claimed that vicinal (1,2-disubstituted cyclopentadienes) could be separated from 1,3-disubstituted cyclopentadienes, by converting them into sodium or potassium salts that are insoluble in alkanes [39]. However, specific details of this procedure were not disclosed.

The first report on preparation of 1,2-dibenzylcyclopentadienes was done by Koestler et al. (Scheme 13) [41]. The procedure consisted of a reaction of lithium cyclopentadienide with aroyl chlorides that provided 1,2-diaroylated cyclopentadienes **53**. Their reduction with $LiAlH_4$ gave rise to the respective 1,2-dibenzylated cyclopentadienes **54**, which were not isolated and instead of that were directly converted to 1,1′,2,2′-tetrabenzylated ferrocenes **55–61** upon treatment of the respective reaction mixtures with $FeCl_2$.



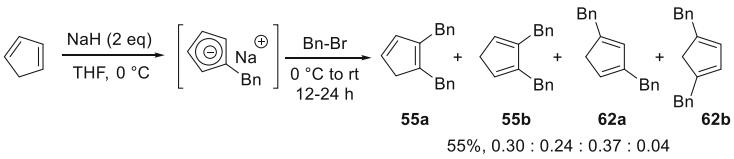
Scheme 12 Dialkylation of cyclopentadiene as a route to 1,2- and 1,3-disubstituted cyclopentadienes **40**, **51**, and **52**



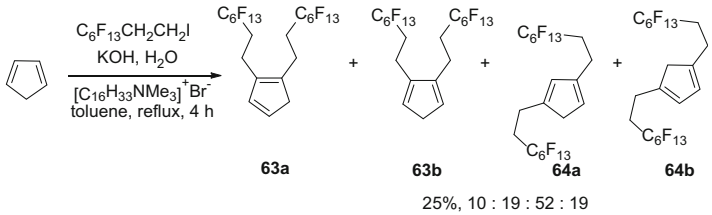
Scheme 13 Synthesis of 1,2-dibenzylated cyclopentadienes **54** and the corresponding ferrocenes **55–61**

A series of benzylated cyclopentadienes was prepared as mixtures of 1,2- and 1,3-regioisomers by two-fold benzylation of cyclopentadiene as reported by Lou et al. [42]. Albeit products **55**, **56**, and **61** bearing the Bn, 4-$MeC_6H_4CH_2$, and 4-$BrC_6H_4CH_2$ substituents were prepared, experimental details are given only for preparation of cyclopentadiene **55** (Scheme 14). For the sake of clarity, it should be noted that the main purpose of the work was preparation of the 1,3-disubstituted cyclopentadienes **62** and their derivatives as substrates for the subsequent Diels-Alder reaction studies.

Alkylation method was also the underlying strategy for preparation of 1,2-disubstituted cyclopentadienes bearing perfluoroalkylated side chains. The pioneering work in this area was done by Kvíčala and Čermák et al. who reported synthesis of 1,2 and 1,3-bis(polyfluoroalkylated) cyclopentadienes by two-fold alkylation of cyclopentadiene with (perfluoroalkyl)ethyl iodides [43]. Four regioisomers **63a**, **63b**, **64a**, and **64b** were formed in 25% combined yield and in the 10:52:19:19 ratio upon alkylation of cyclopentadiene with (perfluorohexyl)ethyl iodide (Scheme 15). (Perfluoroalkyl)ethyl trifluoromethanesulfonates instead of the iodides could be used for alkylation as well. Further studies in this direction revealed that a sequential two-step alkylation of cyclopentadiene is a more convenient route. In this respect, the use of (perfluoroalkyl)ethyl trifluoromethanesulfonates instead of iodides turned out to give better yields of the expected products. Such an approach



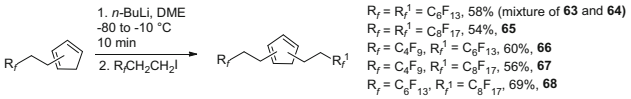
Scheme 14 Dibenzylation of cyclopentadiene as a route to 1,2- and 1,3-disubstituted cyclopentadienes **55** and **62**



Scheme 15 Dialkylation of cyclopentadiene as a route to fluorinated 1,2- and 1,3-disubstituted cyclopentadienes **63** and **64**

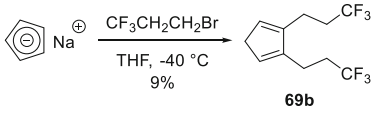
also allowed to prepare not only homo disubstituted cyclopentadienes **63–65**, but also to introduce two different (perfluoroalkyl)ethyl chains **66–68** (Scheme 16). However, it was not possible to determine the ratio of individual regioisomers due to the complex NMR spectra [44]. The prepared cyclopentadienes were then used to synthesize various 1,2- and 1,3-disubstituted ferrocenes and cyclopentadienyl Rh-complexes [45]. A similar approach was used in the synthesis of 1,2- and 1,3-disilylated cyclopentadienes bearing perfluoroalkylated chains attached to the silicon atom [46, 47]. A mixture of silylated cyclopentadienes was used to synthesize the corresponding Ti and Rh cyclopentadienyl complexes.

A couple of years later Braun et al. synthesized selectively 2,3-bis(3,3,3-trifluoropropyl)cyclopentadiene **69b** by reacting sodium cyclopentadienide with 3,3,3-trifluoropropyl bromide in THF at −40°C (Scheme 17) [48]. Workup and isolation provided the title compound in 9% isolated yield. Its structure was unequivocally confirmed by single crystal X-ray analysis. The low isolated yield of **69b** and the used arduous procedure for its isolation raise a question whether another double bond isomer of **69** as well as 1,3-disubstituted cyclopentadienes could not have been formed. It is reasonable to presume that they might have been unnoticed or undetected or because of difficulties associated with analysis of the complex reaction mixture.

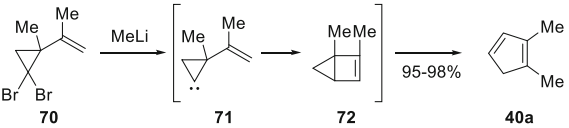


Scheme 16 Alkylation of perfluoroalkylated cyclopentadiene as a route to fluorinated 1,2- and 1,3-disubstituted cyclopentadienes **63–68**

Scheme 17 Preparation of **69b** via bisalkylation of cyclopentadiene



Scheme 18 Rearrangement of **70** to 1,2-dimethylcyclopentadiene **40a**



4.2 Rearrangements

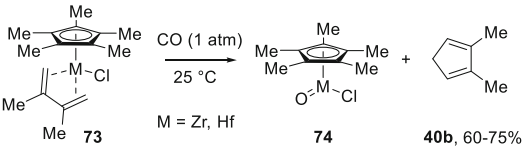
Formation of 1,2-dimethylcyclopentadiene **40a** was observed during a reaction of 1,1-dibromo-2-methyl-2-isopropenylcyclopropane **70** with methyl lithium at −78°C by Scattebøl et al. (Scheme 18) [49, 50]. It was assumed that the crucial step was formation of carbene **71** that intramolecularly reacted with the double bond forming a strained intermediate (bicyclopentene) **72** that underwent rearrangement into the 1,2-dimethylcyclopentadiene **40a**. Interestingly, the reaction was highly selective, and it was claimed to give **40a** in 95–98% yields along with a minor amount of 3,4-dimethylpenta-1,2,4-triene.

4.3 Pyrolysis

Cramers et al. observed formation of 1,2-dimethylcyclopentadienes **40** in minor amounts during pyrolysis of 2,4-dimethylphenol at 640°C [51].

4.4 Insertion of CO into Transition Metal Complexes

An interesting and selective procedure for synthesizing **40b** was designed by Teuben et al. (Scheme 19), who utilized insertion of CO into *cis*-Cp*M(2,3-dimethylbuta-



Scheme 19 CO insertion into butadiene Zr and Hf complexes **73** and formation of 1,2-dimethylcyclopentadiene **40b**

1,3-diene)Cl complexes of zirconium and hafnium **73** as the key step. The reaction furnished 2,3-dimethylcyclopentadiene **40b** in 60–75% and the respective metal oxo complex **74** as the side product [52, 53]. The labeling study with ^{13}CO clearly demonstrated incorporation of the ^{13}C atom into the cyclopentadiene framework.

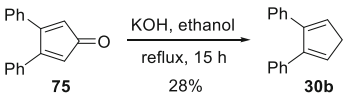
5 Specific Synthetic Approaches to 1,2-Diarylated Cyclopentadienes

The first synthesis of 1,2-diphenylcyclopentadiene **30** was reported by Allen et al. as early as 1946 (Scheme 20). The synthetic method relied on reduction of the carbonyl group of 3,4-diphenylcyclopentadienone **75** with KOH in anhydrous ethanol under reflux. It provided, after workup, 2,3-diphenylcyclopentadiene **30b** in 28% isolated yield [54].

Other routes to 1,2-diphenylcyclopentadienes **30** were reported by Rio et al. who studied dehydration of 3,4-diphenylcyclopenten-2-ol and reduction of 4-chloro-3,4-diphenylcyclopenten-2-on with $LiAlH_4$ and obtained the title compound in 11% yield [55, 56]. A more reliable and higher yielding method was reported later by Mu et al. (Scheme 21). It consisted of reduction of 3,4-diphenyl-2-cyclopentenone **76** with $NaBH_4$ to 3,4-diphenyl-2-cyclopentenol and the subsequent dehydration with concentrated HCl forming a mixture of two isomeric 1,2-diphenylcyclopentadienes **30a** and **30b** in 31% yield (after two steps) in the 93:7 ratio [57, 58]. The cyclopentadiene was converted to the corresponding zirconocene complex, which was tested as a polymerization catalyst.

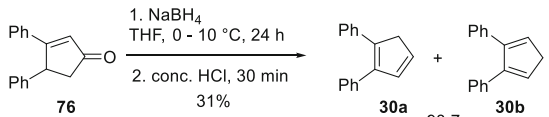
Formation of 1,2-diphenylcyclopentadiene **30a** was also observed upon photochemical rearrangement of 1,2-diphenyl-3-vinylcyclopropene **77** by Padwa et al. 1,2-Diphenylcyclopentadiene **30a** was obtained in 67% yield (Scheme 22) [59]. A similar result was achieved by using also photochemical rearrangement of 3-phenyl-3-(1-phenylvinyl)cyclopropane **78** by Zimmermann et al. (Scheme 23). However, 1,2-diphenylcyclopentadiene **30a** was a minor product along with a vinylallene, while 3-vinylindene was the major one [60].

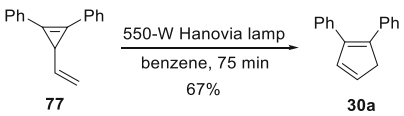
A synthesis of 1,2-bis(*p*-methoxyphenyl)cyclopentadiene **32b** based on a one-step pinacol reduction/dehydration of diketone **79** with a huge excess of



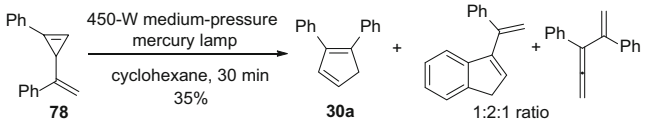
Scheme 20 Reduction of diphenylcyclopentadienone **75** to 2,3-diphenylcyclopentadiene **30b**

Scheme 21 Synthesis of regioisomeric 1,2-diphenylcyclopentadienes **30** from cyclopentenone **76**





Scheme 22 Synthesis of 1,2-diphenylcyclopentadiene **30a** via photochemical rearrangement of **77**

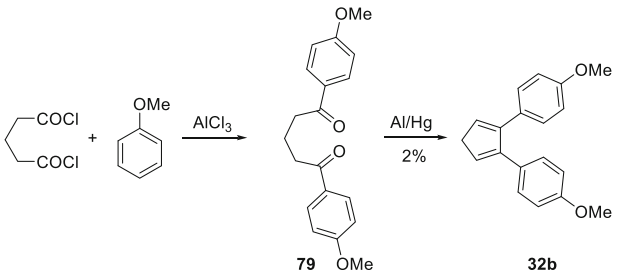


Scheme 23 Synthesis of 1,2-diphenylcyclopentadiene **30a** and other products via photochemical rearrangement of **78**

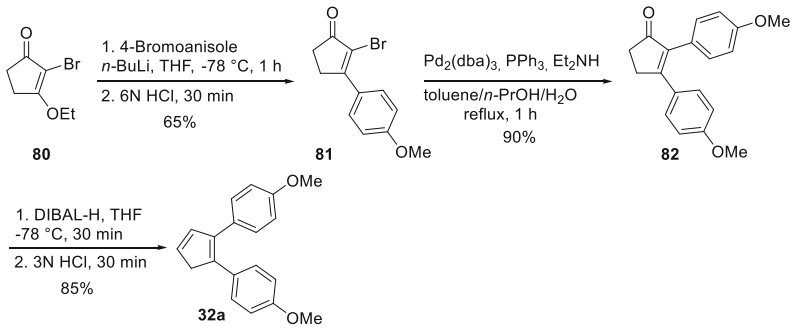
aluminum amalgam was reported by Rosenblum et al. (Scheme 24) [61]. The cyclopentadiene **32b** was isolated in just ~2% yield; however, the authors claim, as state in the original report, that only an analytical sample of the crude reaction mixture was subjected to isolation. The diketone **79** itself was prepared by two-fold Friedel-Crafts reaction of glutaryl chloride with anisole.

Another approach to 1,2-diarylcyclopentadienes was designed by Katzenellenbogen et al. (Scheme 25) [62]. It utilized a conjugated addition/elimination sequence of anisyllithium to 2-bromo-3-ethoxycyclopent-2-en-1-one **80** forming 2-bromo-3-(4-methoxyphenyl)cyclopent-2-en-1-one **81** in 65% yield. Its subsequent Suzuki-Miyaura cross-coupling with 4-methoxyphenylboronic acid yielded 2,3-bis-(4-methoxyphenyl)-cyclopent-2-enone **82** in 90% yield. Finally, reduction of the ketone to alcohol with DIBALH and its treatment under acidic conditions furnished the cyclopentadiene **32a** in 85% yield.

Cross-coupling reactions were also the basis for synthesis of a series of unsymmetrically substituted 1,2-diarylated cyclopentadienes [63]. It relied on sequential cross-coupling of 1,2-dibromocyclopentene with various aryl nucleophiles under Suzuki-Miyaura, Negishi, or Stille coupling conditions forming 1,2-diarylated



Scheme 24 Synthesis of 1,2-bis(4-methoxyphenyl)cyclopentadiene **32b** from **79**

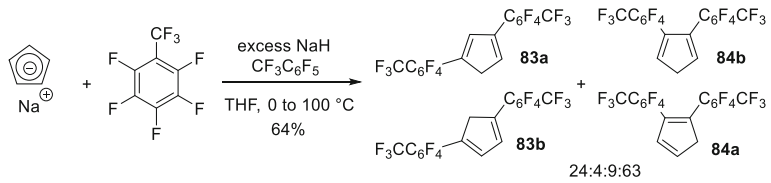


Scheme 25 Synthesis of 1,2-bis(4-methoxyphenyl)cyclopentadiene **32a** from **80**

cyclopentene. The subsequent epoxidation of the double bond followed by treatment with an acid yielded the corresponding products. Although synthetic details are not available, the prepared cyclopentadienes were tested as inflammatory agents (COX I and COX II activity).

A synthesis of a mixture of 1,2- and 1,3 di(perfluorotolyl)cyclopentadienes **83** and **84** was reported by Deck et al. [64] (Scheme 26) by using perfluorotoluene with sodium cyclopentadienide in the presence of excess of NaH. It gave rise to an inseparable mixture of 1,2- and 1,3-di(perfluorotolyl)cyclopentadienes in 64% yield. Nonetheless, it was claimed that isomeric cyclopentadienes **83a**, **83b**, **84a**, and **84b** were formed in 24:4:9:63 ratio. Interestingly, when the same reaction was carried out with perfluorobenzene only 1,3-isomers were isolated and characterized [65]. A general discussion on synthesis and properties of (perfluoroaryl)-cyclopentadienes, and formation of the respective cyclopentadienyl complexes can be found elsewhere [66].

Interestingly, application of perfluorinated and highly fluorinated 1,2-bis (perfluorophenyl)cyclopentadienes such as **85** and **86** (Fig. 3) as electrolytes for batteries was reported [67]. However, their preparation was not described.



Scheme 26 Synthesis of 1,2- and 1,3-perfluorotolylated cyclopentadienes **83** and **84** via arylation of sodium cyclopentadienide

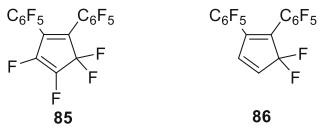


Fig. 3 Highly fluorinated 1,2-di (perfluorophenyl)substituted cyclopentadienes **85** and **86**

6 Complexes Bearing 1,2-Disubstituted Cyclopentadienes (Prepared from the Corresponding Cyclopentadienyl Salts)

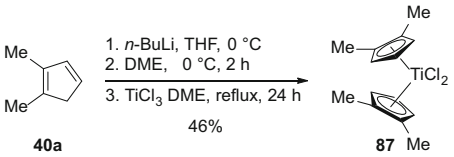
6.1 Titanocenes

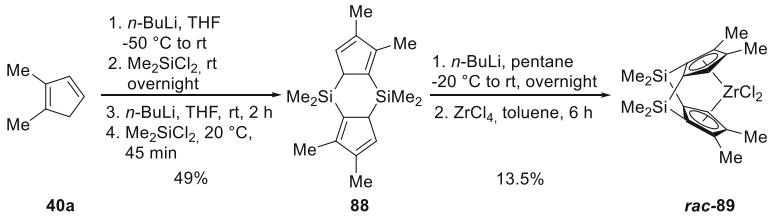
The first report regarding synthesis of titanocene **87** was described by Stuck et al. in 1980. In their paper, they were dealing with ^{1}H and ^{13}C NMR spectra of titanocenes bearing variously substituted cyclopentadienyl ligands; however, no experimental details were available and they claimed that the synthetic endeavors will be disclosed in the forthcoming paper. Unfortunately, the procedure has never been published [68]. The second synthesis of **87** was described by Callstrom et al. in 1994 [69]. They prepared 1,2-dimethylcyclopentadiene **40a** by the alkylation/elimination method from cyclopentenone **38**. **40a** was converted to the lithium cyclopentadienylide, which directly underwent complexation with $TiCl_3$ furnishing **87** in 46% yield (Scheme 27). X-ray photoelectron spectroscopy of a group of variously disubstituted titanocene dichlorides was recorded to study whether the rather large steric requirements of the cyclopentadienyl ligands exert greater or lesser impact on the binding energy of the titanium center relative to the electronic effect of alkyl substitution.

6.2 Zirconocenes

1,2-Dimethylcyclopentadiene **40a** served as the starting material for preparation of the bissilylbridged zirconocene ***rac*-89** by a two-step reaction sequence as reported by Britzinger et al. (Scheme 28) [29]. The initial lithiation of 1,2-dimethylcyclopentadiene **40a** with *n*-BuLi followed by a reaction with Me_2SiCl_2 yielded a monobridged derivative that after the second lithiation and a reaction with

Scheme 27 Preparation of titanocene **87**





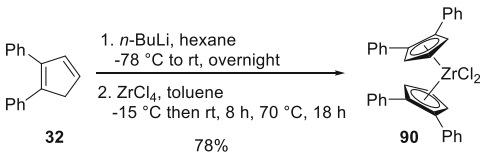
Scheme 28 Formation of the bis(dimethylsilylene)-bridged zirconocene **89**

the second portion of Me_2SiCl_2 provided the bis(dimethylsilylene)-bridged dicyclopentadiene **88** in 49% yield. Finally, its lithiation and reaction with $ZrCl_4$ gave rise to the 3.5:1 mixture of zirconocene ***rac*-89** and presumably ***meso*-89** as judged from the ^{1}H NMR of the isolated material.

Combination of ***rac*-89** with MAO was used to polymerize propylene yielding polymers with low and medium isotacticity. Further experiments in this direction indicated that conversion of **89** to active catalysts involves degradation of the strained ligand framework and that the intact **89** does not appear to be an effective catalyst.

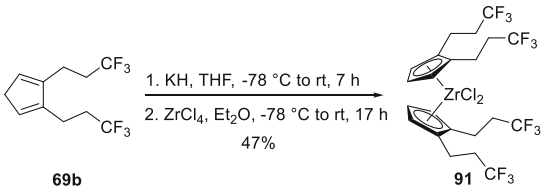
Lithiation of 1,2-diphenylcyclopentadiene with *n*-BuLi followed by complexation with $ZrCl_4$ provided the respective zirconocene **90** in 78% yield (Scheme 29) [57, 58]. The formed bis(1,2-diphenylcyclopentadienyl)zirconium dichloride **90** was tested as a catalyst for polymerization of ethylene and propylene in a combination with MAO. In the former case it exhibited lower catalytic activity in comparison with Cp_2ZrCl_2 (1.96×10^{-3} kg vs 3.69×10^{-3} kg (mol Zr)$^{-1}$ h^{-1}), but it produced high molecular weight polyethylenes ($M_h > 1.0 \times 10^6$ g mol^{-1}) with high melting transition temperatures. In the latter one its use resulted in the formation of atactic oligomers ($M_n = 1{,}150$ g mol^{-1}), but exhibited high catalytic activity (4.2×10^6 g (mol Zr)$^{-1}$ h^{-1}).

A reaction of 2,3-bis(3,3,3-trifluoropropyl)cyclopentadiene **69b** with KH furnished the respective potassium salt that upon a reaction with $ZrCl_4$ gave rise to zirconocene **91** in 47% yield (Scheme 30) [48]. Zirconocene **91** was used in the MAO activated polymerization of ethylene. It showed a higher activity (219.7 kg mol^{-1} h^{-1} bar^{-1}) than the non-fluorinated analogue (75 kg mol^{-1} h^{-1} bar^{-1}) at 50°C.



Scheme 29 Formation of bis(1,2-diphenylcyclopentadienyl)zirconium dichloride **90**

Scheme 30 Formation of bis(1,2-di(3,3,3-trifluoropropyl) cyclopentadienyl)zirconium dichloride **91**

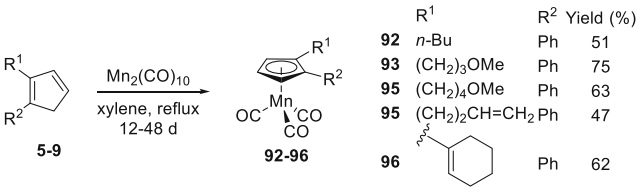


6.3 Manganocenes

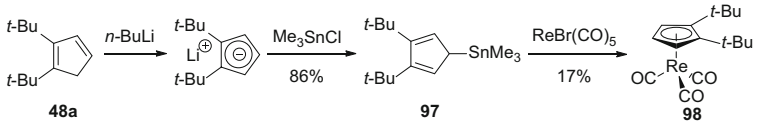
Cozak et al. reported isolation of 1,1′,2,2′-tetraethylmanganocene, which was an impurity during the synthesis of 1,1′-diethylmanganocene [70]. However, further experimental details were not disclosed. A series of 1,2-disubstituted manganocenes **92–96** bearing alkyl and aryl substituents was prepared by Chung et al. by reacting the cyclopentadienes **5–9** directly with $Mn_2(CO)_{10}$ in boiling xylene (Scheme 31) [18]. It is worth of mentioning that during preparation of **92** dealkylation was observed forming phenylmanganocene.

6.4 Rhenocenes

1,2-Di(*t*-butyl)substituted rhenocene **98** was prepared by Katzenellenbogen et al. [33]. A reaction of 1,2-di(*t*-butyl)cyclopentadienyllithium, generated in situ by lithiation of **48a** using *n*-BuLi, with Me_3SnCl yielded 86% of 2,3-di(*t*-butyl)-5-trimethylstannyl-1,3-cyclopentadiene that upon a reaction with $ReBr(CO)_5$ formed η^5-1,2-di(*t*-butyl)cyclopentadienyl)tricarbonylrhenium **98** in 17% yield (Scheme 32). A more efficient and practical approach to **98** (45%) was based on a direct reaction of 1,2-di(*t*-butyl)cyclopentadiene **48a** with $Re_2(CO)_{10}$ at 160°C (Scheme 33) [34]. The rhenocene **98** was used as a starting material for preparation of η^5-1,2-di(*t*-butyl)cyclopentadienyl)$Re(CO)_2(N_2)$ that itself was used to synthesize elusive η^5-1,2-di(*t*-butyl)cyclopentadienyl)$Re(CO)_2$(alkane) complexes (alkane = cyclopentane or hexane).

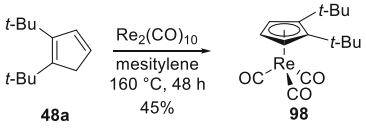


Scheme 31 Formation of manganocenes **92–96** from **5–9**



Scheme 32 Formation of **98** from **48a** via Li and Sn cyclopentadienyl anions

Scheme 33 Direct formation of **98** from **48a**



6.5 Ferrocenes

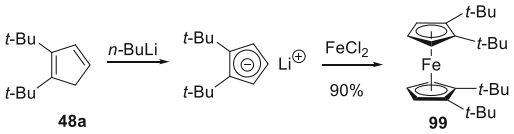
Synthesis of 1,1′,2,2′-tetra(*t*-butyl)ferrocene **99** was reported by Hughes et al. Initially, 1,2-di(*t*-butyl)cyclopentadiene **48a** was converted to the respective lithium cyclopentadienide upon lithiation with *n*-BuLi. Then, a reaction with $FeCl_2$ provided 1,1′,2,2′-tetra(*t*-butyl)ferrocene **99** in 90% yield (Scheme 34) [31].

A series of arylated ferrocenes **100–103** bearing phenyl, *p*-tolyl, 4-methoxyphenyl, and 4-trifluoromethylphenyl substituents were prepared from 1,2-disubstituted cyclopentadienes **30–31,** and **33** by using the same methodology as already described above by Kotora et al. (Scheme 35) [22]. The corresponding ferrocenes **100–102** were isolated in 42, 65, and 64% yields, respectively. In case of 1-(4-methoxyphenyl)-2-(4-trifluoromethyl)cyclopentadiene the corresponding product was obtained as an inseparable mixture of ***rac-*** and ***meso-*****103**.

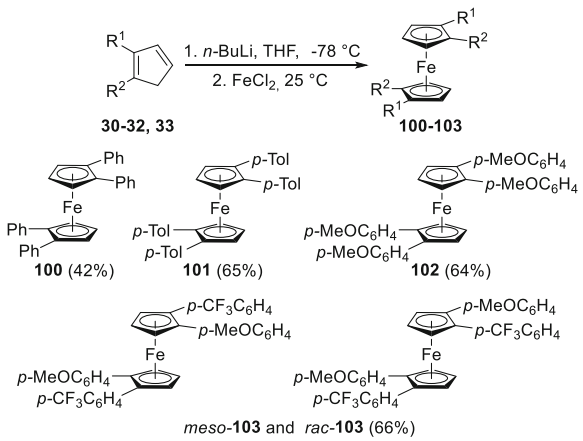
A series of tetrakis(polyfluoroalkylated) ferrocenes was prepared by reaction of $FeCl_2$ with lithiated di((perfluroalkyl)ethyl)cyclopentadienes by Kvíčala, Čermák et al. Since the reaction was carried out with a mixture of 1,2- and 1,3-disubstituted cyclopentadienes, the respective ferrocenes were also obtained as inseparable mixture of regioisomers with yields in the range of 43–62% [45]. It is worth of mentioning that lithiation was carried out at −80°C to avoid potential dehydrofluorination and it, gratifyingly, was not observed.

De Meijere et al. prepared an interesting series of ferrocenes **104–106** possessing the [2.2]paracyclophane scaffold [19]. After formation of lithium cyclopentadienide by adding MeLi to **12** it was reacted with $FeCl_2 \cdot 2THF$ to yield ferrocene **104** (its

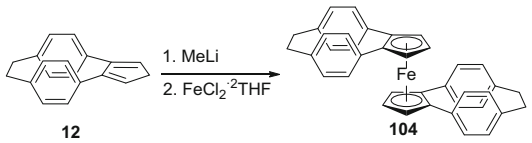
Scheme 34 Formation of 1,1′,2,2′-tetra(*t*-butyl) ferrocene **99**



Scheme 35 Formation of ferrocenes **100–103**



Scheme 36 Synthesis of **104**



yield was not specified) (Scheme 36). Although formation of two isomeric (*anti* and *syn*) dinuclear ferrocenes was envisaged starting from **15**, its treatment with MeLi, CpLi, and $FeCl_2$·2THF led to isolation of only *syn* diferrocene **105** from the reaction mixture in 36% yield (Scheme 37). Since it was not specified what were other components of the reaction, it cannot be excluded the *anti* diferrocene was formed as well. Finally, a mixture of **12** and **15** was metallated with MeLi and addition of $FeCl_2$·2THF followed to furnish a mixture of the oligomeric ferrocene **106** and ferrocene **104** in 10 and 71% yields, respectively (Scheme 38).

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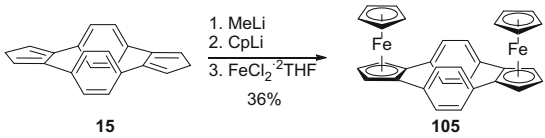
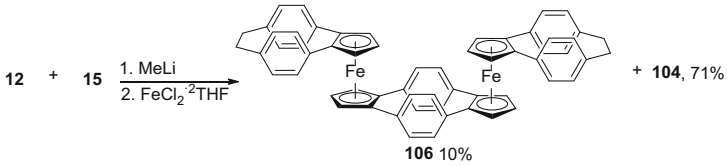
6.6 Ruthenocenes

Synthesis of bis(1,2-di(*t*-butyl)cyclopentadienyl)ruthenium **99** was also reported by Hughes et al. [33]. 1,2-Di(*t*-butyl)cyclopentadiene **48a** was treated with TlOEt to give (1,2-di-*tert*-butylcyclopentadienyl)-thallium **107** (46%), which reacted with

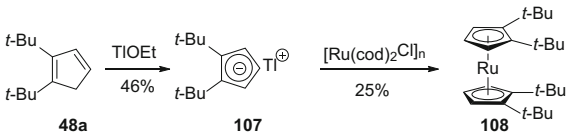
Scheme 37 Synthesis of **105**





Scheme 38 Synthesis of a mixture of **106** and **104**

Scheme 39 Synthesis of bis(1,2-di-*tert*-butylcyclopentadienyl) ruthenium **108**

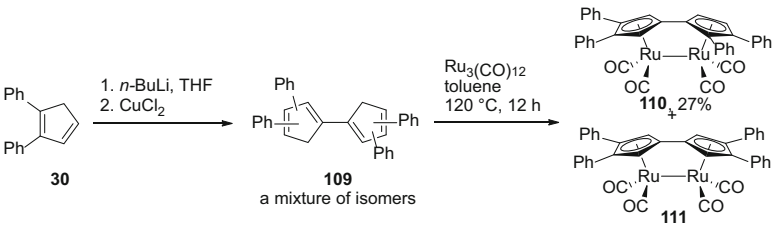


polymeric $[Ru(COD)Cl_2]_n$, giving rise to bis(1,2-di(*t*-butyl)cyclopentadienyl)ruthenium **108** in 25% yield (Scheme 39).

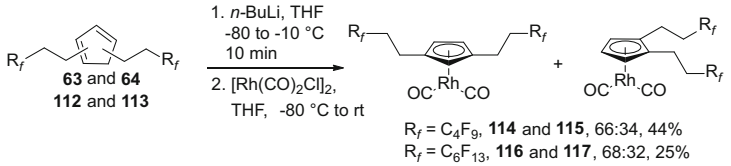
Interestingly, 1,2-diphenylcyclopentadiene **30a** was used in the preparation of an inseparable mixture of tetraphenyldihydrofulvalene isomers **109**, which in turn was converted to a mixture of symmetrical and unsymmetrical 1,2,2′,3′--(tetraphenylfulvalene)tetracarbonyldiruthenium **110** and **111** in 4:1 ratio as reported by Vollhardt et al. (Scheme 40) [71]. Crystallization of the crude reaction mixture yielded 27% of a dimeric complex **110**. Complex **111** was not isolated and its presence was judged from NMR analysis of the reaction mixture.

6.7 Rhodocenes

Mixtures of di((perfluoroalkyl)ethyl)cyclopentadienes were prepared by Kvíčala, Čermák et al. [45]. Lithiation of mixtures of di((perfluoroalkyl)ethyl)cyclopentadienes **63**, **64**, **112**, and **113** with *n*-BuLi gave rise to the corresponding mixtures of lithium cyclopentadienides (Scheme 41). Their subsequent reaction with $[Rh(CO)_2Cl]_2$ furnished mixtures of 1,2- and 1,3-disubstituted rhodocenes **114**, **115**, **116**, and **117** in 44 and 25% yields, respectively. The complexes were partially separable by using column chromatography; hence assignment of individual signals was feasible. On the other hand, it was claimed that the obtained rhodocenes were not stable and underwent slow degradation even under appropriate inert storage conditions.

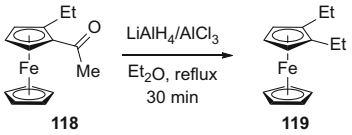


Scheme 40 Application of 1,2-diphenylcyclopentadiene **30** in synthesis of **110**



Scheme 41 Preparation of rhodium complexes **114**, **115**, **116**, and **117**

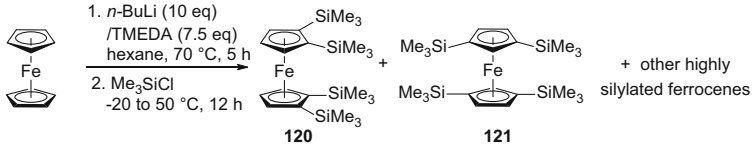
Scheme 42 Reduction of 1-acetyl-2-ethylferrocene **118** to 1,2-diethyl ferrocene **119**



6.8 *Other Methods for Preparation of 1,2-Disubstituted Cyclopentadienyl Sandwich Complexes*

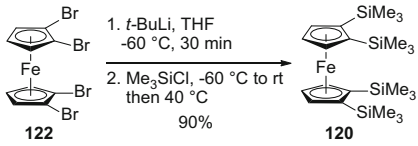
Preparation of 1,2-diethylferrocene **119** was reported by Bublitz et al. by reduction of 1-acetyl-2-ethylferrocene with $LiAlH_4/AlCl_3$ in the quantitative yield (Scheme 42) [72]. The starting ferrocene **118** – 1-acetyl-2-ethylferrocene was prepared by acetylation of ethylferrocene under the standard conditions [73], the same approach was applied in a synthesis of 1,1′,2,2′-tetraethylferrocene from 1,1′--diethylferrocene. The procedure was based on acetylation of 1,1′-diethylferrocene that furnished a mixture of 1,1′-diacetyl-3,3′-diethylferrocene, 1,1′-diacetyl-2,3′--diethylferrocene, and 1,1′-diacetyl-2,2′-diethylferrocene in ~5:3:1 ratio. The subsequent reduction of the mixture with $LiAlH_4/AlCl_3$ yielded a mixture of corresponding tetraethylated ferrocenes in 55, 36, and 8% yields. Individual isomers were separated by using preparative GC [74].

Metallation of ferrocene with *n*-BuLi in toluene or hexane in the presence of TMEDA was reported by Halasa and Tate, and it furnished a mixture of lithiated ferrocenes to various degrees. The corresponding mixture of polymetallated ferrocenes was treated with trimethylsilyl chloride (Scheme 43) providing a mixture of



Scheme 43 Formation of a mixture of tetrasilylated ferrocenes **120** and **121**

Scheme 44 Selective preparation of 1,1′,2,2′-tetrakis (trimethylsilyl)ferrocene **120**

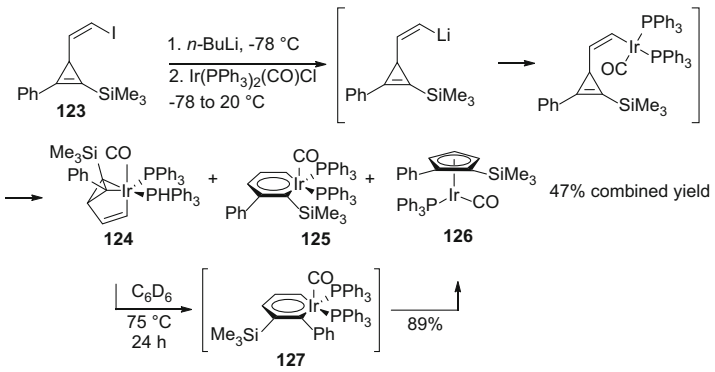


polysilylated derivatives, out of which a mixture of 1,1′,2,2′- and 1,1′,3,3′--tetrasilylated ferrocenes **120** and **121** was separated and characterized [75]. A more selective and efficient method for preparation of 1,1′,2,2′-tetrakis (trimethylsilyl)ferrocene **120** was developed by Butler et al. [76] (Scheme 44). The process relied on bromine-lithium exchange in 1,1′,2,2′-tetrabromoferrocene **122** followed by a reaction with trimethylsilyl chloride that provided the title ferrocene **120** in 90% isolated yield.

An interesting approach to 1,2-disubstituted cyclopentadienyl complexes of Ir was reported by Haley et al. (Scheme 45) [77]. They demonstrated that a reaction of (*Z*)-1-trimethylsilyl-2-phenyl-3-iodovinylcyclopropene **123** followed by addition of Vaska's complex ($Ir(PPh_3)_2(CO)Cl$) resulted in mixture of three Ir-compounds: iridatricyclo[3.1.0.$0^{2,6}$]hexane **124**, iridabenzene **125**, and 1-trimethylsilyl-2-phenylcyclopentadienyliridium complex **126** in a 10:2:3 ratio and the 47% combined yield. Heating of the purified mixture of **124**-**126** in C_6D_6 at 75 °C resulted in the formation of **126**. Further studies showed that the pure isolated complex **124** also rearranges to the cyclopentadienyl complex **126** under the same conditions in almost quantitative yield (89% isolated yield). However, as an intermediate was not identified the expected iridabenzene **125**, instead the NMR analysis revealed the presence of the regioisomeric iridabenzene **127** that then rearranged to the cyclopentadiene complex **126**.

6.9 X-Ray Diffraction Analyses

To cover additional aspects of chemistry of 1,2-disubstituted cyclopentadiene ligands, it should be noted that structures of several prepared transition metal complexes bearing various 1,2-disubstituted cyclopentadiene ligands were unequivocally confirmed by single crystal X-ray diffraction analyses. Among these belong



Scheme 45 Formation of Ir complexes **124–126** from

titanocene **87** [69], zirconocenes ***rac*-89** [29] and **90** [57, 58], ferrocenes **99** [31], **101** [22], and **120** [76], and ruthenocene **110** [71].

7 Conclusion and Outlook

There has not been devoted much attention to synthesis of 1,2-disubstitued cyclopentadienes, their application in organic synthesis or in chemistry of cyclopentadienyl complexes. On the other hand, as far as synthetic approaches are concerned, several semi-general pathways have been designed and executed and they constitute a promising foundation for further synthetic endeavors in this direction.

As far as application of 1,2-disubstituted cyclopentadienes in chemistry is concerned, their conversion to the respective cyclopentadienyl complexes has been of limited interest. Substituents attached to the cyclopentadienyl scaffold in positions 1 and 2 can impart unique electronic and steric effects that can modulate properties of the central metal atom. Such a combination of effects thus can change catalytic properties. This has been nicely demonstrated by several studies regarding polymerization of olefins with substituted zirconocenes.

In summary, despite the fact that this area of cyclopentadiene chemistry remains largely unexplored, it offers considerable space for further diverse research. One such direction is design and preparation of chiral cyclopentadienyl complexes based on the utilization of chiral moieties attached to the maternal cyclopentadiene scaffold via 1,2-disubstituted link. But this is another story that will be dealt with in another chapter.

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Synthesis and Application of Novel Chiral Cp Ligands in Transition Metal Catalysis

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Contents

Abstract Chiral cyclopentadienyl groups and their respective metal complexes have been studied for several decades. However, it is only in the last decade that this field has gained significant momentum, primarily through the introduction of chiral C2-symmetrical 1,2-cyclopentadienes and unsymmetrically substituted chiral 1,2-cyclopentadienes and indenes as precursors for chiral complexes, especially those involving late transition metals. The utilization of chiral C2-symmetrical cyclopentadienyl (Cp) ligands allows for the circumvention of diastereomer formation upon complexation with the desired transition metal center. This is particularly advantageous for unsymmetrically substituted ligands, which often necessitate

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tedious racemate separation. In all cases, a multi-step synthesis is required, depending on the nature of the chiral backbone. Unsymmetrically substituted Cp rings can bypass the need for a multi-step synthetic approach but generally require the separation of racemates to obtain enantiomerically pure metal complexes. An alternative method involves conjugating achiral Cp-metal complexes to a carrier molecule, which enables the insertion of the conjugate into the active center of an enzyme protein hull. This approach establishes a chiral environment for asymmetric transformations. The resulting metal complexes find extensive applications in C-H functionalization reactions, as well as various cycloaddition reactions.

Keywords Asymmetric catalysis · Chirality · Cp ligands · Transition metal complexes · Synthesis

Abbreviations

Ac	Acetyl
AIBN	2,2'-Azobis(isobutyronitrile)
Ar	Aryl
BINOL	1,1′-Bi-2-naphthol
Bn	Benzyl
BOC	*tert*-Butyloxycarbonyl
i-Butyl	Isobutyl
n-Bu	*n*-Butyl
s-butyl	Secondary butyl
t-butyl	Tertiary butyl
Bz	Benzoyl
CMP	Concerted metalation deprotonation
COD	1,5-Cyclooctadiene
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
Cp^X	Chiral cyclopentadienyl
Cy	Cyclohexyl
DCE	1,2-Dichloroethane
DCM	Dichloromethane
de	Diastereomeric excess
DIBAL	Diisobutylaluminium
DMBA	2,2-Dimethylbutyric acid
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
Et	Ethyl
equiv.	Equivalent
Fc	Ferrocenyl

h	Hour
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HMPA	Hexamethylphosphoric acid triamide
HPLC	High-performance liquid chromatography
KMO	Kynurenine 3-monooxygenase
Me	Methyl
min	Minute
MOM	Methoxymethyl
MOPS	3-(N-morpholino)propanesulfonic acid
Ms	Methanesulfonyl
MS	Molecular sieves
MW	Microwave
NBS	N-Bromosuccinimide
NPhth	Phthalimide
OPiv	Pivalate
Ph	Phenyl
i-Pr	Isopropyl
n-Pr	*n*-Propyl
Py	Pyridine
rac	Racemic
re	Regioisomeric excess
rt	Room temperature
Sel.	Selectivity
T	Temperature
TBDPS	*tert*-Butyldiphenylsilyl
Tf	Triflate
TFE	Tetrafluoroethylene
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	*N,N,N,N*-Tetramethylethylenediamine
TMP	Tetramethylpiperidine
TMS	Trimethylsilyl
*p*Ts	*para*-Tosyl

1 Introduction

Cyclopentadienyl (Cp) ligands belong to the first broadly investigated ligand systems since the onset of transition metal chemistry in the second half of the twentieth century [1, 2]. Especially the stabilization of a large variety of structurally different mono- and oligonuclear compounds throughout the whole range of the transition metals and beyond has made it such a highly popular ligand system [3]. Substitution of the cyclopentadienyl ring directly influences the electronic properties of the metal

center as well as the steric environment, allowing the modification of reactivity and steric accessibility to a large extent. The best-known derivative is the permethylated pentamethylcyclopentadienyl (Cp*) ligand as more electron-rich derivative of the Cp ligand. Practical consequences of utilizing the Cp* instead of the Cp ligand can be found in various reactions, e.g. C-H activation and functionalization reactions. Also, the metal attached to the Cp* ring system plays a significant role for the reactivity and catalytic performance of the formed metal complex when compared under rather identical reaction conditions [4, 5]. Indenyl and other benzannulated derivatives of the Cp system have also found widespread application from organometallic chemistry to catalysis [6–8].

2 Short History of Chiral Cp Ligands

Cp-transition metal complexes can be chiral-at-metal compounds or can possess chiral Cp or Cp-derived ligands like indenyl groups, providing the chirality to the metal complex [9]. The chiral-at-metal Cp-transition metal complexes have been found to afford even diastereomeric complexes, which are stable enough to be separated in the same way as it can be done for organic compounds and were in general also used for asymmetric catalysis [10, 11]. This chapter will, however, focus on Cp and derived complexes possessing chirality at these ligands and their application in asymmetric catalysis. The early developments of synthesis and application of chiral Cp-metal complexes have been compiled in a standard reference by R. Halterman [12]. In half-sandwich Cp-metal complexes different types of chirality can be identified, which are introduced by the substitution pattern of the Cp ring and depend on the structural symmetry of the Cp ligand. An overview is given in Fig. 1. Differently disubstituted Cp rings like in **CpM1** and **CpM1'** gave enantiomeric complexes upon complexation to a metal center, usually as a racemic mixture. Chiral substituted Cp rings like in **CpM2** yield only one complex, however, free rotation of the chiral group around the bonding axis to the Cp ring usually does not allow significant selective chiral induction in catalytic reactions. This changes when the Cp

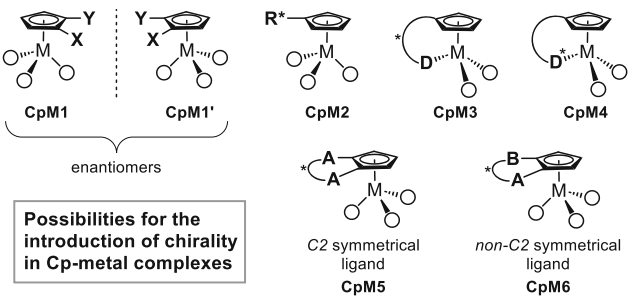
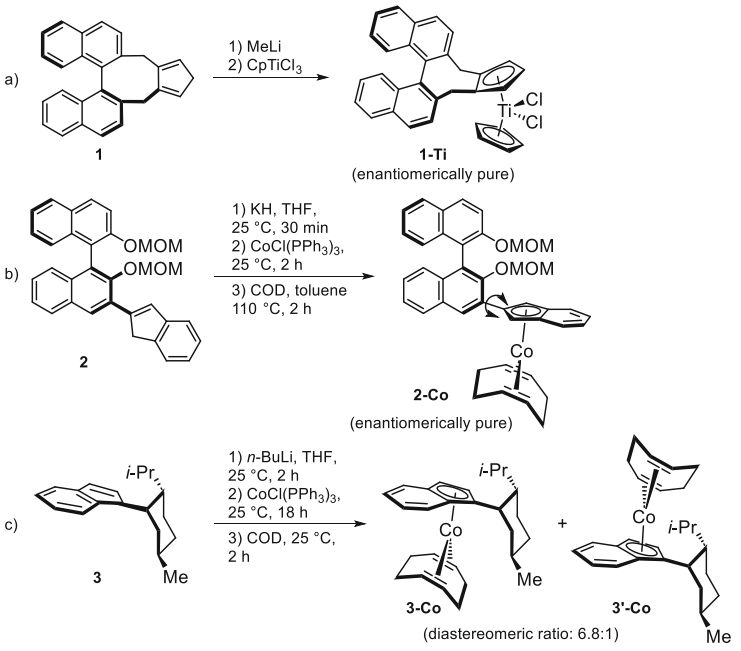


Fig. 1 Stereochemistry in half-sandwich cyclopentadienyl transition metal complexes



Scheme 1 Examples for the synthesis of chiral cyclopentadienyl and indenyl ligands

groups are connected by a linker to a donor group (**D**) allowing additional coordination to the metal center. Chirality can here be present in the linker (**CpM3**) or in the donor group itself (**CpM4**), leading to a chiral environment at the metal center. Finally, cyclic 1,2-disubstitution of Cp ring with chiral groups in the backbone of the adjacent second ring system allows the synthesis of complexes of the type **CpM5** and **CpM6**, which are the main focus of this book chapter.

For ligands used in **CpM6** the complexation to a metal center experiences the same problematic issues as in the case of **CpM1/ CpM1'**; upon complexation diastereomers are formed, which need to be separated as exclusive diastereoselective metalation is rarely observed. This problem can be circumvented by using C2 symmetrical ligands like for **CpM5**, where complexation from either side leads to the identical complex, making further separation obsolete. Even in situ generation of chiral complexes as catalysts is possible by the latter methodology, depending on the completeness of the complexation of course.

These scenarios can be illustrated by examples from the literature (Scheme 1). Colletti and Halterman described a binaphthyl-Cp-based titanium complex **1-Ti** in 1989 [13]. The synthesis was straightforward, utilizing an enantioselective Kharasch cross-coupling to synthesize the chiral binaphthyl backbone, contributing to pave a pathway toward the synthesis of such chiral 1,2-disubstituted cyclopentadienes such as **1**. As the backbone is C2 symmetrical, metalation and complexation with $CpTiCl_3$ delivered only one enantiomer of the complex **1-Ti** (Scheme 1a). Convenient

synthesis of a binaphthyl-indenyl ligand, where the 2-indenyl ligand is connected to the 3-position of the 2,2′-substituted binaphthyl, led to compound **2**, possessing rather high rotational freedom around the binaphthyl-indenyl connecting bond [14]. Deprotonation and metalation with a cobalt(I) salt delivered only one enantiomer of **2-Co** (Scheme 1b). Later experiments proved that the complex is a suitable catalyst for [2 + 2 + 2] cycloadditions, however, without inducing any stereoselectivity in the transformation, presumably due to the lack of a stable chiral environment at the metal center. Finally, menthyl-substituted indenyl ligand **3** is an instructive example to demonstrate the synthesis of chiral metal complexes from unsymmetrically substituted Cp derivatives [15]. Metallation of **3** with *n*-BuLi followed by transmetallation to $CoCl(PPh_3)_3$ resulted in the formation of a diastereomeric mixture of complexes **3-Co** and **3'-Co**, because complexation is possible from both sides of the unsymmetrical indenyl fragment. The separation required ligand exchange to COD due to stability of the resulting complexes, which were then separated by chromatography and crystallization. They are suitable catalysts for enantioselective photochemical [2 + 2 + 2] cycloaddition reactions [16, 17]. The Cp version of this ligand bearing a menthyl group has been one of the first chiral Cp ligands synthesized and investigated [18].

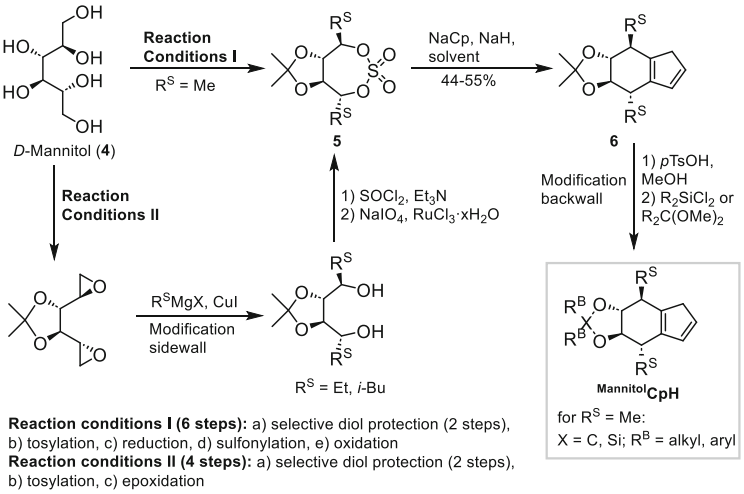
Successful applications of chiral Cp ligands in catalysts have been rather rare until the rise of novel C2-symmetrical ligands over the last decade [19].

3 Synthesis of Ligands and Complexes with C2 Symmetry and Their Application

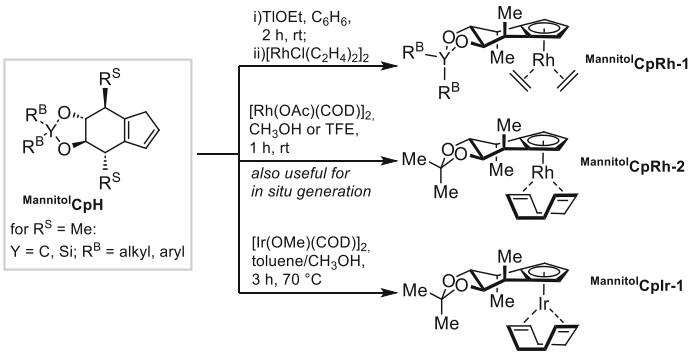
The application of C2-symmetrical Cp ligands has gained a lot of momentum from the novel approaches toward the synthesis of novel ligand systems as well as application in novel catalytic transformations. This area has therefore been reviewed recently to keep up with the developments [20, 21]. The most important classes for such ligands are discussed in the following sections.

3.1 Mannitol-Based Ligands

The synthesis of mannitol-based cyclopentadiene precursors was presented by Cramer and coworkers as a novel approach toward chiral, C2-symmetrical Cp ligands, utilizing a convenient chiral motif from the chiral pool of sugars as backbone for the Cp ligand [22]. The transformation of mannitol into the cyclic sulfate as prerequisite for the Cp ligand synthesis has been described for the assembly of chiral phospholane ligands [23]. The synthesis sequence for mannitol-based Cp ligands is compiled in Scheme 2. The sequence sets out with installation of hydroxyl protecting groups on (*D*)-mannitol (**4**) in the first part, followed by introduction of



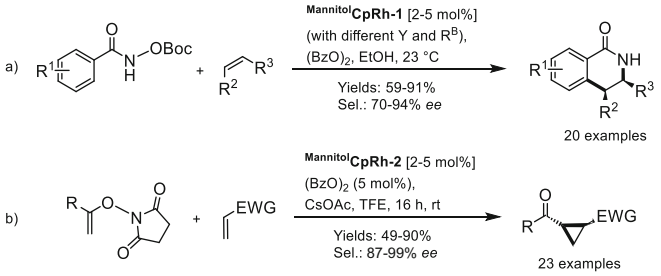
Scheme 2 Synthetic route to chiral mannitol-based cyclopentadienes



Scheme 3 Metal complexation conditions for $^{\text{Mannitol}}$**CpH** ligands

the sidewall substitution. Finally, the hydroxy groups were converted to cyclic sulfates (**5**) as leaving groups for the following reaction with sodium cyclopentadienide and sodium hydride, affording the ligand precursor (**6**) by two-fold 1,2-alkylation of the cyclopentadiene. Postfunctionalization by deprotection and installation of different groups at the backwall afforded the ligands $^{\text{Mannitol}}$**CpH** ready for complexation.

The complexation of the $^{\text{Mannitol}}$**CpH** ligand was exemplified for rhodium and iridium complexes (Scheme 3). The classical methodology utilized thallium (I) ethoxide as base, deprotonation of the Cp ligand under mild conditions and exclusion of light, followed by reaction with $[RhCl(C_2H_4)_2]_2$ as rhodium source and furnishing the bis-ethylene complex [22]. An advanced methodology utilized the complex $[Rh(OAc)(COD)]_2$ containing the COD ligand and a acetate counter anion, which adopts an important role during the complexation [24]. Coordination



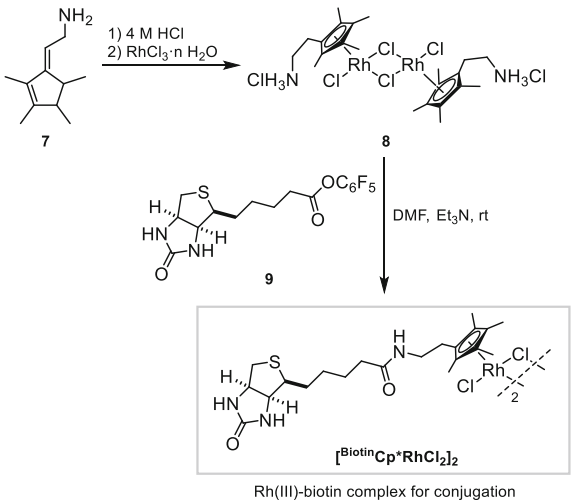
Scheme 4 Catalytic transformations catalyzed by $^{\text{Mannitol}}$**CpRh** complexes

can occur devoid of previous metalation by just adding the metal complex and cyclopentadiene ligand together in methanolic solution. Good to excellent yields of the corresponding complexes $^{\text{Mannitol}}$**CpRh-1** and $^{\text{Mannitol}}$**CpRh-2** can be obtained by this method, which is also useful for the in situ generation of the precatalyst. This methodology was also applied for the synthesis of iridium (I) complexes with the $^{\text{Mannitol}}$**CpH** ligand exemplified by $^{\text{Mannitol}}$**CpIr-1**, utilizing $[Ir(OMe)(COD)]_2$ as metal source, although due to the slower complexation rate requiring higher temperatures for the coordination of the metal to the Cp ligand.

The $^{\text{Mannitol}}$**Cp**Rh(I) complexes have been utilized for several C-H functionalization reactions (Scheme 4). In a benchmark reaction for C-H functionalization also applied to other catalytic systems, Cramer et al. reacted aryl hydroxamates and alkenes to furnish dihydroisoquinolones (Scheme 4a) [22]. The reaction was evaluated using a series of precatalysts $^{\text{Mannitol}}$**CpRh-1** with modified backwalls, resulting in the formal [4 + 2] process leading to the heterocyclic ring formation with very good to excellent yields and selectivities. The same group applied $^{\text{Mannitol}}$**CpRh-2** in the enantioselective cyclopropanation of electron-deficient olefins with N-enoxysuccinimides (Scheme 4b) [25]. Again the transformation worked very well with very good yields and selectivities of up to 95% *ee*. In a formal synthesis of KMO inhibitor UPF-648 this key step was applied and the performance of the isolated catalyst and the in situ prepared precatalyst compared, providing only neglectable differences in their performance.

3.2 Streptavidin∩Biotin-Cp-Based Ligand

Another approach toward the creation of defined chiral confinements around a Cp-metal center utilized "natural chirality" by developing an artificial metalloenzyme based on a metal complex incorporated into a protein hull. This project was initiated by collaborative work by the groups of Ward and Rovis, leading to an approach toward the enantioselective synthesis of dihydroisoquinolones as described already above (Scheme 4) [26, 27]. The general approach has up to date

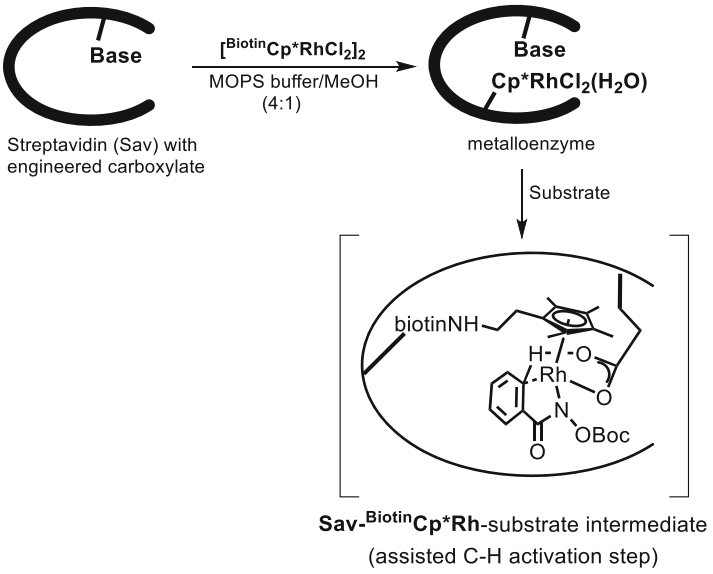


Scheme 5 Synthesis of Rh (III)-biotin complex as precursor for conjugation with streptavidin

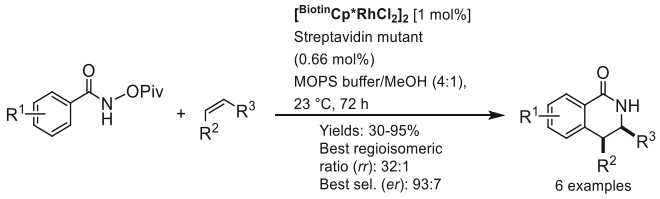
been utilized in a variety of reactions interesting for synthetic purposes, e.g. in enantioselective hydrogenations with Rh-diphosphine complexes, allylic alkylations with Pd-phosphine complexes, and asymmetric transfer hydrogenations with Ru-arene-diamine complexes [28]. The chiral environment is provided by a protein, allowing the introduction of achiral Cp-metal complexes as catalytic centers, which minimizes the preparative work on the side of the metal complex, however, knowledge in protein science is a pre-requirement to assemble the final catalyst. The vehicle used for applying a Cp*Rh-catalyst for the enantioselective C-H activation reaction described in Scheme 7 is the streptavidin-biotin system [29]. The biotin as the cofactor is covalently bound to the metal complex, according to the process depicted in Scheme 5. The amino-substituted fulvene precursor **7** has been synthesized according to a literature protocol and complexed to yield the dimer **8**. Coupling to the biotin fragment **9** via an activated ester gave the respective biotinylated rhodium precursor **[^{Biotin}Cp*RhCl$_2$]$_2$** in good yield.

The Rh(III)-biotin complex (**[^{Biotin}Cp*RhCl$_2$]$_2$**) is then subjected to conjugation with an engineered streptavidin, containing a glutamic acid or aspartic acid residue in close neighborhood to the reactive site to assist in the asymmetric C-H activation step. During the preparation, the dimeric complex dissociates into monomeric complexes upon coordination of an additional water ligand at each rhodium center. Computational studies allow the conclusion that the C–H activation step is following a concerted metalation-deprotonation (CMD) pathway [30]. The presence of a base significantly lowers the activation energy of this step. Therefore, such a base was engineered in the streptavidin to provide the required support for this reaction step (Scheme 6).

The metalloenzyme was tested in the reaction mentioned above toward the synthesis of dihydroisoquinolones (Scheme 4a). The reaction proceeded smoothly at room temperature to give the product in the best cases with excellent yields and high regioisomeric and enantioselective ratios (Scheme 7). Remarkable is also the highly polar medium used in this reaction.



Scheme 6 Assembly of artificial metalloenzyme using a chiral biotin-Cp*Rh complex

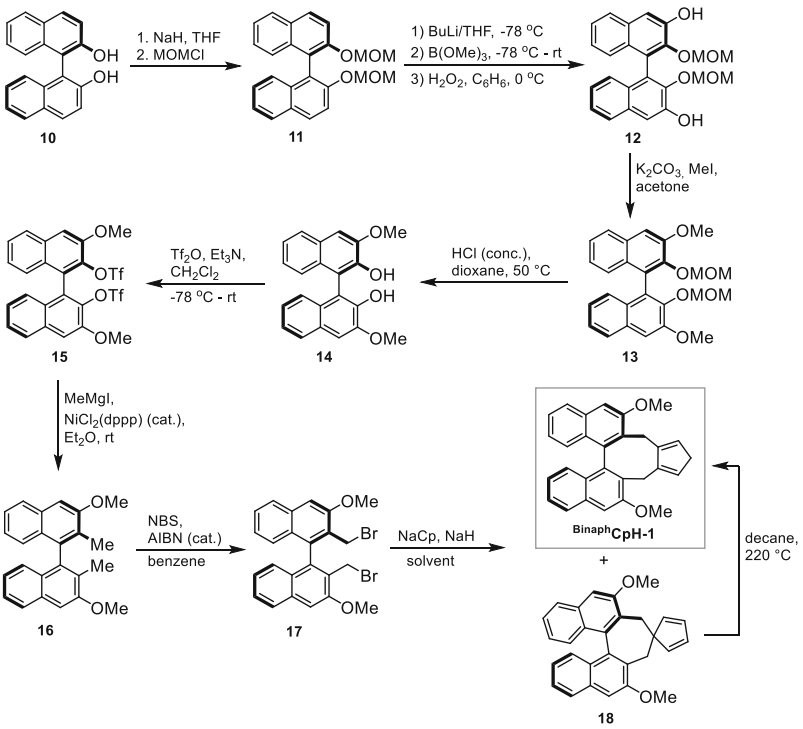


Scheme 7 Asymmetric C-H functionalization reaction applying the artificial metalloenzyme

The groups of Hayashi and Onoda established another Cp*Rh-based metalloenzyme for related C-H functionalizations, bearing a maleimide for linkage to a cysteine residue and dithiophosphate ligands for protection against coordination by amino acids in the protein [31]. Upon addition of silver ions the catalytic center is activated. The authors used the reaction for cycloaddition of acetophenone oxime with diphenylacetylene under C-H activation, yielding the isoquinoline derivatives.

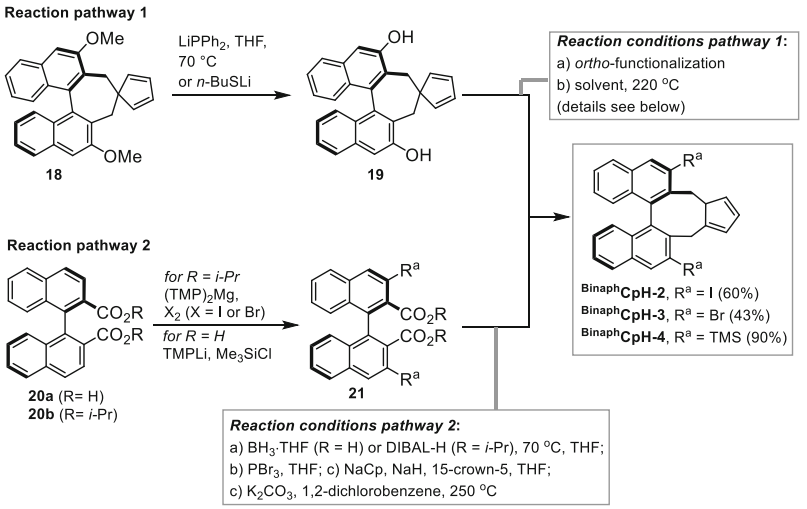
3.3 Binaphthyl-Based Ligands

Binaphthyl-derived cyclopentadienyl ligands are the most widely used chiral cyclopentadienyl ligand class for enantioselective C-H functionalization reactions with late transition metals. They were first synthesized by Colletti and Halterman [32], paving the way for the strategy also followed by modern approaches like



Scheme 8 Synthesis of chiral 1,1'-binaphthyl-based Cp ligands

reported by Cramer and his group in 2013 [33]. It is a highly tunable ligand with a binaphthyl backbone and a modifiable sidewall providing an effective way to control reactivity and enantioselectivity of the reaction. The synthesis of the ligand backbone follows a 7-step protocol derived from Maruoka et al., starting from the commonly available 1,1′-bi(2-naphthol) (BINOL, **10**) to furnish MOM-protected compound **11** after the first step according to Scheme 8 [34]. The compound **11** was then treated with *n*-BuLi in THF and the resulting dianion was quenched with B $(OMe)_3$. The boronate subsequently formed in the 3,3′ position was oxidized to obtain the hydroxy groups (**12**), which were then protected as methyl ethers (**13**). Selective deprotection of the MOM groups and subsequent conversion to triflate groups gave compound **15**, which was subjected to Ni-catalyzed cross-coupling reaction with MeMgI to deliver **16**, followed by radical dibromination of the introduced methyl groups with NBS to obtain **17**. The reaction of **17** with NaCp in the presence of additional NaH gave the expected cyclopentadiene product $^{\text{Binaph}}$**CpH-1** as well as the spiro product **18** in a 1.9:1 mixture, respectively. The spiro compound **18** can be converted to the desired ligand $^{\text{Binaph}}$**CpH-1** via thermal rearrangement at 220 °C without the loss of chiral purity [33].

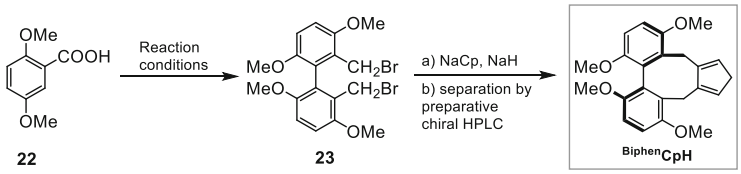


Scheme 9 Synthesis of 3,3'-functionalized $^{\text{Binaph}}$**CpH** ligands

Table 1 Reaction conditions for derivatization of the 3- and 3′-position

Reaction conditions pathway 1: ortho-functionalization				
	Reagents	R^a	Compound	Yield [%]
1	Tf_2O, NEt_3	OTf	$^{\text{Binaph}}$**CpH-5**	83
2	(a) Tf_2O, NEt_3	Me	$^{\text{Binaph}}$**CpH-6**	76
	(b) Cross-coupling	Bn	$^{\text{Binaph}}$**CpH-7**	99
		C=CTIPS	$^{\text{Binaph}}$**CpH-8**	85
		Ph	$^{\text{Binaph}}$**CpH-9**	92
3	CuI, PhI	OPh	$^{\text{Binaph}}$**CpH-10**	35
4	NaH, R^aX	OBn	$^{\text{Binaph}}$**CpH-11**	85
		OMOM	$^{\text{Binaph}}$**CpH-12**	92
		$O(CH_2)_2Bn$	$^{\text{Binaph}}$**CpH-13**	85
		OTIPS	$^{\text{Binaph}}$**CpH-14**	80
		O*i*-Pr	$^{\text{Binaph}}$**CpH-15**	86
		OTBDPS	$^{\text{Binaph}}$**CpH-16**	79

Several derivatives were synthesized by variations in the sidewall on the stage of the spiro compound **18** as well as using 1,1′-binaphthyl-2,2′-dicarboxylic acid as starting material. The spiro compound (**18**) was treated with $LiPPh_2$ [35] or *n*-BuSLi for the cleavage of the methoxy ether connection, releasing the hydroxy groups according to Scheme 9. The *ortho*-position was subjected to further functionalization to introduce alkyls, ethers, and aryl groups via reaction pathway 1, finally undergoing thermal rearrangement to obtain the Cp derivatives $^{\text{Binaph}}$**CpH-5** to **-16** (Scheme 9, Table 1) [33, 36, 37]. The derivative $^{\text{Binaph}}$**CpH-5** was obtained from **19** by treating it with Tf_2O in the presence of a base. Further cross-coupling reactions from

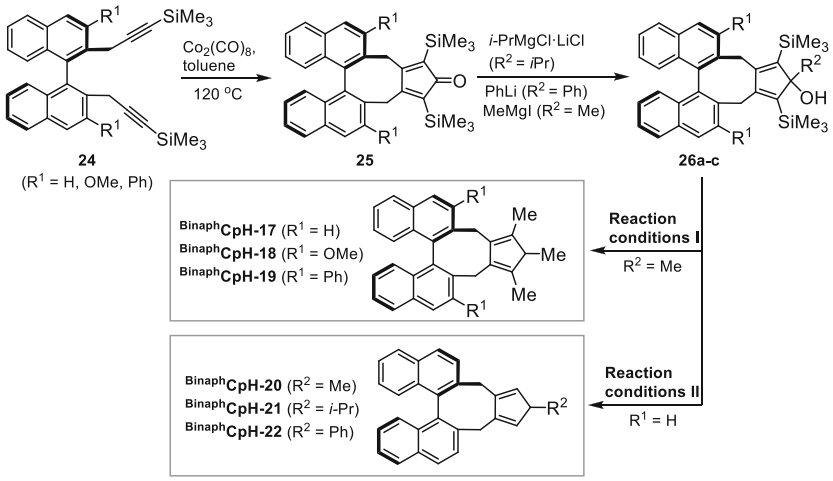


Scheme 10 Overview on the synthetic approach toward $^{\text{Biphen}}$**CpH** ligands

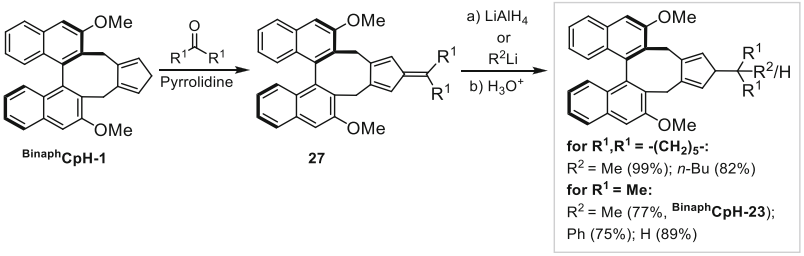
$^{\text{Binaph}}$**CpH-5** enabled the isolation of cyclopentadienes with other alkyl and aryl groups in the 3- and 3′-position (**$^{\text{Binaph}}$CpH-6** to **-9**) [33]. The *ortho*-aryloxy derivatives (**$^{\text{Binaph}}$CpH-10**) were obtained via a copper-catalyzed Ullmann coupling with iodobenzene and alkoxy-substituted derivatives (**$^{\text{Binaph}}$CpH-11 to -16**) were obtained via Williamson ether synthesis according to Table 1 [36]. Another method for the modulation of the biaryl scaffold utilized enantiopure 1,1′-binaphthyl-2,2′--dicarboxylic acid derivatives (**20a, 20b**) for the formation of *ortho*-silylated and halogenated binaphthyl-Cp ligands (**21**) [38] as shown in reaction pathway 2, Scheme 9. The *ortho*-halogenated ligands (**$^{\text{Binaph}}$CpH-2** and **-3**) were obtained by treatment of **20b** (R = *i*-Pr) with $(TMP)_2Mg$, followed by quenching using elemental bromine or iodine, while the *ortho*-silylated product (**$^{\text{Binaph}}$CpH-4**) was obtained by deprotonation of dicarboxylic acid **20a** with excess TMPLi in presence of Me_3SiCl, according to reaction conditions pathway 2.

A biaryl derivative $^{\text{Biphen}}$**CpH** based on the 2,2′-dimethoxy biphenyl core was synthesized from a commercially available carboxylic acid (**22**) as shown in Scheme 10. The diacid was iodinated on both rings and then converted to the methyl ester, which then underwent dimerization according to modified Lin's protocol in the presence of a nickel complex to form the biphenyl moiety [39]. The desired product was formed by sequential steps of reduction, bromination (delivering the key compound **23**), and double alkenylation followed by chiral resolution via preparative chiral HPLC [38].

Multi-substituted binaphthyl-based Cp ligands were reported by You and coworkers in 2020, providing the Cp ring with additional bulk for increased selectivity (Scheme 11) [40]. The completely substituted cyclopentadienyl ring was assembled by an intramolecular [2 + 2 + 1] cyclisation of **24** via a dicobalt-carbonyl complex to afford cyclopentadienones (**25**), according to Shibata et al. [41]. The required diyne precursor compounds were synthesized from an intermediate already described (**17**), commonly also used for construction of the chiral binaphthyl-Cp's by reaction with metallated cyclopentadienes [42, 43]. Methyl, isopropyl, and phenyl groups were introduced by addition of MeMgI, *i*-PrMgCl·LiCl, and PhLi to the ketone to obtain tertiary alcohols (**26a-c**). Penta-substituted cyclopentadienes were obtained via Stille cross-coupling after both TMS groups were replaced with iodine to obtain $^{\text{Binaph}}$**CpH-17** to **-19**. The reduction of the hydroxyl group followed by the removal of the TMS groups led to the desired substituted cyclopentadiene ligand precursors $^{\text{Binaph}}$**CpH-20** to **-22**.



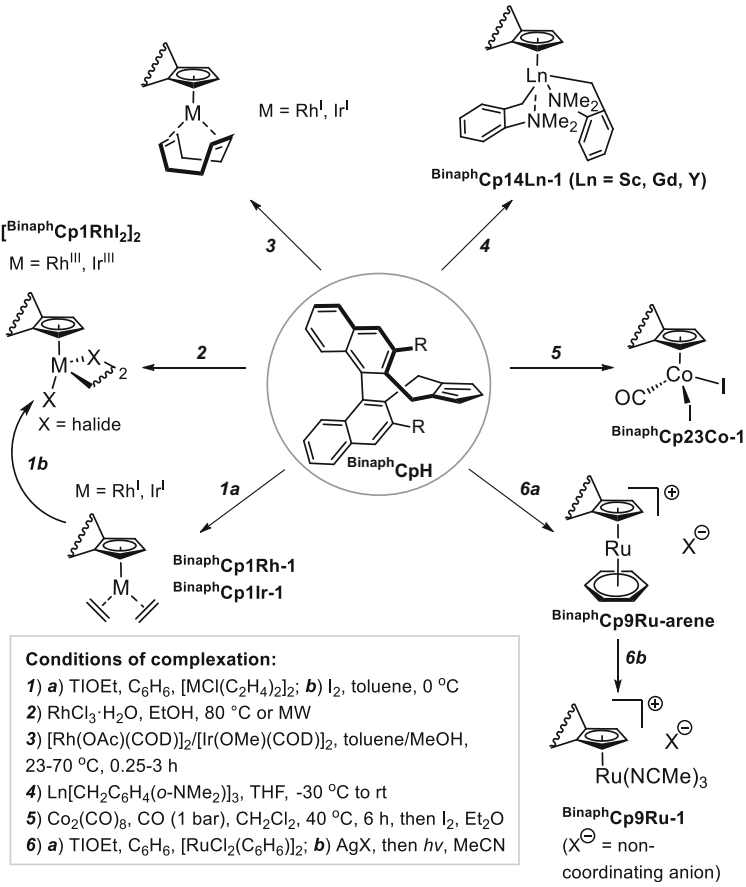
Scheme 11 Alternative approach toward the synthesis of functionalized $^{\text{Binaph}}$**CpH** ligands



Scheme 12 Postfunctionalization of chiral $^{\text{Binaph}}$**CpH-1** derivatives

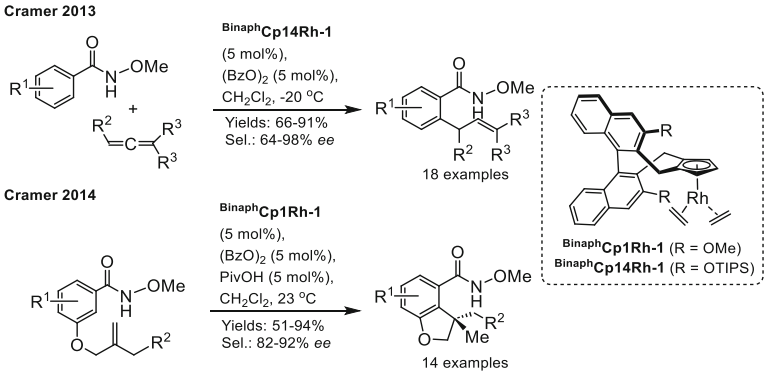
The group of Cramer reported the assembly of cyclopentadiene ligand precursors with bulkier analogs on the Cp ring in 2018. The precursor $^{\text{Binaph}}$**CpH-1** underwent condensation with a ketone to furnish the corresponding fulvenes **27**, which were further transformed by reduction with $LiAlH_4$ or by the addition of LiR (R = Me, $-(CH_2)_5$-), yielding the free cyclopentadienes (Scheme 12) [44].

The aforementioned binaphthyl-based Cp ligands have been complexed by a series of late and early transition metals like the group 9 metals (Rh, Ir, or Co) and scandium so far and have been used for various applications in catalysis as exemplified in Scheme 13 for $^{\text{Binaph}}$**CpH** ligands. The Rh(I) and Ir(I) complexes are synthesized using thallium ethoxide as base and their corresponding M(I) ethylene chloride as metal precursor as shown in Scheme 13 to obtain $^{\text{Binaph}}$**Cp1Rh-1** [36, 45] and $^{\text{Binaph}}$**Cp1Ir-1** (condition of complexation 1a) [46]. Other Rh(I) and Ir(I) complexes can also be synthesized via mild complexation using corresponding acetoxy- or alkoxy-metal precursor complexes (condition of complexation 3)



Scheme 13 Overview on various transition metal complex syntheses from $^{\text{Binaph}}$**CpH** derivatives

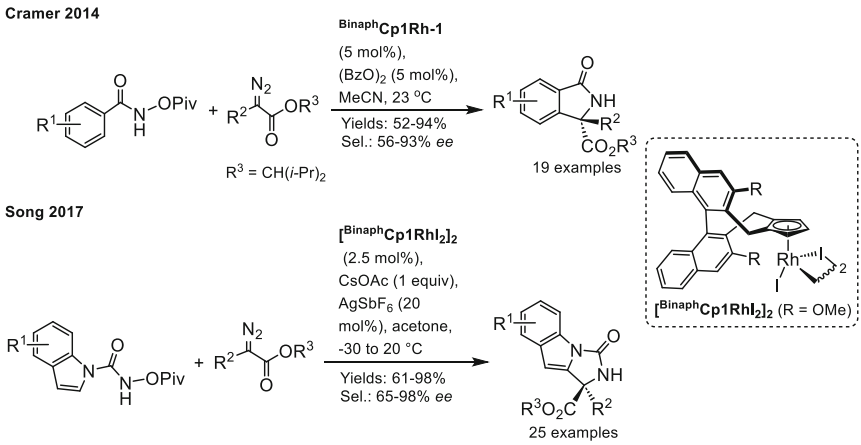
[24]. The Rh(III) and Ir(III) dimeric halide complexes were obtained in two different ways, depending on the substitution of the Cp ring. The $Cp^{X}M(I)$ ($^{\text{Binaph}}$**Cp1Rh-1** and $^{\text{Binaph}}$**Cp1Ir-1**) complexes possessing di-substitution on the Cp ring can be easily converted to the corresponding $Cp^{X}M(III)$ ([$^{\text{Binaph}}$**Cp1RhI$_2$]$_2$** and [$^{\text{Binaph}}$**Cp1IrI$_2$]$_2$**) complexes by oxidation with iodine [46–48]. The $^{\text{Binaph}}$**Cp'H** preligands containing tetra- or penta-substitution on the cyclopentadienyl ring can be converted to $^{\text{Binaph}}$**Cp'M(III)** complexes using $MCl_3{\cdot}3H_2O$ (M = Rh, Ir) in EtOH either by heating at 80 °C or via microwave heating depending on the steric hindrance (condition of complexation 2) [40, 49]. Ligands such as $^{\text{Binaph}}$**CpH-17,** $^{\text{Binaph}}$**CpH-18,** $^{\text{Binaph}}$**CpH-20 and** $^{\text{Binaph}}$**CpH-21** are metalated with $RhCl_3{\cdot}nH_2O$ via heating to 80 °C while $^{\text{Binaph}}$**CpH-19** and $^{\text{Binaph}}$**CpH-22** required microwave heating. The chiral half-sandwich rare earth metal complexes of scandium, yttrium, and gadolinium were obtained by an acid–base reaction. The synthesis of lanthanide (Ln) complexes is also straightforward, commencing from $Ln[CH_2C_6H_4(o\text{-}NMe_2)]_3$ and one equivalent of binaphthyl-substituted cyclopentadiene ligand in THF as



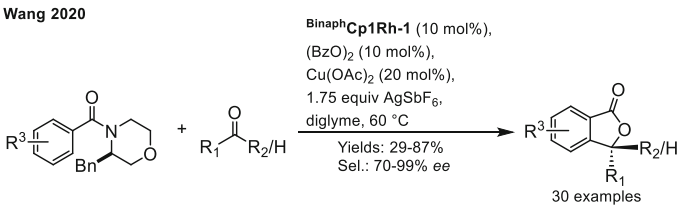
Scheme 14 Asymmetric C-H functionalization reactions using **^{Binaph}Cp1Rh-1**

shown for the Sc, Y, and Gd complexes **^{Binaph}Cp14Sc-1**, **^{Binaph}Cp9Gd-1** and **^{Binaph}Cp14Y-1** (condition of complexation 4) [50]. The $Cp^{X}Co(III)$ (like **^{Binaph}Cp23Co-1**) complexes of trisubstituted cyclopentadienes were obtained from the precursor $Co_2(CO)_8$ by reaction with the ligand under CO atmosphere for 6 h and subsequent oxidation with iodine (condition of complexation 5) [51]. The cationic sandwich complex $Cp^{X}Ru(II)$ (**^{Binaph}Cp9Ru-1**) having three free coordination sites was obtained upon treatment of **^{Binaph}CpH** with $[RuCl_2(C_6H_6)]_2$. The complex was reacted with a thallium base according to reaction condition 6 to obtain the cationic sandwich complex **^{Binaph}Cp9Ru-arene**. The complex then underwent an anion exchange from chloride to the hexafluorophosphate anion, being finally transformed into the desired complex **^{Binaph}Cp9Ru-1**, when benzene decoordinates in exchange for acetonitrile ligands upon photolysis. The use of $[RuCl_2(C_6H_6)]_2$ instead of the more common $[RuCl_2(cymene)]_2$ reduced the formation of the corresponding ruthenocene by-product [37].

The working groups of Cramer, Wang, Li, You, Lam, Song, and Hou reported several enantioselective transformations using the chiral **^{Binaph}Cp'** ligands containing different metals like Rh, Ru, Ir, Co and rare earth metals like Sc, Y, Gd, La, and Sm [52, 53]. The complexes were especially used in enantioselective C-H functionalization reactions like coupling, annulation, or cycloaddition reactions toward C-C and C-N bond formation. The most common coupling partners reported so far for the C-H functionalization reactions are alkynes [35, 54–58], alkenes [59–64], allenes [65], diazo compounds [47, 66–69], aldehydes [36], and Michael acceptors like nitroalkenes [48]. Chiral **^{Binaph}Cp'** ligands, first reported by Cramer in 2013 [33], were applied for the $Cp^{X}Rh(III)$-catalyzed *ortho*-allylation of N-OMe-aryl-hydroxamates via C-H functionalization obtaining high enantioselectivity and good yields (Scheme 14, above). The optimization studies showed that the **^{Mannitol}CpRh(III)** complex containing the first generation chiral Cp^{X} ligand was outperformed by the **^{Binaph}Cp14Rh-1**. The presence of the bulkier substituent OTIPS on the **^{Binaph}Cp'** ligand resulted in improved enantioselectivity. The same group extended this reaction to internal alkenes using another derivative **^{Binaph}Cp1Rh-1** for the synthesis of dihydrobenzofurans in high enantioselectivity



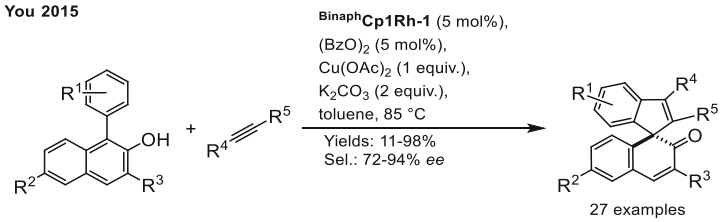
Scheme 15 Asymmetric C-H functionalization reactions using [^{Binaph}**Cp1RhI$_2$]$_2$**



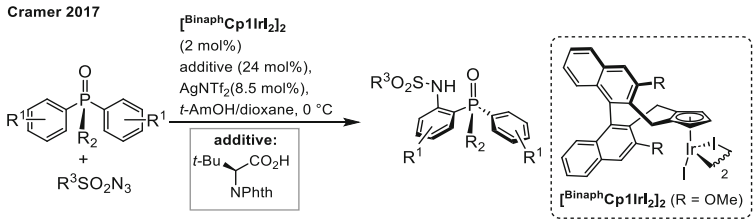
Scheme 16 Asymmetric synthesis of enantioenriched phthalides using ^{Binaph}**Cp1Rh-1**

and good yields in 2014 (Scheme 14, below) [45]. The presence of an *ortho*-methoxy substituent on the biaryl scaffold increased the enantioselectivity in comparison with more bulkier ^{Binaph}**Cp'** ligands, containing O*i*-Pr (^{Binaph}**Cp15Rh-1**) and OTIPS (^{Binaph}**Cp14Rh-1**).The meta-alkoxy group can act as a secondary directing group in order to facile reaction at more hindered *ortho*-position.

The group of Cramer in the same year synthesized chiral isoindolones via [4 + 1] annulation reaction by varying the coupling partner to diazo compounds in a benzamidazation reaction [69]. The ^{Binaph}**Cp14Rh-1** catalyst applied possesses bulky OTIPS substituents allowing the hydroxamate to orient in such a way that it is pointing away from both OTIPS moieties and the bulky 3-(2,4-dimethyl-pentyl) ester group thus determining the stereoselectivity (Scheme 15, above). Later in 2017, Song and coworkers extended this reaction using precatalyst [^{Binaph}**Cp1RhI$_2$]$_2$**, activated with $AgSbF_6$ to synthesize fused indolo compounds with high yields and enantioselectivities (Scheme 15, below) [47]. Similarly, Wang et al. reported the synthesis of enantioenriched phthalides using Cp^{X}Rh(I) complex ^{Binaph}**Cp1Rh-1** with excellent enantioselectivities and good yields in 2020 [70]. After the amide-directed arene C-H bond activation, the intermolecular addition to the aldehyde takes place and subsequent lactonization yields the final product (Scheme 16). Both the



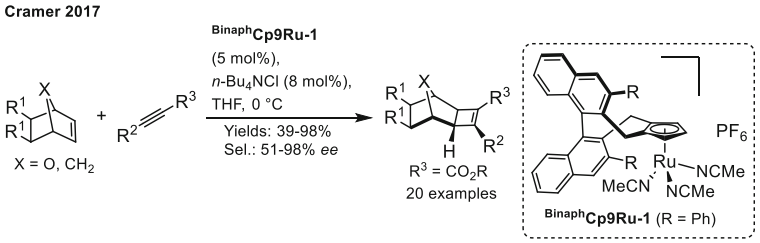
Scheme 17 Asymmetric synthesis of chiral spirocyclic compounds from 2-naphthols and alkynes



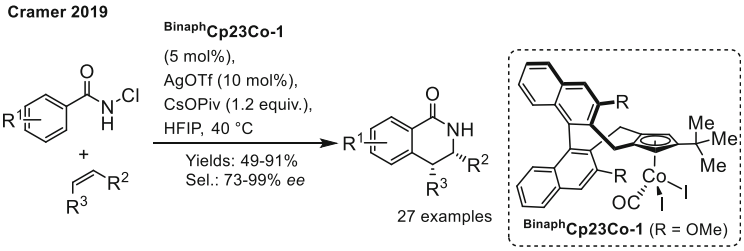
Scheme 18 Ortho-amidation of prochiral phosphorus oxides using a chiral Ir(III) complex

chiral amide auxiliary and chiral catalyst was crucial for increased enantioselectivity. However, the use of stochiometric amounts of copper and expensive silver salt additives was inevitable for the reaction. Several chiral spirocyclic compounds are also synthesized using the complex (**^{Binaph}Cp1Rh-1**) via a [3 + 2] annulation reaction of alkynes with C-H coupling partners. In 2015, You and coworkers reported the synthesis of chiral spirocyclic β-naphthalenones bearing an all carbon quaternary center from 1-aryl-2-naphthols using the chiral **^{Binaph}Cp1Rh-1** catalyst and stochiometric oxidant $Cu(OAc)_2$ (Scheme 17) [58].

An Ir(III)-catalyzed reaction was reported by Cramer and coworkers using the complex **[^{Binaph}Cp1IrI$_2$]$_2$** for the enantioselective amidation of phosphine oxides by sulfonyl azides. High enantioselectivity was achieved in a synergistic process with the assistance of an amino acid additive, leading to a complexed intermediate involved in the rate-limiting and enantio-determining step (Scheme 18) [71]. The cationic Cp^{X}Ru(II) complexes having three free coordination sites can facilitate reactions demanding more than two coordination sites. In 2017, Cramer and coworkers reported a cationic binaphthyl-Cp^{X}Ru(II) (**^{Binaph}Cp9Ru-1**) complex to catalyze the enantioselective pyran synthesis via a [4 + 2] hetero-Diels-Alder cyclization of yne-enones [37]. Later, the same complex was applied in the presence of *n*-Bu_4NCl to perform a [2 + 2] cycloaddition of strained norbornene derivatives with internal alkynes to obtain *exo*-cyclic cyclcobutanes (Scheme 19). Even though the cationic complex itself showed promising reactivity, it did not provide much stereoinduction. The in situ binding of chloride to the cationic complex is crucial for achieving high enantioselectivity and reactivity [72]. A chiral binaphthyl-based Cp'Co(III) complex (**^{Binaph}Cp23Co-1**) was utilized by Cramer and coworkers for

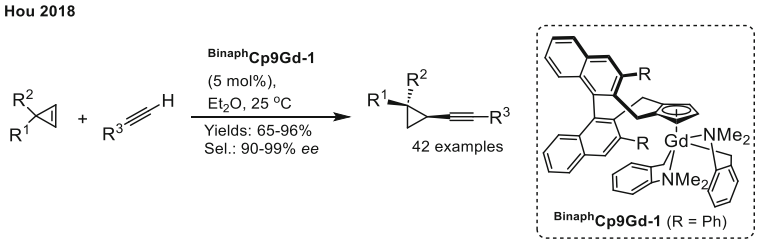


Scheme 19 Asymmetric [2+2] cycloaddition using a chiral Cp^x-ruthenium complex



Scheme 20 Synthesis of dihydroisoquinolones by ortho-C-H-functionalization with a cobalt complex

the synthesis of dihydroisoquinolones via C-H functionalization of *N*-chlorobenzamides with alkenes (Scheme 20) [51]. A trisubstituted Cp ring with an OMe-substituted biaryl backbone and a *tert*-butyl group as third substituent gave very high enantioselectivity but decreased reactivity. The reactivity was further increased by changing the solvent and base to HFIP and CsOPiv, respectively, furnishing a 90% yield and high enantioselectivities. The complex was reported to give larger enantioselectivity compared to the chiral **^{Binaph}Cp'Rh(III)** complexes described previously. Hou and coworkers first reported the synthesis and application of **^{Binaph}Cp'** complex with lanthanides for the coupling of alkenes with pyridines, where ortho-alkylated products were obtained selectively in good yields and high enantioselectivity [50]. Later in 2018, the same group reported a Gd-catalyzed addition of terminal alkynes to cyclopropenes to form chiral enantioenriched alkynylcyclopropanes in high yields using **^{Binaph}Cp9Gd-1** (Scheme 21) [73]. The study suggests that the change in the size of the metal atom can have a greater impact in the selectivity of the reaction.

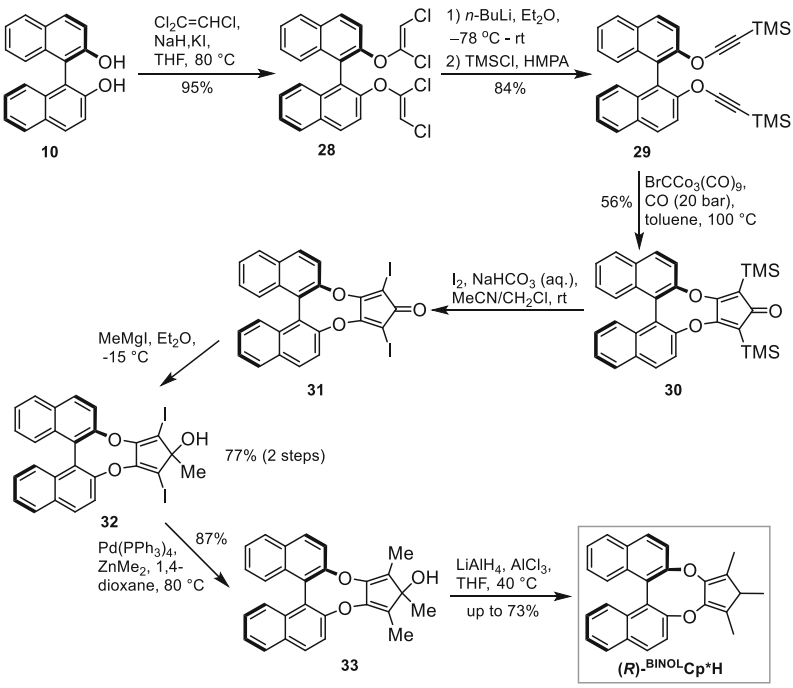


Scheme 21 Alkynyl C-H-addition to cyclopropenyl substrates using Cp^x-gadolinium complexes

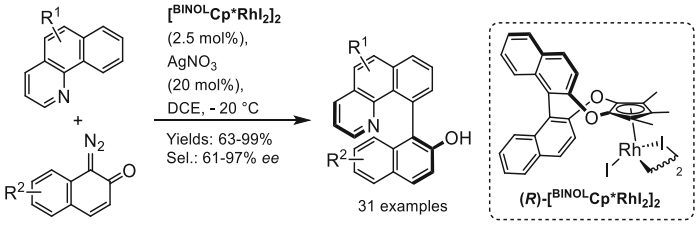
3.4 BINOL-Based Ligands

The binaphthyl-based ligands described earlier have found a structurally closely related congener, the BINOL-derived Cp ligands, where the binaphthyl backbone is linked via oxygen atoms to the Cp ligand [74]. This class of chiral cyclopentadienes is considered to be much easier synthetically accessible, however, also a sequence of at least seven steps is required (Scheme 22). The sequence starts out from enantiomerically pure (*R*)-BINOL (**10**), which is double O-alkynylated by reaction with trichloroethylene to yield **28**. Subsequent elimination with *n*-BuLi and quenching with TMSCl gave the protected alkynyl ether **29**. A [2 + 2 + 1] cycloaddition in the presence of a methylidyne cobalt cluster furnished the corresponding cyclopentadienone **30**. Desilylative iodination followed by reaction with methylmagnesium halide to alkylate the ketone gave the fully substituted cyclopentadiene **32**. Palladium-catalyzed Negishi cross-coupling with $ZnMe_2$ led to the alkylation of the vinyl iodide functionalities and furnished compound **33**. Finally, elimination reactions with lithium aluminium hydride in the presence of a Lewis acid allowed the isolation of the final ligand **(*R*)-$^{\mathbf{BINOL}}$Cp*H**. The same sequence was adopted for a 3,3′-dimethoxylated derivative under identical conditions. No other derivatives, e.g. including aromatic groups in the 3/3′-position were synthesized by this approach, in contrast to the binaphthyl-based compounds. The metalation of the ligand **$^{\mathbf{BINOL}}$Cp*H** was performed according to the pathway described earlier (see Scheme 13), using $[Rh(OAc)(COD)]_2$ in the presence of sodium carbonate as the base in toluene/MeOH resulted in good yields for different substitution pattern on the Cp ring.

The Rh(I)-complex **(*R*)-[$^{\mathbf{BINOL}}$Cp*RhI$_2$]$_2$** was screened as catalysts for the reaction between benzo(*h*)quinolines and 1-diazonaphthoquinones to furnish the corresponding heterobiaryl compounds as configurationally rather stable compounds (Scheme 23). The reaction involves cyclometallation and reaction with the diazo compound in an electrophilic process. No isotope effect in a competition experiment was observed, suggesting that the C-H activation process might be not involved in the turnover-limiting process.



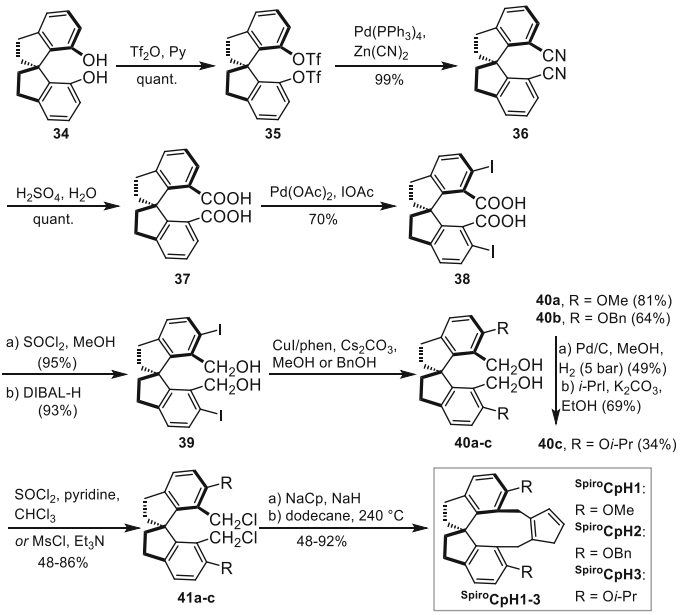
Scheme 22 Synthetic approach toward **(R)-^{BINOL}Cp*H** ligands



Scheme 23 Asymmetric catalysis application for ^{BINOL}Cp* ligands in the reaction between benzo (h)quinolines and 1-diazonaphthoquinones

3.5 SPINOL-Based Ligands

You and coworkers synthesized the first Cp ligands containing the 1,1′--spirobiindane backbone (**SCp**, here ^{Spiro}**Cp**), which are then used as an essential class of ligands in several asymmetric catalysis [75]. The main idea behind the ^{Spiro}**Cp** ligands was inspired by the pioneering work from the Zhou group, where they have made a variety of 1,1′-spirobiindane-based phosphoramidite [76],

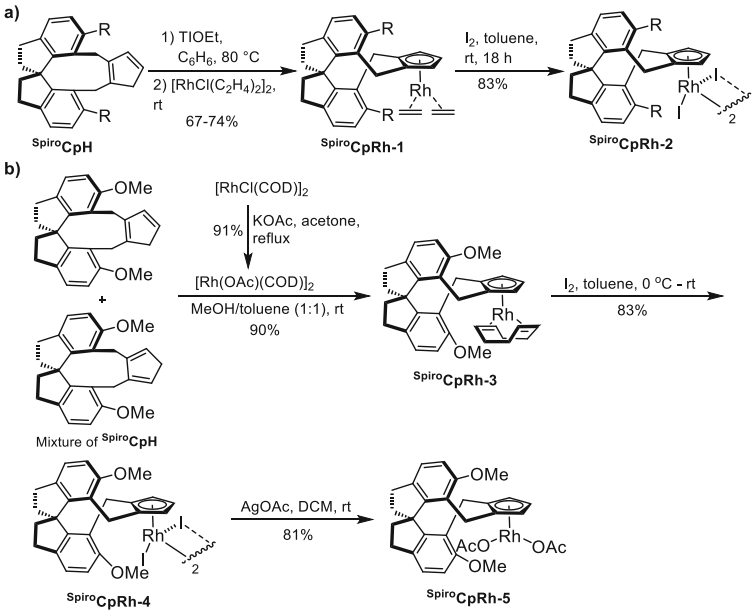


Scheme 24 Synthesis of different ^{Spiro}CpH ligands

phosphine [77], and oxazoline [78] ligands, which showed impressive activity in many asymmetric transformations.

The synthesis of the **^{Spiro}Cp** ligand class commenced from the diol **34** (Scheme 24), which is then converted to bistriflate **35** to generate dicarbonitrile **36** by cyanation reaction using $Zn(CN)_2$ and $Pd(PPh_3)_4$. Hydrolysis of dinitrile **36** with dilute H_2SO_4 produced the corresponding dicarboxylic acid **37**. The diiodide **38** is generated from dicarboxylic acid **37** by Pd-catalyzed direct ortho C-H iodination [79]. Further esterification followed by reduction gave diol **39**, which then underwent spirobiindane backbone modification. Methoxylation and benzyloxylation at the 6,6′-position of diol **39** by a Cu-catalyzed reaction generated modified diols **40a** and **40b**, respectively [80]. Debenzylation followed by etherification of **40b** furnished isopropoxy-substituted diol **40c**. The chlorination of **40a-c** with MsCl or $SOCl_2$ gave dichlorinated products **41a-c**. In the next step, introduction of the cyclopentadiene group was done by double alkenylation using sodium cyclopentadienide followed by thermal rearrangement [21, 22] to afford the final ligand **^{Spiro}CpH1-3** for complexation.

The complexation of the **^{Spiro}CpH** ligands with rhodium metal is carried out using the same classical methodology that has been mentioned for all preceding ligands (Scheme 25, a). Thallium(I) ethoxide is used as a base for deprotonation of **^{Spiro}CpH** ligand, followed by a reaction with the rhodium-olefin complex $[RhCl(C_2H_4)_2]_2$ as rhodium metal source, affording the chiral bisethylene rhodium complex **^{Spiro}CpRh-1**. Later on, rhodium-diiodo spirobiindane dimer complex

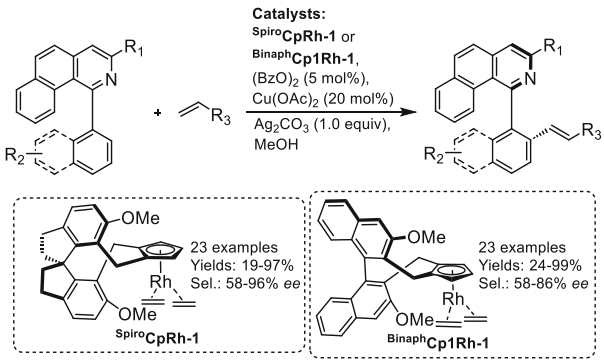


Scheme 25 Complexation of ^{Spiro}CpH ligands with different rhodium complexes and derivatization

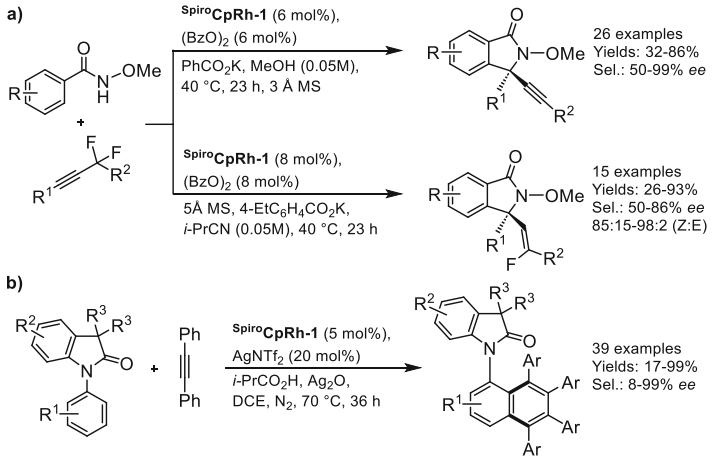
^{Spiro}CpRh-2 has been synthesized from **^{Spiro}CpRh1**, which is also employed in asymmetric catalysis [81]. Xia and Li synthesized Rh-diacetoxy spirobiindane complex **^{Spiro}CpRh-5** from Rh-diiodo spirobiindane dimer complex, which was prepared through a slightly different synthetic route (Scheme 25, b) [82]. Initially they synthesized $[Rh(OAc)(COD)]_2$ from $[RhCl(COD)]_2$ by reaction with KOAc, which is then reacted with the mixture of **^{Spiro}CpH** ligands to afford **^{Spiro}CpRh-3**. In the next step Rh-diiodo spirobiindane dimer complex **^{Spiro}CpRh-4** has been made from **^{Spiro}CpRh-3** and reacted with AgOAc to afford Rh-diacetoxy spirobiindane complex **^{Spiro}CpRh-5**.

The chiral **^{Spiro}CpRh** complexes have been employed in several C-H functionalization reactions [83–88], some of which will be discussed in this book chapter. When the You group initially revealed the **^{Spiro}CpRh** complex motif, they used it for asymmetric *N*-directed oxidative coupling of biaryls with alkenes (Scheme 26) [75]. The axially chiral biaryls were formed in excellent yield and selectivities up to 96% *ee*. When compared to their previous studies with a structurally similar Cramer' **^{Binaph}CpRh** complex, it is noteworthy that the **^{Spiro}CpRh-1** exhibits slightly better enantioselectivity than **^{Binaph}Cp1Rh-1** as catalyst [89].

Wang and coworkers developed a solvent-dependent protocol for the enantioselective synthesis of alkynyl and monofluoroalkenyl isoindolinones from *N*-methoxybenzamides and α,α-difluoroalkyne by using the **^{Spiro}CpRh-1** catalyst (Scheme 27, a) [90]. Interestingly, MeOH as a solvent afforded alkynyl isoindolinones whereas the monofluoroalkenyl isoindolinones were afforded in



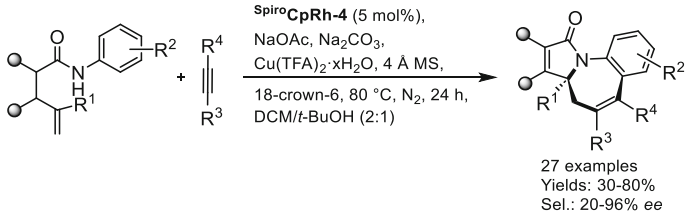
Scheme 26 Ortho-alkenylation of biaryls using chiral $Cp^xRh(I)$ complexes



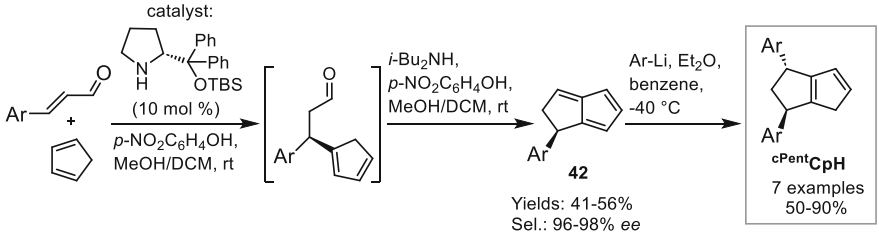
Scheme 27 Asymmetric transformations applying ^{Spiro}**CpRh-1** as catalyst

i-PrCN. In both cases, the products formed in high yield and high enantioselectivity. The same group reported the enantioselective synthesis of C-N axially chiral N-aryloxindoles from N-aryloxindoles and alkynes by using the ^{Spiro}**CpRh-1** catalyst in a Satoh-Miura-type reaction (Scheme 27, b) [91]. The amide's carbonyl group acts as a chelating functionality, assisting in the double C-H activation to afford the desired atropisomers with up to 99% yield and 99% *ee*.

Xia and Li reported the asymmetric synthesis of 1-azabicyclo[5.3.0]decanes via rhodium-catalyzed (3 + 2 + 2) annulation of alkenyl amides and alkynes by using ^{Spiro}**CpRh-4** as catalyst (Scheme 28) [82]. The mechanistic study revealed a unique catalytic pathway that involved the N-H/C-H bond dual activation and formation of the key 8-membered rhodacycle intermediate.



Scheme 28 Asymmetric cyclization reaction of unsaturated aryl amides and alkynes



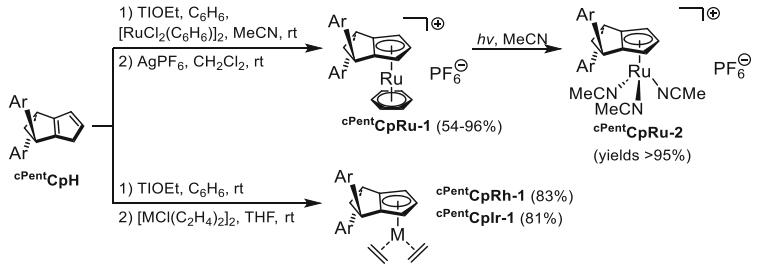
Scheme 29 Synthesis of ^{cPent}**CpH** ligands including an organo-catalytic reaction step

3.6 Annelated Cyclopentane-Based Ligands

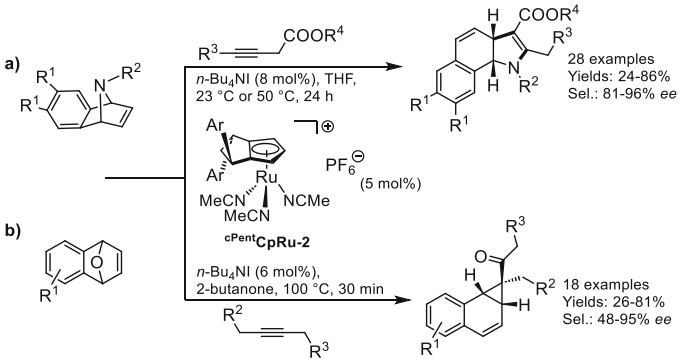
Cramer synthesized simple C2-symmetrical chiral Cp ligands that consist of a Cp-annellated five-membered ring with two aryl groups (^{cPent}**CpH**) [92]. The initial step consists of an organo-catalyzed ene-type reaction followed by intramolecular condensation reaction, which was first reported by Hayashi and coworkers (Scheme 29) [93, 94]. The resulting chiral cyclopentane-fused fulvenes underwent diastereoselective addition with aryl lithium reagent to form cyclopentane-fused diaryl ligands in excellent enantioselectivity.

The reaction of ligands with thallium(I) ethoxide followed by complexation with $[RuCl_2(C_6H_6)]_2$ and a cation exchange with $AgPF_6$ formed air- and moisture-stable complexes (Scheme 30). Subsequent photolysis in the presence of acetonitrile generated cationic ^{cPent}**CpRu-2** complexes with excellent yields. Also, the corresponding group 9 metal complexes ^{cPent}**CpRh-1** and ^{cPent}**CpIr-1** can be generated from the free ligands by applying thallium(I) ethoxide and $[MCl(C_2H_4)_2]_2$ (M = Rh or Ir) for complexation. Titanocene complexes have additionally been generated from this ligand class, however no significant amount of asymmetric induction was observed in cyclization and cross-coupling reactions with synthesized catalysts [95].

Cramer's group used the chiral cationic catalyst ^{cPent}**CpRu-2** for the asymmetric synthesis of dihydrobenzoindoles from azabenzonorbornadienes and alkynes (Scheme 31, a) [92]. The neutral ^{cPent}**CpRuI** complex is the active catalyst in this



Scheme 30 Complexation of ^{cPent}**CpH** ligands with ruthenium, rhodium, and iridium precursors



Scheme 31 Asymmetric alkyne addition reactions using ^{cPent}**CpRu-2**

reaction, which is generated in situ from cationic ^{cPent}**CpRu-2** and tetra-*n*-butylammonium iodide. It is worth noting that chiral ^{cPent}**Cp** ligand motif outperformed ^{Binaph}**Cp**-based ligands in terms of reactivity and enantioselectivity. Using the same catalyst, Cramer's group developed an asymmetric synthesis of benzonorcaradienes from oxabenzonorbornadienes and alkynes (Scheme 31, b)) [96]. Various tricyclic benzonorcaradienes were synthesized using the ^{cPent}**CpRu-2** catalyst with good yields and enantioselectivities.

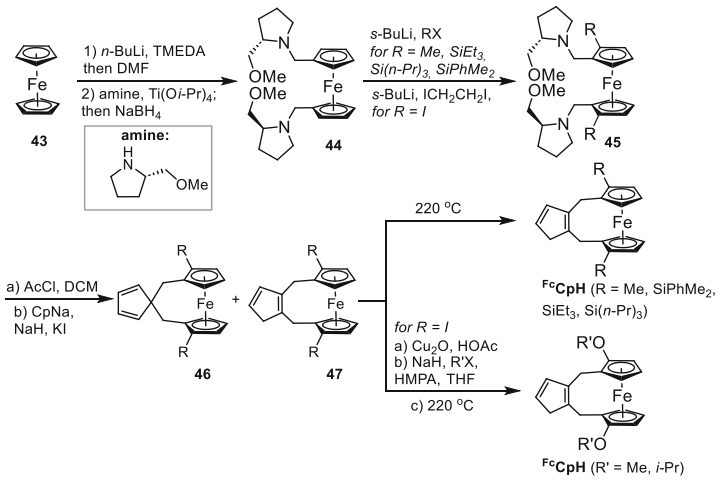
3.7 Ferrocenyl-Based Ligands

A planar-chiral ferrocene backbone-containing a chiral Cp ligand was synthesized by Wang et al. in 2020 [97]. The general idea of the approach was the generation of a planar-chiral 1,1′;2,2′-tetrasubstituted ferrocene by introducing a chiral auxiliary on each Cp ring and subsequent diastereoselective di-*ortho*-functionalization thereof. Afterward, the chiral auxiliary will be cleaved off and finally the Cp ring moiety will

be installed on the ferrocene fragment. The synthesis started with sequential dilithiation and diformylation of ferrocene (**43**) to obtain 1,1′-diformyl ferrocene, which further underwent reductive amination with (*S*)-2-(methoxymethyl)-pyrrolidine to obtain chiral ferrocenyl diamine **44**. Afterward, the chiral ferrocenyl diamine underwent a highly diastereoselective di-*ortho*-functionalization using *s*-BuLi, followed by quenching with electrophiles to obtain different *ortho*-functionalities (compound **45**) as shown in Scheme 32. Auxiliary cleavage in **45** using acetyl chloride in DCM was followed by installation of the Cp ring by reaction with sodium cyclopentadienide. An inseparable mixture of Cp derivatives (**46** and **47**) was formed, furnishing the targeted 2,2′-dimethyl- and 1,1′-disilyl-substituted ^{Fc}**CpH** ligands on heating at 220 °C. Besides that, 1,1′-dialkoxyferrocenyl Cp ligands could also be obtained from the iodides using acetic acid and cupric oxide, followed by alkylation and thermal treatment at 220 °C to give the desired products according to Scheme 32.

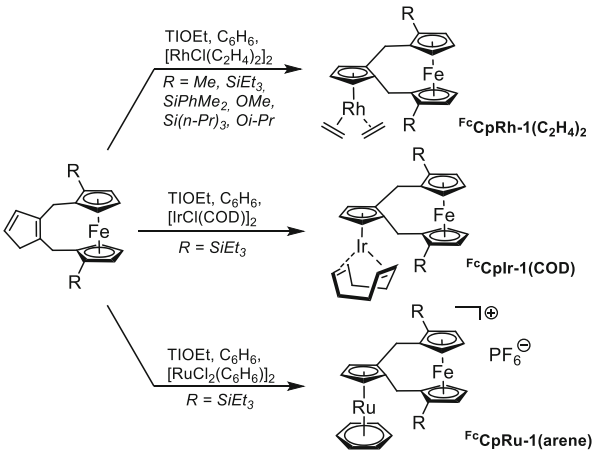
The chiral ferrocenyl-Cp ligands (^{Fc}**Cp**) were subjected to the preparation of bimetallic compounds by complexation with rhodium, iridium, and ruthenium precursors. The practical process was undertaken using the typical complexation techniques for Ir, Ru, and Rh complexes as already shown in the sections before to obtain the ^{Fc}**CpRh**, ^{Fc}**CpIr**, and ^{Fc}**CpRu** complexes (Scheme 33). Single crystal X-ray crystallography studies suggest that the chiral ferrocenyl moieties fold a little away from the metal centers.

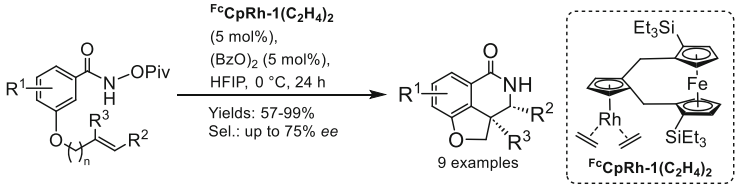
The potential use of the complex is yet to be explored. So far only one reaction is reported to obtain tricyclic lactams in moderate to good yields and enantioselectivities via CpRh^{I}-catalyzed asymmetric intramolecular amidoarylation of olefin-tethered benzamides, using the complex ^{Fc}**CpRh-1(C_2H_4)$_2$** (Scheme 34).



Scheme 32 Synthetic pathway for ferrocenyl-based Cp ligands

Scheme 33 Synthesis of transition metal complexes using ^{Fc}CpH ligands as precursor

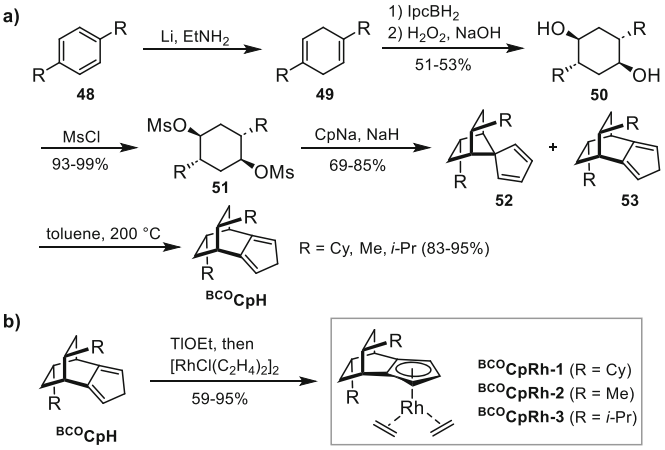




Scheme 34 Synthesis of annulated tricyclic compounds using a chiral ^{Fc}**CpRh-1(C$_2$H$_4$)$_2$** as catalyst

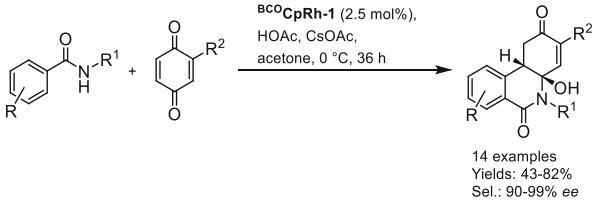
3.8 Bicyclo[2.2.2]Octane-Based Ligands

Wang and coworkers synthesized a new class of chiral C2-symmetric bridged-ring-fused Cp ligands and showcased their potential application in asymmetric C-H activation [98]. The ligand design was inspired from previously reported synthesis of bicyclo[2.2.2]octane-fused cyclopentadienes by Vollhardt and Halterman [99–101]. Ligand synthesis started from 1,4-dialkylbenzenes **48**, which undergo Birch reduction to form 1,4-cyclohexadienes **49** (Scheme 35, a). Following an asymmetric hydroboration-oxidation sequence of 1,4-cyclohexadienes **49** with monoisopinocampheylborane (IpcBH$_2$), C2-symmetrical chiral *cis*-cyclohexane-1,4-diols **50** were formed. The generated diols were then mesylated to produce diesters **51**, which were subsequently reacted with CpNa and NaH to produce a mixture of annulated cyclopentadienes **52** and **53**. Thermal treatment at 200 °C generated the desired bicyclo[2.2.2]octane-fused cyclopentadienes ^{BCO}**CpH**. The corresponding Rh complexes were made by classical reaction with thallium(I)-ethoxide and [RhCl(C$_2$H$_4$)$_2$]$_2$ (Scheme 35, b).



Scheme 35 Synthetic pathway for the construction of ^{BCO}CpH ligands and rhodium complexes

Scheme 36 Synthesis of tricyclic hydrophenanthridinones applying amides and quinones and ^{BCO}CpRh-1 as catalyst



After the successful synthesis of bicyclo[2.2.2]octane-fused cyclopentadienyl rhodium catalysts, Wang's group used these catalysts in asymmetric C-H activation reactions of N-methoxybenzamides and quinones to make a number of tricyclic hydrophenanthridinones of significant synthetic importance with a maximum of 82% yield and 99% *ee* (Scheme 36) [98]. Use of previously reported ^{Binaph}**Cp**- and ^{Spiro}**Cp**-based rhodium catalysts led to inferior results compared to the ^{BCO}**Cp**-bearing rhodium catalysts (**BCOCpRh1-3**) for the same reaction. Structural analysis of Wang's catalyst showed that the side wall of the ligand is more vertically and less horizontally extended which makes the metal center more accessible, contrasting the situation with ^{Binaph}**Cp**- and ^{Spiro}**Cp**-based rhodium catalysts.

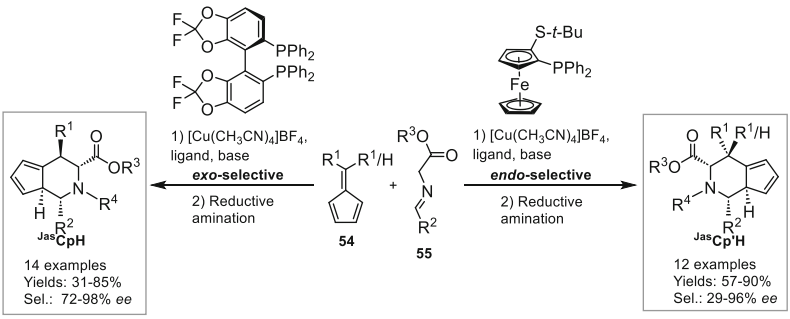
4 Synthesis of Complexes Without C2 Symmetry and Their Application

4.1 ^{Jas}Cp-Based Catalysts

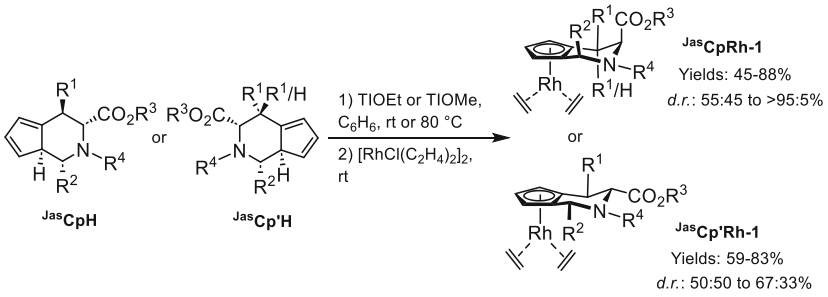
Antonchick, Waldmann, and coworkers demonstrated a three-step gram scale synthesis of a novel class of chiral piperidine-fused Cp ligands (**^{Jas}Cp**) [102]. These chiral ligand classes (**^{Jas}CpH** and **^{Jas}Cp'H**) were synthesized via enantioselective [6 + 3] cycloadditions of fulvenes (**54**) and imino esters (**55**), which allowed rapid structural variation and tuning (Scheme 37). Further modification of secondary amines by reductive elimination broadens the ligand pool significantly. The ligands differ from previously discussed ones as they don't possess C2-symmetry.

Subsequent complexation reaction with thallium(I) ethoxide or thallium (I) methoxide and $[RhCl(C_2H_4)_2]_2$ resulted in the formation of the corresponding **^{Jas}CpRh** catalyst (Scheme 38). Since the substituents on the ligands had little steric influence, the **JasCp** ligands encountered facial selectivity issues during the metalation reaction. As a result, metalation of such unsymmetrically substituted Cp's resulted in the formation of a mixture of diastereoisomers in different ratios. In some cases they appeared to be either inseparable or required complex chromatographic conditions with two different zones on a column, one with neutralized silica for separating diastereomers and one with neutral alumina to get rid of possibly decomposed Rh complexes from silica (performed at −40 ° C under argon).

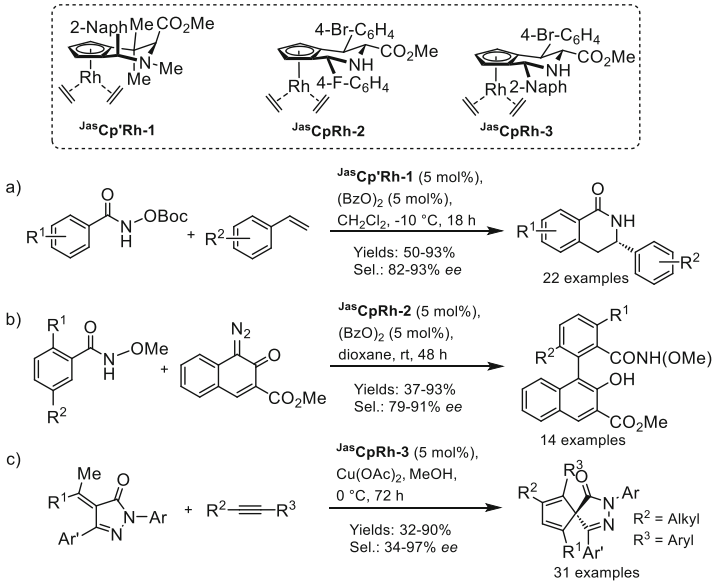
^{Jas}CpRh/^{Jas}Cp'Rh-type catalysts have been employed in several C-H functionalization reactions [103–105]. Only a handful of them will be discussed in the following. Initially, Antonchick, Waldmann, and coworkers performed annulation reaction of hydroxamates and olefins by screening different **^{Jas}CpRh/^{Jas}Cp'Rh** catalysts and found **^{Jas}Cp'Rh-1** was optimal for the reaction (Scheme 39, a) [102]. Enantioselectivity was greatly influenced by the bulkiness and pattern of the substituents on the ligands. They also reported a novel approach for atroposelective synthesis of biaryls from benzamides and diazonaphthoquinones by using the



Scheme 37 Synthetic access to the family of ^{Jas}CpH and ^{Jas}Cp'H ligands

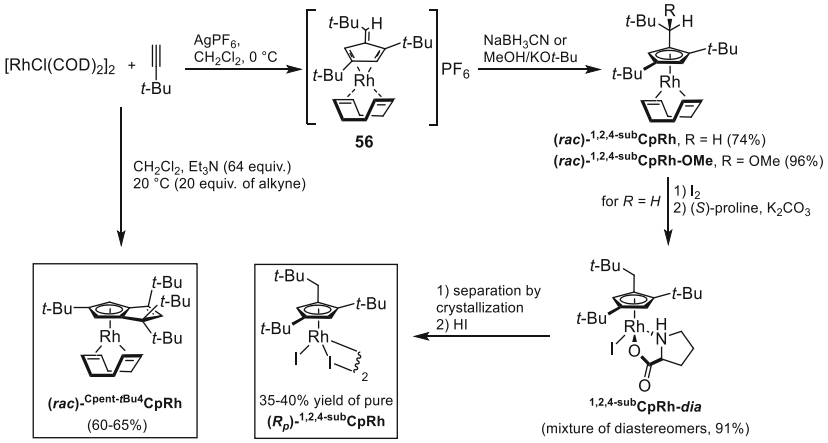


Scheme 38 Metallation procedure for ^{Jas}CpH and ^{Jas}Cp'H ligands with rhodium precursors



Scheme 39 Asymmetric catalysis using ^{Jas}CpRh- and ^{Jas}Cp'Rh-complexes

^{Jas}CpRh-2 catalyst (Scheme 39, b). Using this unprecedented approach, they were able to construct a series of axially chiral biaryls with excellent yields and selectivities by direct C-H arylation of benzamides. In a subsequent study they performed enantioselective annulation of α-arylidene pyrazolones through a formal C(sp^3)-H activation by using **^{Jas}CpRh-3** as catalyst (Scheme 39, c) [106]. The reaction proceeded under mild reaction conditions and spiropyrazolones were formed with good yields and enantioselectivities.

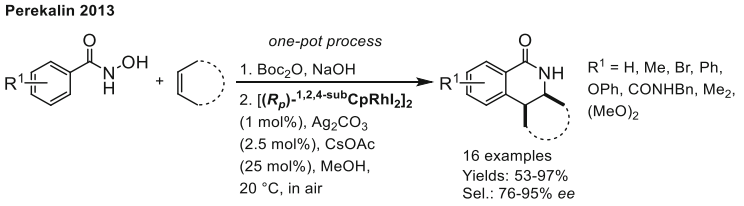


Scheme 40 Synthesis and chiral separation of newly constructed Cp^x-rhodium complexes

4.2 Planar-Chiral Cyclopentadienyl or Indenyl Catalysts

Significantly fewer chiral Cp-based ligands are relying on planar chirality without an annulated ring system and have also been used in asymmetric catalysis. A general challenge like described before is the selective formation of single enantiomers of the metal complexes being used as precatalysts for asymmetric catalytic transformations. Usually, such complexes need to be separated by classical separation techniques for racemic compounds used in organic synthesis, like preparative HPLC or crystallization.

An alternative approach was reported by the group of Perekalin, who synthesized a chiral Cp ring in the coordination sphere of a rhodium complex (Scheme 40, right) [107]. The formal [2 + 2 + 1] cycloaddition at low temperatures utilizing $[RhCl(COD)]_2$ as precursor in the presence of excessive *tert*-butylacetylene delivered the cationic cyclopentadienone complex **56** with 64% yield. Unfortunately, using other terminal alkynes mostly led to the formation of oligomerization products. Subsequent hydride addition or alkoxide addition to **56** resulted in aromatization and formation of the rhodium complexes **(*rac*)-$^{1,2,4\text{-sub}}$CpRh** or **(*rac*)-$^{1,2,4\text{-sub}}$CpRh-OMe** with generally very good yields. Conversion to the dinuclear iodide complexes with >80% yield allowed in the following step the reaction with enantiomerically pure (*S*)-proline to give the diastereomeric complexes (**$^{1,2,4\text{-sub}}$CpRh-*dia***). These are then undergoing chiral separation by crystallization, leading to the isolation of **(R_p)-$^{1,2,4\text{-sub}}$CpRh** with yields around 35–40% and a diastereomeric purity of >98:2. Treatment with aqueous HI allowed reconstruction of the diiodide complex **[(R_p)-$^{1,2,4\text{-sub}}$CpRhI$_2$]$_2$**. A slight modification of the route led to the formation of an annulated Cp ring containing four *tert*-butyl groups, one of which was pointing toward the side of the metal center and possesses hindered rotation around the C-C axis (compound **(*rac*)-$^{\text{Cpent-}t\text{Bu4}}$CpRh**, Scheme 40, left) [108]. The ligands obtained



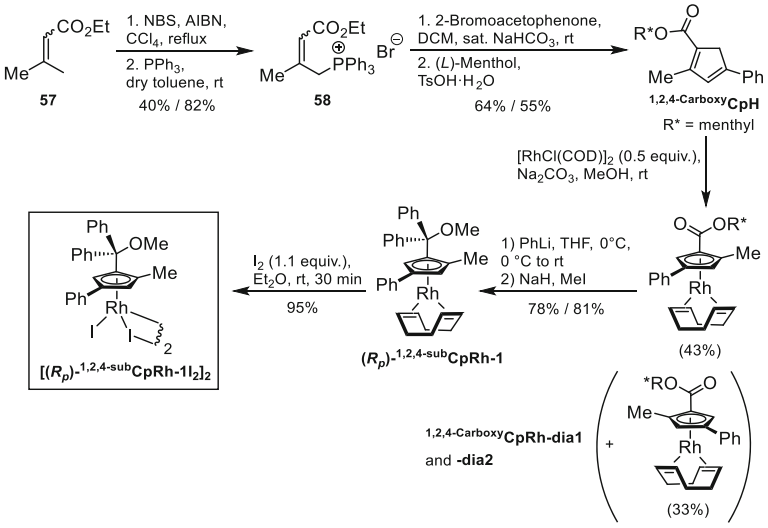
Scheme 41 Application of **[(R$_p$)-$^{1,2,4\text{-sub}}$CpRhI$_2$]$_2$** as catalysts in a benchmark C-H functionalization

a significantly larger buried volume compared to the Cp* ligand. Separation was possible by chromatography of a chiral amino alcohol complex.

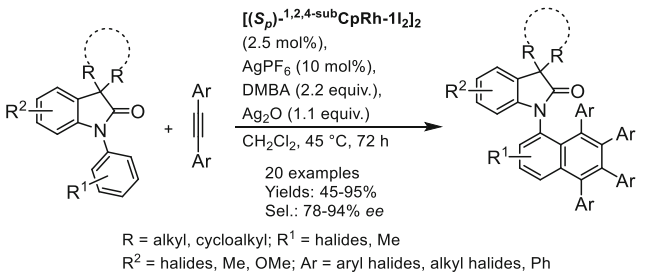
The complex **[(*R$_p$*)-$^{1,2,4\text{-sub}}$CpRhI$_2$]$_2$** was evaluated as chiral catalyst in the synthesis of dihydroisoquinolines from aryl hydroxamic acids and olefins like norbornene [107]. Optimized reaction conditions allowed the reaction to proceed at room temperature in air, although in situ O-acylation via a BOC group was necessary as other derivatives like the pivaloyl derivatives reacted much slower. The reaction proceeds with mediocre to excellent yield and in general very good enantioselectivities (Scheme 41).

The synthesis of a modified chiral Cp system relying on exclusive planar chirality was presented by the group of Wang [109]. They were inspired by earlier work from the group of Takahashi, who assembled chiral 1,2,4-trisubstituted cyclopentadienes using a menthyl group and complexed them by rhodium, to separate the resulting diastereomers by preparative HPLC [110]. Building upon this approach, the de novo synthesis of a chiral Cp ligand was undertaken in a way that the two diastereomers of the subsequently formed Rh(I) complex can be separated by chromatography. In this case simple silica column chromatography under air was employed. The synthetic sequence is exemplarily given for the preparation of precatalyst complex **[(*R*$_p$)-$^{1,2,4\text{-sub}}$CpRh-1I$_2$]$_2$** in Scheme 42.

The synthesis started out from 3-methylacrylate (**57**) by bromination and subsequent conversion into a phosphonium bromide salt **58**, followed by [3 + 2] cycloaddition with 2-bromoacetophenone to deliver the trisubstituted chiral cyclopentadiene in satisfying yield. Transesterification with (*L*)-menthol delivered the menthyl ester **$^{1,2,4\text{-Carboxy}}$CpH**, which is then subjected to metalation with a Rh (I)-COD precursor. Two diastereomers **$^{1,2,4\text{-Carboxy}}$CpRh-*dia1*** and ***-dia2*** are formed in a 1:1 ratio, which can conveniently be separated by column chromatography over silica gel to allow the isolation of the individual diastereomers with >99% *de*. Reaction with PhLi and ensuing methylation of the free hydroxy group smoothly delivered the chiral complex **(*R$_p$*)-$^{1,2,4\text{-sub}}$CpRh-1**. Subsequent oxidation with iodine delivered the complex **[(*R*$_p$)-$^{1,2,4\text{-sub}}$CpRh-1I$_2$]$_2$**, structurally related to the complex **[(*R$_p$*)-$^{1,2,4\text{-sub}}$CpRhI$_2$]$_2$** discussed before. Derivatives of **[(*S*$_p$)-$^{1,2,4\text{-sub}}$CpRh-1I$_2$]$_2$** exhibiting different substitution pattern have been prepared in an identical fashion.

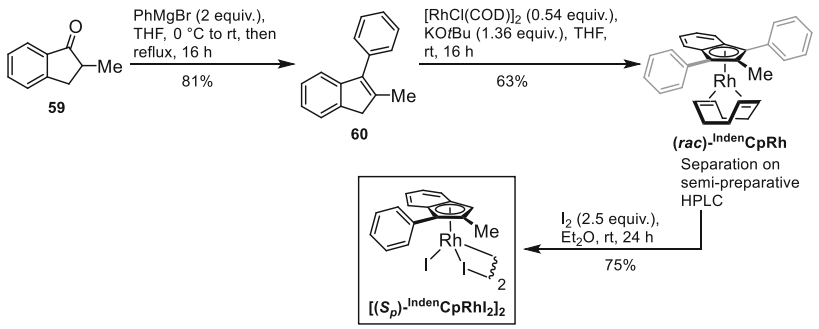


Scheme 42 Stepwise construction of a chiral Cp ring and isolation of planar-chiral rhodium complexes



Scheme 43 Asymmetric synthesis of chiral biaryls by naphthyl ring construction using alkynes

Precatalysts of the type **[(S_p)-$^{1,2,4\text{-sub}}$CpRh-1I_2]$_2$** have been investigated in two asymmetric C-H activation reactions. Beside the benchmark reaction of *O*-Boc aryl hydroxamate with olefins, which was accomplished with up to 96% yield and 89% *ee* selectivity, a second reaction, the reaction of *N*-phenyloxindole with diphenylacetylene for the assembly of C-N axially chiral *N*-aryloxindoles, has been investigated. The latter transformation includes a double C-H activation and addition of two alkynes to the aromatic benzene ring, leading to highly substituted naphthyl groups, allowing to introduce axial chirality (Scheme 43). The yield and selectivities observed are mostly very good to excellent under rather mild reaction conditions. 2,2-Dimethylbutyric acid (DMBA) and stoichiometric amounts of silver oxide are required, however, for this unusual transformation to proceed.



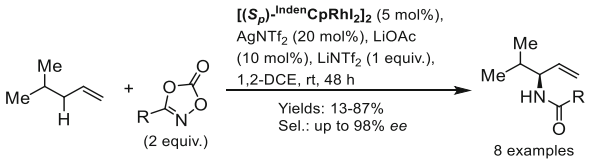
Scheme 44 Synthesis of chiral indenyl-rhodium complexes from substituted indan-1-one

Interestingly, the reactions turned out to be very sensitive to the steric environment provided by the chiral Cp ring and showed opposing trends on the reaction performance in dependence from the bulkiness of sterically demanding groups on the quaternary carbon center attached to the Cp ring.

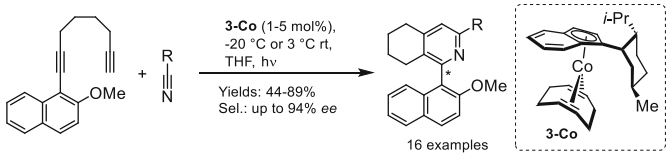
Only single examples of comparable catalyst systems based on the indenyl ligand have been reported. An 1-indenyl-1-naphthyl biaryl system with a tethering sulfide group for coordination to the rhodium atom was investigated for allylic substitution with the dimethyl malonate anion, mediated by π-allyl complex in the coordination sphere of the rhodium center [111–113]. Selectivities of up to 66–68% *ee* were achieved and the substitution pattern of the indenyl ligand turned out to be crucial for the general feasibility of the reaction, whose stereo induction was interpreted as structural indenyl effect.

A different approach albeit with structurally somewhat comparable indenyl ligands was undertaken by the groups of Baik and Blakey [114]. They introduced electronic asymmetry in the catalyst structure to control the asymmetric transformation. The methodology relies on a quite simple planar prochiral indenyl ligand **60**, which can be synthesized in a straight forward fashion (Scheme 44). Starting material is 2-methyl-indan-1-one (**59**), which upon reaction with phenylmagnesium bromide undergoes an addition/elimination sequence, leading to 2-methyl-3-phenyl-1*H*-indene (**60**). Metallation with $[RhCl(COD)]_2$ in the presence of base delivered the racemate of the corresponding rhodium complexes (***rac*)-^{Inden}CpRh**. The racemate can be quite conveniently separated by semi-preparative HPLC. Finally, oxidation of the enantiomers by iodine allowed the isolation of the enantiomerically pure dimeric complex **[(*S*$_p$)-^{Inden}CpRhI$_2$]$_2$**.

The dinuclear complexes were used in allylic C-H amidation reactions using dioxazolone compounds as amination reagents (Scheme 45). The reactions are running at mild conditions, however, requiring certain additives to proceed. The chiral induction is in general excellent in these reactions, providing evidence that even structurally simple unsymmetrical indenyl ligands can be useful for asymmetric catalysis. The reaction also accepts a variety of different residues in the allyl substrate, while still proceeding with high enantioselectivities.



Scheme 45 Application of **[(S$_p$)-^{Inden}CpRhI$_2$]$_2$**.as catalyst for C-H amidation

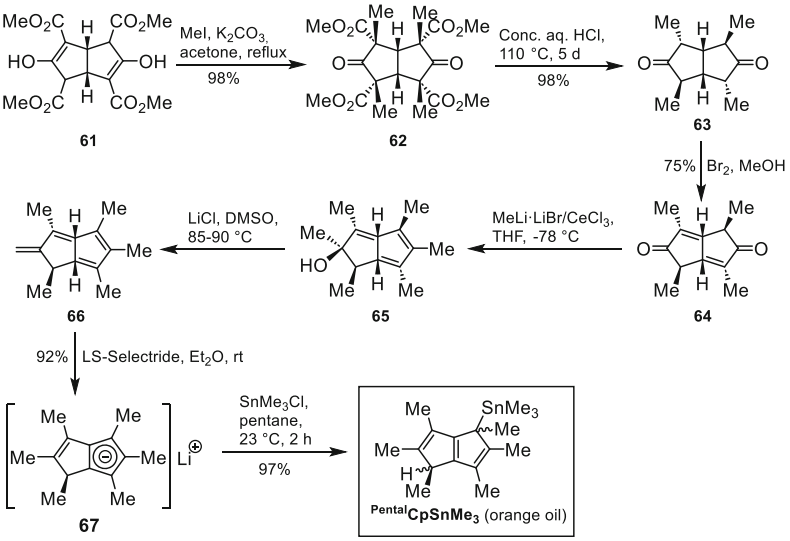


Scheme 46 Asymmetric [2+2+2] cycloaddition using catalyst **3-Co**

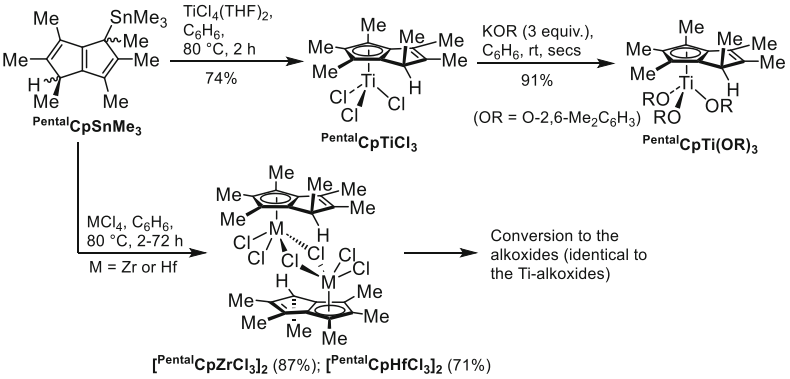
4.3 Chiral Indenyl or Related Catalysts

There are only few examples of unsymmetrical indenyl ligands that have been utilized for catalytic purposes. An example from our group has been described in Scheme 1c for a chiral cobalt complex, that formed a mixture of stereoisomers upon complexation, in the favor of one of the diastereomers with a ratio of 6.8:1. The complex has been utilized in asymmetric [2 + 2 + 2] cycloaddition reactions of diynes and nitriles to furnish substituted 1-naphthyl tetrahydroisoquinoline compounds (Scheme 46) [16, 17]. As a peculiarity this transformation has been executed at low reaction temperatures and irradiation with visible light to furnish optimal enantioselectivity. Conversion into a thermal variant by exchanging the COD ligand for phosphites led to precatalysts, which do not allow achieving high enantioselectivities as at least 50 °C reaction temperature is required to perform the reaction [14]. A later example demonstrated that substituted five-membered ring systems in the backbone of the formed biaryl are sufficient to obtain significant enantioselectivity [115]. Attempts to use the catalyst **3-Co** in the synthesis of helicenes unfortunately only gave low selectivities albeit excellent yields [116].

Another example is the use of a chiral (hydro)permethylpentalenyl ligand in complexes of group 4 metals (titanium, zirconium, and hafnium) for the polymerization of lactide dimers. In this investigation by the group of O'Hare enantiomerically pure and racemic complexes were prepared and screened toward their activity in the ring-opening polymerization of *L*- and *rac*-lactide [117]. The synthesis is presented in Scheme 47 and was starting out from compound **61**, subjected to a series of steps comprising methylation, decarboxylation, and elimination, finally yielding the ligand precursor **66** as a quite sensitive compound [118]. Lithiation with LS-selectride furnished the Li salt **67**, which was then reacted with trimethylchlorostannane, furnishing the stannylated compound ^{Pental}**CpSnMe$_3$**, the actually used ligand transfer reagent.



Scheme 47 Synthetic pathway toward the assembly of metallated ligand $^{\text{Pental}}\mathbf{CpSnMe_3}$



Scheme 48 Synthesis of Group 4 metal complexes with ligand precursor $^{\text{Pental}}\mathbf{CpSnMe_3}$

The ligand transfer reagent is theoretically present in four different diastereomers, however the ^{1}H NMR showed a 50:50 mixture. Nevertheless, it can be assumed that all isomers are present in the mixture. The complexation with titanium as group 4 metal and subsequent exchange of the halide for alkoxide ligands is presented as a showcase for this chemistry (Scheme 48) [116]. In the case of titanium the reaction of $^{\text{Pental}}\mathbf{CpSnMe_3}$ with $TiCl_4(THF)_2$ leads to a monomeric titanium complex $^{\text{Pental}}\mathbf{CpTiCl_3}$, which can then get converted to the alkoxides $^{\text{Pental}}\mathbf{CpTi(OR)_3}$ by simple reaction with the corresponding potassium alkoxides in benzene at room

temperature with excellent yield. In this permethylated system, upon complexation, the methyl group of the stereogenic center at C1 is anti to the metal center, most likely due to the steric hindrance associated with the methyl groups in the plane of the (hydro)permethylpentalenyl ligand. Intriguingly, this is enough steric direction to obtain only one single diastereomer upon complexation, which would also be possible from the other side of the planar Cp moiety. In the case of zirconium and hafnium, the reaction with the metal tetrachlorides delivered the dimeric, chloro-bridged compounds ($[^{Pental}CpMCl_3]_2$, **M = Zr, Hf**) due to the larger metal centers ability to coordinate to the sufficiently Lewis-basic chloride of a second complex. Reaction with the alkoxides, however, delivered the corresponding monomeric complexes in the same fashion as with the titanium complexes with in general very good yields.

The synthesized compounds were utilized afterward in the polymerization of lactide monomers under different conditions and with different alkoxide groups.

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Planar Chiral Ferrocenes: A Concise Introduction

Petr Štěpnička

Abstract Due to its intrinsic beauty and unique properties, bis(η^5-cyclopentadienyl) iron or ferrocene continues to attract the attention of chemists even after seven decades from its discovery. One of the particularly attractive and active fields is the preparation of planar-chiral ferrocene derivatives, which found manifold use as auxiliary ligands in enantioselective transition metal catalysis and organocatalysis. This chapter briefly illustrates the historical context and recent trends in this area, paying particular attention to the development of synthetic routes leading to planar-chiral ferrocenes.

Keywords C-H activation · Directed metalation · Ferrocene · Planar chirality · Synthesis

Abbreviations

Ac	Acetyl
Ar	Aryl
Boc	*tert*-butyloxycarbonyl
BPPFA	2-[1-(Dimethylamino)ethyl]-1,1′-bis(diphenylphosphino)ferrocene
DMAP	4-(Dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
Fc	Ferrocenyl
H-L-Val-OH	L-valine

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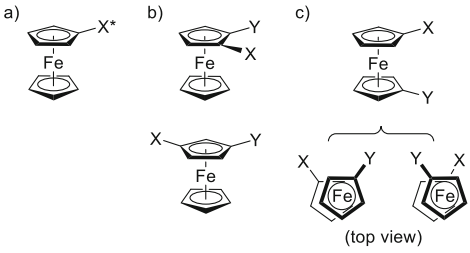
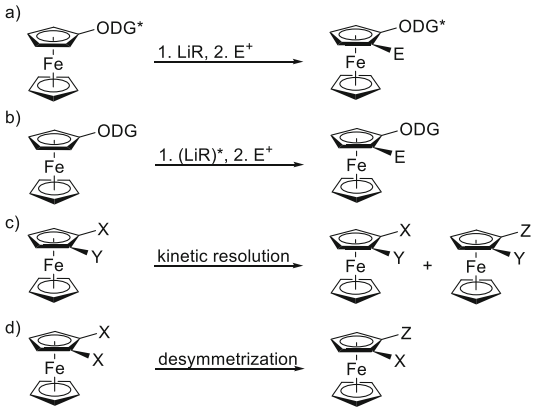
HPLC	High-performance liquid chromatography
n-BuLi	*n*-butyllithium
ODG	*Ortho*-directing group
Ph	Phenyl
PPFA	2-[1-(Dimethylamino)ethyl]-1-(diphenylphosphino)ferrocene
R	An unspecified hydrocarbyl substituent
t-Bu	*tert*-butyl
TMEDA	*N,N,N′,N′*-tetramethyl-1,2-diaminoethane

Cyclopentadienide anions have been widely applied as versatile auxiliary ligands for transition metals [1]. The first compound featuring π-coordinated $C_5H_5^-$ anion, bis(η^5-cyclopentadienyl)iron or ferrocene, [Fe(η^5-C_5H_2)$_2$] (**1**), was discovered and structurally characterized in the early 1950s [2]. Since then the chemistry of cyclopentadienyl complexes rapidly developed, resulting in a vast family of structurally diverse and widely practically utilized compounds [3–7]. When it comes to chiral metallocene derivatives, however, compounds derived from the exceptionally stable ferrocene, which is the archetypal representative of cyclopentadienyl metal complexes, still dominate due to their applications in catalysis. This chapter, which was partly adapted from Ref. [2] with permission from the Royal Society of Chemistry, attempts to briefly illustrate the chemistry of chiral ferrocenes, mainly focusing on the synthetic routes leading to these compounds. Given the enormous number of chiral ferrocene derivatives synthesized to date and their manifold applications, this chapter cannot adequately cover all aspects. Therefore, the reader is referred to review articles and books cited here that summarize the chemistry of chiral ferrocene compounds in more detail [3–21].

Generally, there are three types of chirality encountered in ferrocene derivatives: central, planar, and helical (Scheme 1). While central chirality is usually associated with the substituent(s) appended to the ferrocene core, the other two chirality types reflect the specific steric properties of the ferrocene unit. Generally, planar chirality in cyclopentadienyl complexes is enabled by the coordination of a metal center, formally [$(C_5H_5)Fe^+$–$C_5H_5^-$] for ferrocene, which differentiates the two enantiotopic faces of the planar and aromatic cyclopentadienide anion. In contrast, helical chirality results from blocking the rotation of the parallel cyclopentadienyl rings along the molecular axis in heteroannularly substituted ferrocene derivatives,



Scheme 1 Representative types of ferrocenes with (**a**) central, (**b**) planar, and (**c**) axial chirality (X, Y = various substituents; additional substituents can be present at the unsubstituted cyclopentadienyl ring)

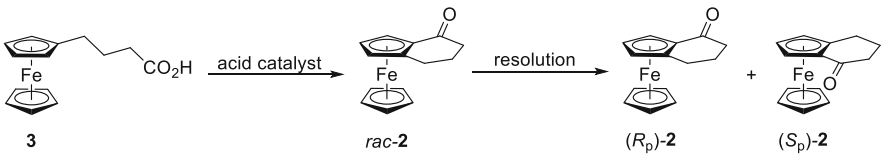


Scheme 2 Synthesis of planar-chiral ferrocenes: (**a**) diastereoselective lithiation/functionalization of ferrocenes with chiral ortho-directing groups (ODG*), (**b**) diastereoselective lithiation/functionalization of ferrocenes with ortho-directing groups (ODG) and chiral bases, (**c**) kinetic resolution of racemic ferrocenes, and (**d**) desymmetrization of achiral ferrocenes (X, Y, Z = various substituents, E^+ = electrophile). Routes (**a**) and (**b**) were equally well applied for the synthesis of planar-chiral ferrocenes through the C−H bond activation/functionalization sequence

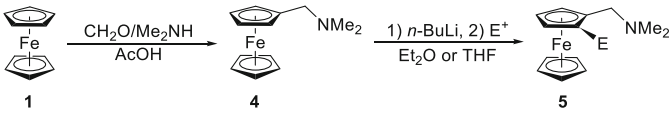
either in the solid state or by bridging the cyclopentadienyl rings (such as in ferrocenophanes).

There are several main routes toward chiral ferrocenes that differ depending on the type of chirality introduced (Scheme 2). Ferrocene derivatives with central chirality are synthesized in conventional manner by attaching or generating a chiral center in a molecule containing the ferrocene moiety. In contrast, planar chiral derivatives are typically obtained by diastereoselective methods when a suitable functional group at the ferrocene unit is used to direct further functionalization to the adjacent position at the ferrocene core (usually position 2 and rarely position 3). Without any chiral "influence," this functionalization expectedly gives rise to a racemic mixture of planar chiral products. In contrast, reactions performed with a chiral directing group or a chiral reagent can produce mixtures enriched with one of the two stereoisomers. These reactions often employ the lithiation/electrophilic quenching approach, using either a chiral ferrocene derivative and common organolithium compound or, alternatively, a simple ferrocene derivative and a chiral metalating agent during the metalation step. More recently, this approach was extended toward C−H bond activation reactions at the ferrocene moiety. Methods relying on kinetic resolution and desymmetrization of suitable ferrocene derivatives remain less widely explored and practically utilized [22, 23].

Initial attempts at preparing planar-chiral ferrocenes were based on the conventional synthetic approaches developed for organic compounds [24, 25]. These methods typically afforded racemic mixtures of enantiomers, which were resolved either via diastereoisomeric derivatives or, less commonly, by chromatography over chiral stationary phases [26]. The first planar chiral ferrocene derivative resolved into (R_p)- and (S_p)-enantiomers was 1,2-(α-ketotetramethylene)ferrocene (**2**), which is



Scheme 3 Synthesis of **2**



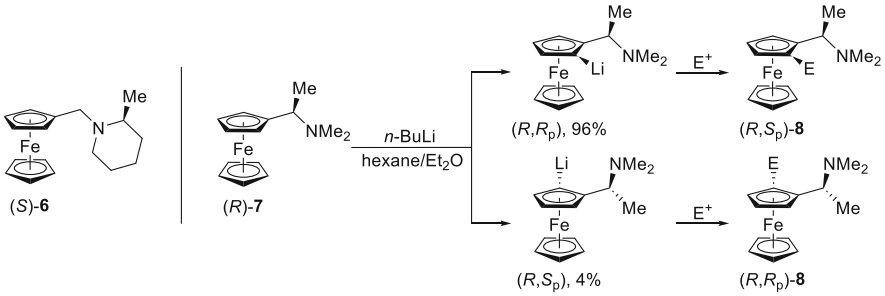
Scheme 4 Synthesis and lithiation of [(dimethylamino)methyl]ferrocene (**4**)

accessible (in racemic form) by acid-catalyzed intramolecular acylation from 4-ferrocenylbutanoic acid (**3**) [27]. This compound was resolved via diastereomeric hydrazones obtained from (−)-menthylhydrazine [28], and the absolute configuration of the (+)-isomer was established using chemical methods (Scheme 3) [29].

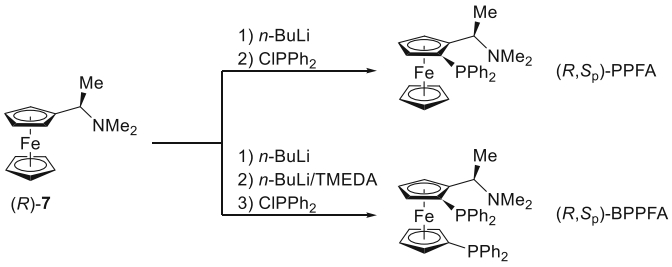
Later on, the development of synthetic routes toward planar chiral ferrocenes became intimately associated with the design, synthesis, and applications of chiral ferrocene ligands, mostly phosphines, in homogeneous transition metal catalysis. These compounds are usually obtained by diastereoselective functionalization of chiral starting materials and, hence, combine central chirality with chirality at the cyclopentadienyl plane. Compounds featuring only planar chirality remain less common.

Access to such planar chiral ferrocenes was opened in 1965 through the research of Hauser and coworkers [30], showing that initial lithiation of [(dimethylamino)-methyl]ferrocene (**4**) [31, 32] with *n*-butyllithium *n*-BuLi occurs preferentially in position 2 of the ferrocene unit and that an excess of *n*-BuLi is needed to achieve lithiation at the unsubstituted cyclopentadienyl ring (Scheme 4). Soon afterwards, the concept of directed *ortho*-lithiation was extended into diastereoselective variants using chiral aminoferrocenes **6** [33, 34] and **7** [35] (Scheme 5). Of these compounds, *N*,*N*-dimethyl-1-ferrocenylethylamine, Ugi's amine (**7**), proved particularly useful for further synthesis because of its synthetic accessibility in optically pure form, high stereoselectivity of the lithiation reaction (*dr* = 96:4), and ability to undergo nucleophilic replacement of the NMe_2 group (S_N1-type substitution) that proceeds with the retention of configuration at the stereogenic carbon [36]. The latter property, a result of the exceptional stabilization of ferrocenylmethylium cations as plausible and even isolable intermediates [37], is preserved for 2-substituted derivatives and was observed for analogous compounds containing other easily leaving groups (e.g., NMe_3^+ and OAc instead of NMe_2 in the side chain), thus widening the scope of accessible compounds.

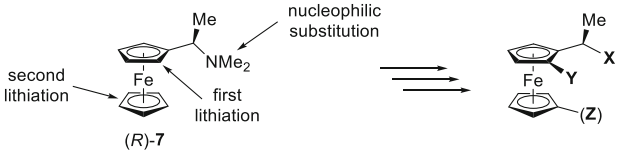
Already in the 1970s, Kumada and coworkers utilized lithiation of Ugi's amine to prepare chiral ferrocene P,N-donors, (R,S_p)-PPFA and (R,S_p)-BPPFA (Scheme 6)



Scheme 5 The structure of (*S*)-**6** and diastereoselective lithiation of Ugi's amine (*R*)-**7** producing planar chiral substitution products **8**. The change in the stereochemical descriptors reflects the changed priority of the substituents according to the Cahn-Ingold-Prelog rules (E > Li)



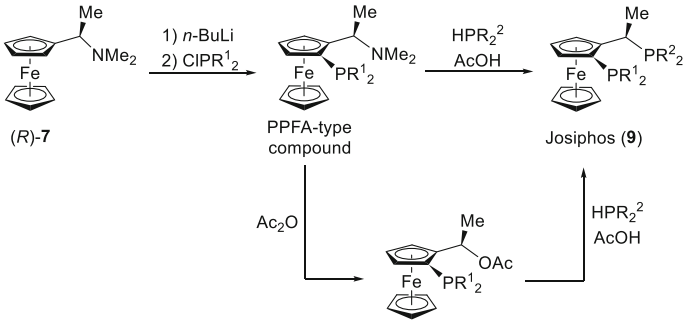
Scheme 6 Synthesis of PPFA and BPPFA from Ugi's amine. The synthesis of BPPFA can be performed in a stepwise manner, which allows the introduction of two different phosphine groups



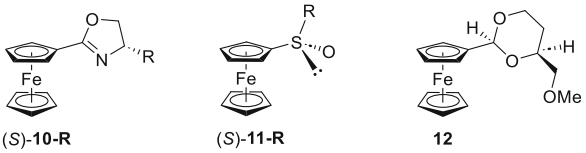
Scheme 7 Schematic depictions of the synthetic transformations of Ugi's amine that affords chiral ferrocene derivatives (X, Y, and Z are various functional groups)

[38], which were evaluated as efficient chiral supporting ligands in asymmetric alkene hydrogenation [39, 40] and ketone hydrosilylation [38] over chiral rhodium catalysts and in alkene hydrosilylation [41] and Kumada cross-coupling using palladium catalysts [42, 43]. The family of chiral phosphinoferrocene ligands (Scheme 7) was further widened via stereoconservative nucleophilic replacement of the NMe_2 group that resulted in a range of multi-donor (usually hybrid [44]) derivatives combining phosphine and other ligating groups (N-, P-, S-, O-donors, etc.) [45], which were also applied in transition metal-mediated asymmetric organic transformations [46].

In particular, replacing the NMe_2 group in PPFA-type compounds with another phosphine moiety produced chiral diphosphines from the Josiphos family



Scheme 8 Synthesis of Josiphos ligands

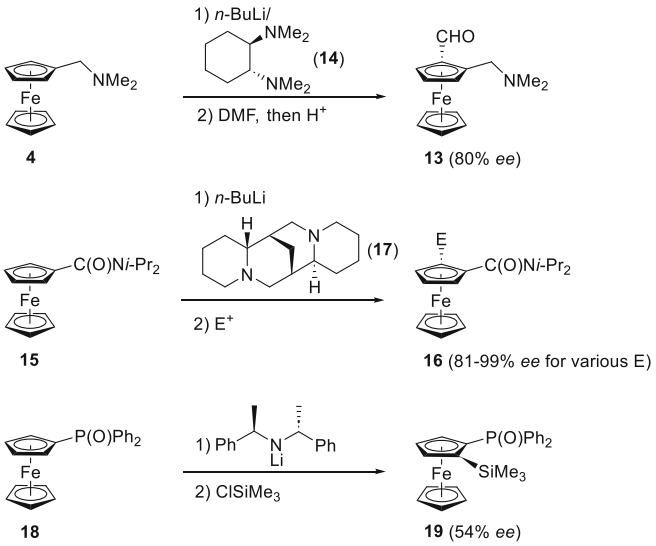


Scheme 9 Examples of chiral ferrocenes used in diastereoselective *ortho*-lithiation reactions (Note: the synthesis of **10-R** and **12** makes use of common chiral pool: while compounds **10-R** are prepared from β-amino alcohols accessible from α-amino acids, (*S*)-1,2,4-butanetriol required for the synthesis of **12** is obtained by reduction of L-malic acid)

(compounds **9** in Scheme 8) [47]. The possibility of independently altering the chirality at the cyclopentadienyl plane and in the side chain as well as the phosphine substituents (R^1 and R^2) in these ligands enabled their tuning according to the particular use, which consequently opened ways to their massive applications in transition-metal catalysis in laboratory and even industry scale [48, 49] and also stimulated the synthesis of numerous, structurally related P,N- and P,P-ligands with varied spacer and donor groups [3–21].

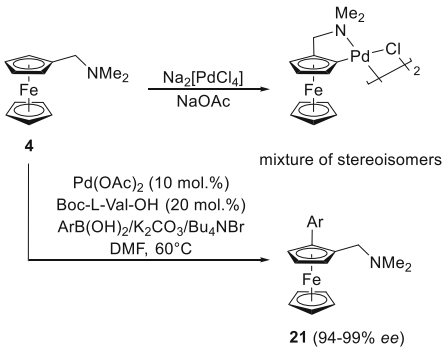
The high efficiency and robustness of the synthetic methods based on diastereoselective *ortho*-lithiation/functionalization of chiral ferrocene amines obviously initiated a search for other applicable chiral directing groups [50]. Among the approaches developed to date, C-chiral ferrocene oxazolines **10-R** [51–53], S-chiral sulfoxides **11-R** [54, 55], and acetal **12** [56, 57] (Scheme 9) proved particularly attractive because they are practical in terms of accessibility and subsequent transformation, produce valuable synthetic intermediates, or even provide a direct access to new ligands (viz., chiral ferrocene oxazolines [51–53, 58, 59]).

As mentioned above, complementary synthetic approaches (Scheme 10) toward planar chiral ferrocenes were developed based on the metalation of prochiral substrates bearing suitable directing groups such as amine **4** [60], tertiary amide **15** [61–64], and phosphine oxide **18** [65, 66] using adducts generated from organolithium compounds and chiral amines (e.g., (1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine (**14**) and (−)-sparteine (**17**)) and chiral amides such as (*R*,*R*)-lithium bis(1-phenylethyl)amide (see the last entry in Scheme 10; 95% yield, *ee* 54%).



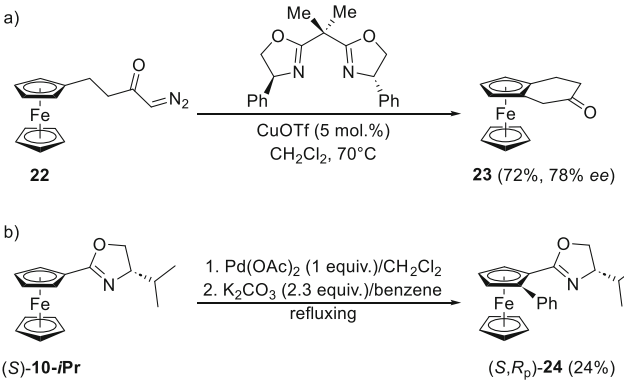
Scheme 10 Directed *ortho*-lithiation of ferrocenes with chiral bases

Scheme 11 Conventional ortho-palladation of amine **4** and the asymmetric variant of this reaction proceeding with concomitant C−C bond formation

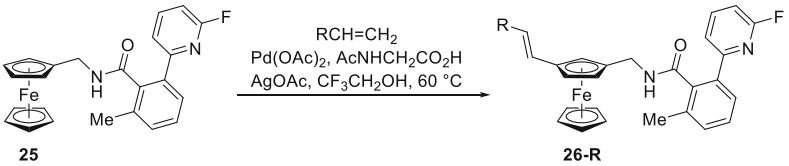


Recently, mixed Li-Zn and Li-Cd amides resulting from bis(1-phenylethyl)amine and analogs, where one 1-phenylethyl substituent was replaced for a terpene residue, were successfully applied in directed lithiation of alkyl ferrocene carboxylates $FcCO_2R$ (Fc = ferrocenyl). The best results (*ee*'s up to 71%) were obtained when $LiNR_2$ and ZnR_2 were combined (E = CH(Me)Ph) [67].

Chiral directing groups or chiral transition metal catalysts were also used to accomplish enantioselective C−H bond activation at the ferrocene moiety [68]. In the 1970s, Sokolov et al. demonstrated that orthopalladation of Ugi's amine produced two diastereoisomeric palladium complexes, analogous to **20** (Scheme 11, top), in an 85:15 ratio [69] and that palladation of achiral amine **4** [70] can be achieved in an asymmetric manner when using *N*-acetyl-L-valine/NaOH as a stoichiometric additive [71, 72]. Several decades later, asymmetric C−H activation of **4** with concomitant C−C bond formation was achieved with the composite



Scheme 12 Asymmetric C−H functionalization of ferrocene derivatives



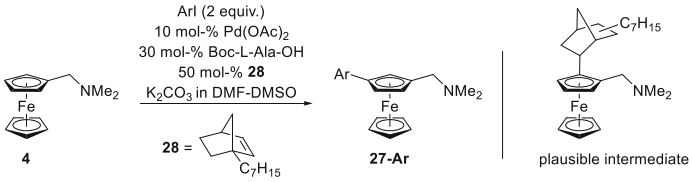
Scheme 13 Catalytic alkenylation of amide **25**

Pd-catalyst and boronic acid to give aryl-substituted compounds **21** (Scheme 11) [73].

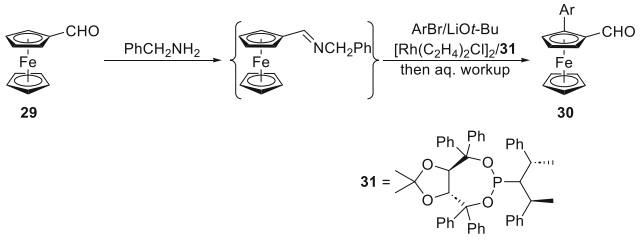
In 1997, Siegel and Schmalz reported that insertion of a carbene in situ-generated from diazo compound **22** in the presence of a chiral copper catalyst produces planar-chiral ketone **23** with a good yield and *ee* (72% and 78%, respectively; see Scheme 12a) [74]. An intermolecular arylation based on C−H activation/C−C bond formation was observed when reacting chiral oxazoline (*S*)-**10-*i*Pr** with benzene in the presence of a palladium catalyst and a base. This reaction produced compound **24** as single diastereoisomer in 24% yield (Scheme 12b). Minor amounts of the doubly arylated product (2,5-isomer) were also detected [75].

During the subsequent research, the array of the directing groups suitable for efficient catalytic C−H bond functionalization reactions of ferrocenes proceeding under the formation of new C−C bonds in enantioselective manner was markedly expanded, e.g., towards ferrocene N-heterocycles, amides, thioamides, azines, and acyl derivatives and even the palette of the tandem reactions was considerably widened [68, 76–84]. As an illustrative example can serve the recently disclosed C−H activation/alkenylation of ferrocene amide **25** containing an extended, pyridine-based directing group. This reaction occurs in position 3 of the ferrocene core and thus offers an alternative access to the difficult-to-prepare 1,3-disubstituted ferrocenes in racemic form [85, 86] (Scheme 13).

An alternative approach to 1,3-disubstituted ferrocenes **27-Ar** has been developed based on remote arylation of amine **4** utilizing a $Pd(OAc)_2$/Boc-L-Val-OH



Scheme 14 Remote, palladium-catalyzed arylation of amine **4**

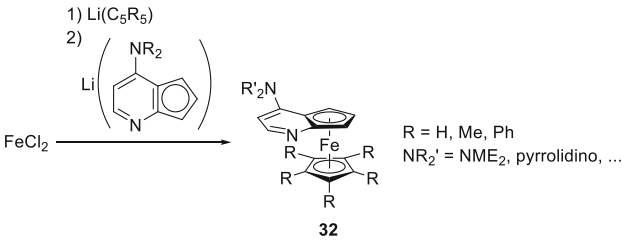


Scheme 15 Asymmetric Rh-catalyzed C−H bond arylation of ferrocene aldehydes

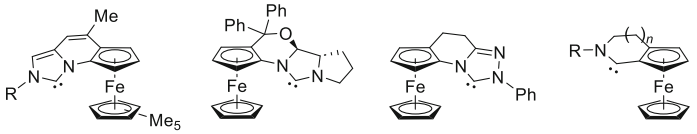
catalyst and a norbornene derivative (racemic), which serves as a temporary blocking group (in position adjacent to the amine substituent) and a mediator in the subsequent functionalization at position 3 of the ferrocene core (Scheme 14). The scope of compounds accessible by this method is very wide because many substituents are tolerated at the aryl halide and the products retain the reactivity of the parent amine (including ortho-functionalization).

In a recent paper, You and coworkers reported on asymmetric, Rh-catalyzed arylation of imine generated in situ from ferrocene carboxaldehyde (**29**) and benzylamine (Scheme 15), which produces (after hydrolysis) 2-arylated ferrocene carboxaldehydes **30-Ar** with up to 83% yield and >99% *ee* under optimized conditions (10 mol-% Rh and 20 mol-% of chiral phosphoramidite ligand **31** at 80°C). This method tolerates various substituents at the aryl bromide (alkyl, OMe, NMe_2, SMe, halide, ester, or heterocycle) and on the unsubstituted C_5H_5 ring of the starting aldehyde (e.g., alkyl, vinyl, aryl) and thus offers an efficient complementary alternative to synthetic routes employing chiral acetal **12**.

Planar chirality is also encountered in suitably annellated ferrocenes [87] (see compound **2** mentioned above). Further examples of such compounds include planar chiral analogs of 3-(dimethylamino)pyridine (DMAP), compounds **32**, which were extensively studied as organocatalysts [87–90]. Initially, these compounds were obtained by sequential addition of cyclopentadienide reagents to $FeCl_2$ (Scheme 16), and the product mixture was separated using chemical methods (via diastereoisomers) or chiral HPLC. Later on, convergent asymmetric routes to these compounds were devised, employing chiral acetal **12** and the analogous compound permethylated at the other cyclopentadienyl ring as the starting materials [91, 92]. Further attractive examples of chiral annellated ferrocenes include chiral ferrocene-based carbene ligands [93–95] represented by compounds **33**–**37** (Scheme



Scheme 16 Synthesis of ferrocene-fused DMAP analogs **32**



Scheme 17 Examples of planar-chiral ferrocene carbene ligands (only the carbene structure is shown even when the free carbene was not isolated but trapped as a ligand; R is usually a sterically demanding and/or aromatic substituent such as isopropyl, phenyl, or mesityl)

17). The synthesis of **33** involved the preparation of a racemic annellated precursor and its resolution into enantiomers. The free carbene was isolated and utilized as both an organocatalyst and an auxiliary ligand in transition metal-mediated reactions [96, 97]. Conversely, carbene **34** was prepared by diastereoselective functionalization of a chiral ferrocene precursor and was isolated in the form of an Ir(I) complex, subsequently tested in Ir-catalyzed quinoline hydrogenation (free carbene was not isolated) [98]. In a similar vein, the planar chiral carbene **35** was obtained in several steps from acetal **12** and isolated in the form of a CuCl complex [99]. The same starting material was used to prepare the homologous compounds **36** and **37**, which were evaluated as ligands in Ir-catalyzed asymmetric transfer hydrogenation and in Cu-catalyzed borylation of *tert*-butyl cinnamate [100–103].

Although far from exhaustive, this overview of the routes leading to planar chiral ferrocene derivatives illustrates the rapid and extensive developments in the area of planar chiral ferrocenes during the approximately seven decades, which passed since the discovery of the parent compound. These developments, which changed chiral ferrocenes from mere laboratory curiosities to useful molecules are driven by wide and rapidly emerging applications of these compounds in fields as diverse as molecular synthesis, catalysis, material science, and bioorganometallic chemistry [104–106]. Even though the currently available synthetic methods offer reliable access to a wide array of ferrocene derivatives, despite revolving around relatively few synthetic principles, further research is still highly desirable as it may result in alternative and possibly more efficient (in terms of both the yield and stereoselectivity) and atom economical processes. These should further widen the scope of accessible compounds and also mitigate problems with subsequent

manipulation of the auxiliary substituents. In this view, approaches based on the functionalization of ferrocene C−H bonds appear particularly attractive. In turn, this research can open further application fields and enable wider applications of chiral ferrocenes in transition metal catalysis as well as in organocatalysis.

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Knölker-Type Catalysts for (Asymmetric) Hydrogenation Reactions

Christoph Topf

Contents

Abstract The catalytic capabilities of Knölker-type complexes, mostly in the context of (transfer) hydrogenation chemistry, have been intensively studied during the past two decades. This happened mainly in response to the popular request for superseding catalysts that rely on scarce and expensive platinum group metals (PGMs). Indeed, the excellent abundance, very low price, and non-toxicity of Fe render these peculiar organoiron compounds ideal candidates for that purpose. The great structural malleability owing to their modular architecture further adds to the benefits of Knölker-complex-derived catalysts. Moreover, owing to their beneficial redox properties, these cyclopentadienone-tagged Fe complexes are also apt for usage in hydrogen autotransfer (hydrogen-borrowing) reactions. This fact opens up new vistas for atom-efficient and low-waste syntheses of a broad array of amines and more elaborated, pharmaceutically relevant heterocycles. However, the most important trait of Knölker-type complexes is their accessibility to chiral modification upon adjustment of the ligand framework which often encompasses the introduction of planar chirality or C2 symmetrical motifs. Furthermore, the pertinent Fe catalysts are amenable to pairing with enantiopure Brønsted acids such that dual catalysis becomes possible. Hence, promising approaches exist which might enable challenging and highly rewarding asymmetric (transfer) hydrogenation reactions that are effected by Fe complexes.

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Keywords Asymmetric catalysis · Chiral ligands · Cyclopentadienone · Hydrogenation · Organoiron compounds

Abbreviations

Ac	Acetyl
BINOL	1,1′-Bi-2-naphthol
Bn	Benzyl
t-Bu	Tertiary butyl
Bz	Benzoyl
Cp	Cyclopentadienyl
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
Et	Ethyl
equiv	Equivalent
EWG	Electron-withdrawing group
glyme	Dimethoxyethane
h	Hour
HA	Hydrogen autotransfer
HB	Hydrogen-borrowing
max	Maximum
Me	Methyl
Ms	Methanesulfonyl
2-Np	2-Naphthyl
OAc	Acetate
OMs	Mesylate
OTs	Tosylate
OTf	Triflate
PFA	Paraformaldehyde
PGMs	Platinum group metals
Ph	Phenyl
i-Pr	Isopropyl
T	Temperature
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	Triethylsilyl
TH	Transfer hydrogenation
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMAO	Trimethylamine *N*-oxide
TMS	Trimethylsilyl
(*S*)-TRIP	(*S*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diylhydrogenphosphate

Ts	Tosyl
UV	Ultraviolet
WGSR	Water gas shift reaction

1 Introduction

In general, Knölker-type hydrogenation catalysts **A** are 16-electron Fe(0) complexes that incorporate a redox-innocent, η^4-coordinated cyclopentadienone motif and two additional π-acidic ligands that can be used to modulate the electronic properties of the central atom. The Lewis basic carbonyl oxygen atom and the Lewis acidic vacancy at the Fe(0) center together constitute a frustrated Lewis pair (FLP) [1] in which, owing to geometric constraints, both entities have no possibility for formation of a dative or coordinate covalent bond between them. Thus, in order to compensate for this predicament, compounds **A** will engage in the heterolytic cleavage of the strong H-H bond if molecular hydrogen is present. This process results in the formation of the crucial half-sandwich Fe(II) hydride $\mathbf{AH_2}$ which actually brings about the reduction of the added substrate that is supposed to be hydrogenated (Fig. 1) [2].

Importantly, isopropanol, formic acid, and paraformaldehyde (PFA) are also capable of forming the pivotal $\mathbf{AH_2}$ intermediate and hence complexes of type **A** can also function as efficient transfer hydrogenation (TH) catalysts [3]. This, in turn, allows for the implementation of the hydrogen-borrowing (HB) concept into catalytic protocols that rely on the Knölker complex scaffold. Following this HB approach, the α-alkylation of ketones and the syntheses of *N*-heteroaromatics become feasible through iron catalysis [4, 5].

2 Historical Background

In the early 1950s Reppe and Vetter were the first to describe the unusual reactivity between Fe-based carbonyls and acetylene derivatives but the exact chemical composition of the obtained compounds remained elusive [6]. Shortly after their findings, several groups reported on the preparation of related compounds [7–10] but it

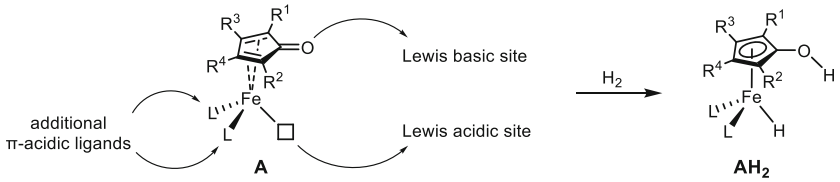
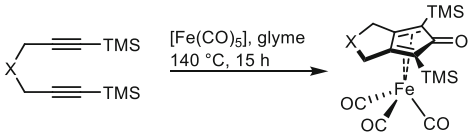


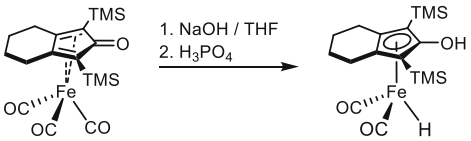
Fig. 1 General structure of an iron-based, Knölker-type catalyst **A** and its reaction with H_2 gas



	X	Yield [%]
1	CH_2	78
2	$(CH_2)_2$	82
3	$(CH_2)_3$	15
4	$(CH_3O_2C)_2C$	84
5	O	85
6	S	76
7	$C_6H_5CH_2N$	86

Scheme 1 [2 + 2 + 1] Cycloaddition of TMS-protected diynes and CO

Scheme 2 Classic synthesis of the original Knölker catalyst



Fe-1 **Fe-2**

was Schrauzer who first delivered an unambiguous proof of the molecular structure of these complexes that are composed of an Fe(0) tricarbonyl core to which a cyclopentadienone fragment is bound and firmly held by π interactions [11].

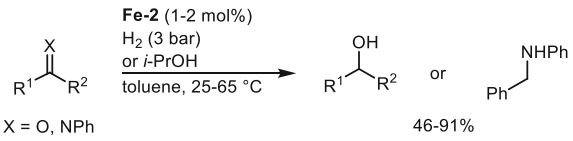
In the 1990s, after having languished in the background for decades, the chemical behavior of these peculiar Fe complexes was systematically studied, coincidently, by Pearson [12–16] and Knölker [17–19]. The latter reported on a convenient method for the syntheses of a series of cyclopentadienone-tagged Fe complexes (Scheme 1) that later ignited a major wave of research into (transfer) hydrogenation catalysis [20].

Finally, the research activities of the Knölker group culminated in a seminal publication that deals with the synthesis and characterization of a very interesting organoiron-based hydride complex [21]. In a reaction that is reminiscent of the classic Hieber base reaction [22], the tagged Fe(0) tricarbonyl **Fe-1** was first treated with NaOH in THF whereupon quenching with phosphoric acid afforded the organometallic hydride **Fe-2** (Scheme 2). Yet, the enormous catalytic potential of Knölker's hydride complex escaped attention of the experts for almost a decade.

3 Catalytic Applications of Knölker-Type Complexes

In continuation of their work with related Ru-based complexes, Casey and Guan discovered the ability of Knölker's hydride **Fe-2** to catalyze the (transfer) hydrogenation of polar double bonds whereby either H_2 gas or *i*-PrOH can be used as reductants (Scheme 3) [23, 24]. Under mild reaction conditions, they were able to convert ketones, aldehydes, and one imine into the desired products. Importantly, the

Scheme 3 Casey's seminal (transfer) hydrogenation experiments



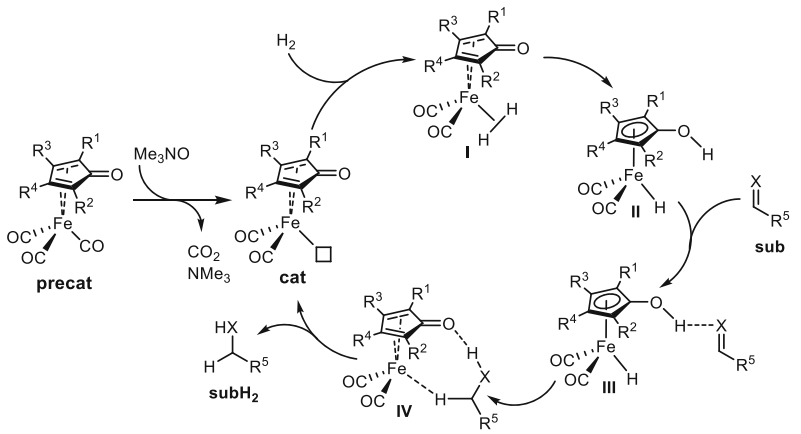
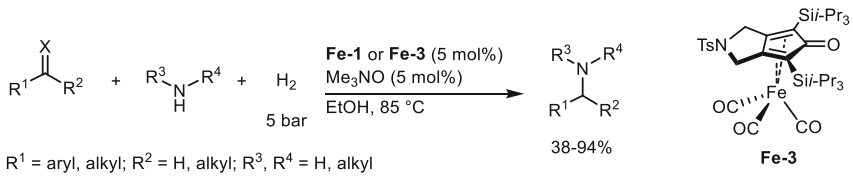


Fig. 2 Catalytic cycle for the hydrogenation of C = X bonds effected by Knölker-type complexes

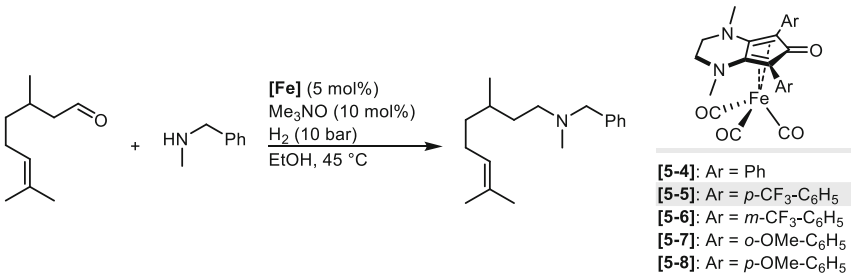
catalytic protocol was chemoselective in that alkynes, ester, epoxides, and non-conjugated double bonds remained intact.

Notably, while the original Knölker catalyst **Fe-2** is utterly sensitive to moisture and air, the precursor compound **Fe-1** is rather stable and much easier to handle. However, since all tagged Fe(0) tricarbonyl complexes comparable to **Fe-1** represent unreactive, 18-electron species they have to be activated in situ so as to provide a vacant coordination site for H_2 binding. The mandatory activation of the respective precatalysts is commonly achieved through selective mono-decoordination of a CO ligand upon addition of trimethylamine *N*-oxide (TMAO) which attacks the electrophilic carbonyl C atom by way of its negatively charged, nucleophilic oxygen atom. The resultant addition product is unstable and readily collapses to leave behind a 16-electron Fe(0) dicarbonyl species that possesses the requisite vacancy. As a further result of this CO-extrusion, CO_2 and NMe_3 are released into the reaction mixture [25]. In normal circumstances, carbon dioxide vanishes and does not further interfere with the overall hydrogenation process whereas trimethylamine is known to form non-productive resting states that lie outside the catalytic cycle (vide infra).

The generally accepted mechanism for the hydrogenation of polar C = X bonds (X = O, NR) catalyzed by Knölker-type complexes is outlined in Fig. 2 [26–29]. The catalytic cycle commences with the reaction of the 18-electron (and often air-stable) species **precat** and TMAO so as to free up a coordination site (□) at the Fe(0) central atom. The 16-electron intermediate thus generated (**cat**) further reacts with molecular hydrogen to form the σ-complex **I**. Consecutive heterolytic cleavage of the H–H bond affords the organometallic Fe(II) hydride **II** that now incorporates a



Scheme 4 Reductive amination of aldehydes and ketones facilitated by Knölker-type catalysts



Scheme 5 Efficient Fe-catalyzed reductive amination of citronellal

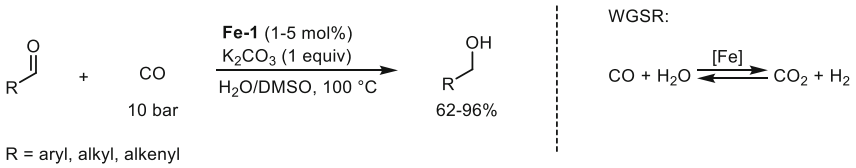
hydroxycyclopentadienide motif. Subsequently, the pendent OH group binds to the heteroatom of the incoming substrate (**sub**) to assemble the loose association **III** that consists of the Knölker-type hydride and **sub**. During the course of an outer sphere mechanism, a proton and a hydride are then transferred from the organoiron moiety to the pertinent X and the C atom, respectively. Finally, disintegration of the entity **IV** liberates the reduced product **subH$_2$** and restores the catalytically active species (**cat**) thus initiating a new iteration.

Interestingly, it has also been proposed that trimethylamine, which is the concomitant by-product of the initial CO dissociation reaction, combines with **cat** to form the corresponding NMe_3 complex which represents a labile, off-cycle resting state [30].

Noteworthy, an analogous cycle can be formulated for transfer hydrogenation processes that deploy proper surrogates for gaseous H_2 (vide supra).

Following up on the initial success of Casey's and Guan's work, Renaud and coworkers have invented a general catalytic method for the reductive amination of aldehydes and ketones that is either mediated by precatalyst **Fe-1** or a slightly modified version thereof, i.e., **Fe-3** which contains a heterocyclic moiety that renders the catalytically active species more active compared to the initial complex (Scheme 4) [31, 32].

Guided by computational chemistry, Solà, Renaud, and Poater quite recently succeeded in the development of a very active reductive amination catalyst that enabled the conversion of an equimolar mixture of citronellal and *N*-benzylmethylamine into the desired tertiary amine below 50°C (Scheme 5) [33]. In a previous theoretical study it was established that equipping the cyclopentadienone motif with electron-withdrawing groups (EWGs), preferentially



Scheme 6 Fe-catalyzed reduction of aldehydes using CO and water as co-solvent

trifluoromethyl substituents, is expected to translate into higher activity of the respective iron catalysts [34]. Yet, the preparation of such Knölker-type complexes that have the CF_3 groups directly attached next to the carbonyl group is not feasible. Thus, the authors proposed the inclusion of a phenyl spacer between the cyclopentadienone ring and the CF_3 substituent. Using this strategy, CF_3-tagged Fe complexes have indeed succumbed to isolation and the predicted, outstanding performance of a *p*-CF_3 derivative was then, strikingly, confirmed in the catalytic experiment.

Remarkably, the research group of Renaud further found that nitrogen-containing Knölker-type complexes such as **Fe-3** (Scheme 4) are also well suitable for the design of water-soluble, Fe-based precatalysts that enable the hydrogenation of ketones and imines in pure H_2O. In that respect, the authors found that placing quaternary ammonium groups at the periphery of the cyclopentadienone scaffold was key to achieve decent yields. Still, the addition of TMAO to the reaction solution was a prerequisite to guarantee catalytic activity [35].

Notwithstanding these achievements, Beller and coworkers were able to demonstrate that the non-modified Knölker precatalyst **Fe-1** is already compatible with aqueous solvents. Meticulous adjustment of the reaction conditions allowed them to perform the TMAO-free hydrogenation of ketones and aldehydes with low catalyst loadings (0.05–5 mol%) in a H_2O/*i*-PrOH mixture. However, the addition of low amounts of K_2CO_3 (0.5–5 mol%) was necessary in order to elicit the catalytic capability from precursor **Fe-1** [36].

The encouraging fact that the simple organoiron complex **Fe-1** is readily reconciled with the presence of significant amounts of water can be exploited for the coupling of two different catalytic transformations. It was again Beller and his team who showcased the usefulness of this concept. They managed to combine the industrially highly relevant water gas shift reaction (WGSR) with the reduction of aldehydes (Scheme 6) [37]. This approach allowed them to apply, as hydrogen donor, a mixture of CO and H_2O which is, in terms of ignitability, less harmful than pure H_2 gas.

The Knölker-type complexes that were hitherto presented suffer from the general drawback that all of them call for the addition of an activator, i.e., either TMAO or K_2CO_3 to develop their full catalytic ability. Yet, with regard to user-friendliness and economic considerations, the deployment of additive-free (transfer) hydrogenation systems is highly sought-after. Therefore, Funk and his team developed the (mono)-acetonitrile complex **Fe-9** which closely resembles the original Knölker precatalyst **Fe-1** [38]. Compound **Fe-9** functions as a catalyst on its own since it easily expels

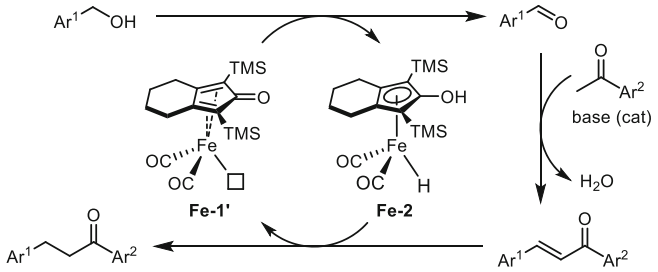
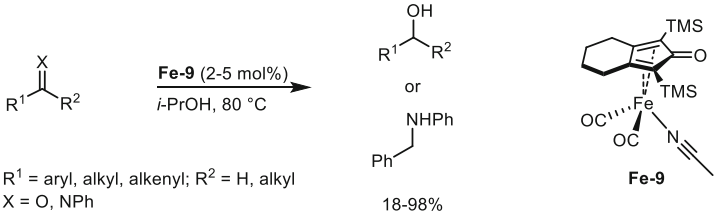


Fig. 3 Fe-catalyzed α-alkylation of ketones with alcohols



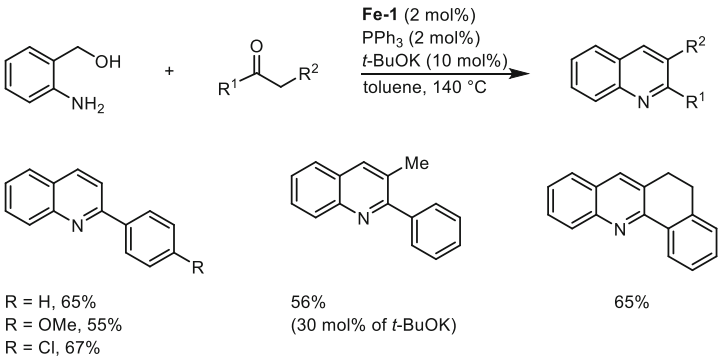
Scheme 7 Transfer hydrogenation of polar C = X bonds facilitated by a thermolabile Fe complex

the coordinated acetonitrile upon heating. This decoordination process generates the active species **Fe-1′** (Fig. 3) that readily reacts with *i*-PrOH to furnish Knölker's hydride **Fe-2** in situ. Hence, Funk's complex provides a very convenient way for the TH of polar double bonds as found in ketones, aldehydes, and imines (Scheme 7).

The fact that the pertinent Fe-catalyzed TH reactions are reversible [20] suggests to deploy Knölker-type complexes as mediators in organic transformations that make use of the hydrogen-borrowing (HB) or, synonymously, hydrogen autotransfer (HA) concept [39]. This, in turn, allows for the design of brisk and atom-efficient C-C coupling approaches. In this connection, Sortais and Darcel proposed a method for the syntheses of extended ketones by way of α-alkylation. Their protocol utilizes the classic Knölker complex **Fe-1**. The reaction sequence of this coupled redox process is delineated in Fig. 3 and starts with the oxidation of a primary alcohol to the corresponding aldehyde through catalyst **Fe-1′** that is concomitantly transformed into hydride **Fe-2**. Ensuing base-catalyzed aldol condensation between the latter and a ketone having an acidic C-H group affords an intermediate enone which is chemoselectively converted into the saturated congener by Knölker's hydride.

The catalytic transformation runs in toluene at 140°C and in the presence of precatalyst **Fe-1** (2 mol%), PPh_3 (2 mol%), and Cs_2CO_3 (10 mol%). Depending on the substitution pattern of the starting materials, the isolated yields of the products amounted to 19–72% [4].

Rewardingly, the same **Fe-1**/PPh_3 pair can also be used in a modified Friedländer quinoline synthesis (Scheme 8) [4]. In the original version of this reaction, 2-aminobenzaldehyde is combined with a variety of ketones to afford the respective



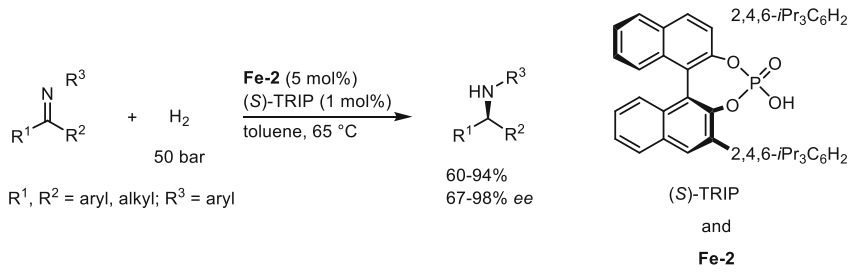
Scheme 8 Fe-catalyzed annulation reaction for the syntheses of quinolines

N-heterocyclic compounds [40]. However, detrimental formation of self-condensation products and the limited stability of the requisite aldehyde hamper, to some degree, the practicality of this method. Rewardingly, application of HB conditions with catalytic amounts of base and usage of fairly stable 2-aminobenzyl alcohol as starting material effectively remedy these issues [41–49].

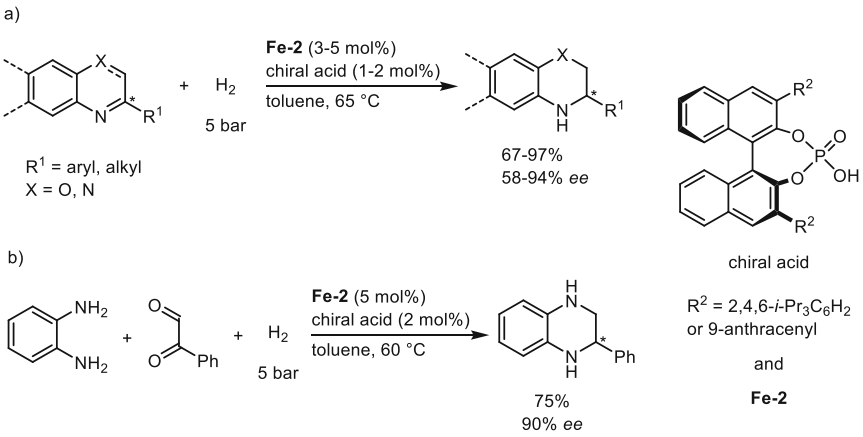
4 Asymmetric (Transfer) Hydrogenations

Given the great success related to the use of Knölker-type complexes in homogeneous redox transformations (vide supra), many research groups have embarked on studies toward the development of efficient asymmetric (transfer) hydrogenation protocols that rely on iron as the catalytically active metal [50–53]. One route to achieve chiral induction during the course of a reduction process that deploys gaseous H_2 as the principal reductant is by way of dual catalysis [54–56]. In this context, seminal work comes from Beller and coworkers who reported on the combined use of a chiral Brønsted acid, i.e., (S)-TRIP and the original Knölker complex **Fe-2** in the asymmetric hydrogenation of imines (Scheme 9) [57]. In this case, enantiopure (S)-TRIP reacts with the substrate imine to form an ion pair that provides a chiral environment for nucleophilic attack of the pertinent catalytically active organoiron hydride. This cooperative approach enables the syntheses of secondary amines with medium to excellent enantioselectivity (67–98% ee).

Interestingly, the implementation of Rh, Pd, or Ir complexes paired with BINOL-derived phosphoric acids in related protocols solely resulted in the formation of racemic mixtures of the targeted amines. This is due to the fact that the mentioned precious-metal-based complexes rather react with the free imine than with the protonated immonium cation that has a chiral phosphate anion in its immediate vicinity. Moreover, the highest *ee* value that was achieved with the Ru analog of the Knölker complex, i.e., Shvo's catalyst amounted to only 8%.



Scheme 9 Fe-mediated, asymmetric hydrogenation of imines effected by dual catalysis

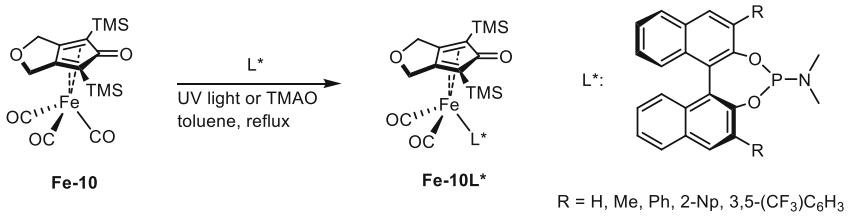


Scheme 10 Knölker-complex-assisted, enantioselective syntheses of benzannulated heterocycles

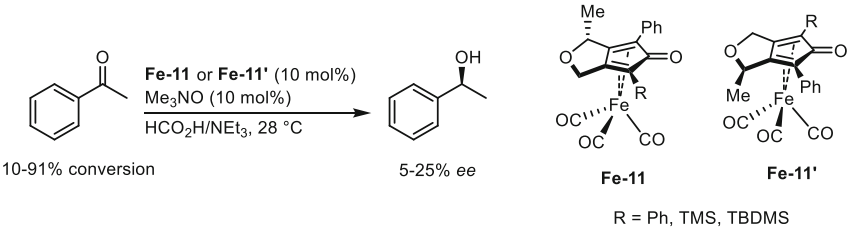
These results clearly highlight the profitable use of base metal complexes in catalysis research, even in challenging and demanding fields such as enantioselective synthesis.

The pioneering dual catalysis approach introduced by the Beller group was further extended to the preparation of chiral quinoxaline and 2H-1,4-benzoxazine derivatives (Scheme 10a) [58]. Here, unmodified (*S*)-TRIP or an anthracenyl-modified version thereof in combination with **Fe-2** gave rise to medium to excellent yields of the fused heterocycles (67–97%) with high *ee* values up to 94%. However, the asymmetric hydrogenation process is, to some degree, hampered by a background reaction that originates from the reduction of the non-protonated substrate heterocycle.

The same catalytic strategy was then applied to a one-pot synthesis of a phenyl-tagged 1,2,3,4-tetrahydroquinoxaline starting from *o*-phenylenediamine and phenylglyoxal (Scheme 10b). In this reaction, the desired product was obtained in good yield (75%) and with high enantioselectivity (90%). Notably, modification of the Knölker complex architecture did not translate into higher *ee* values and neither did the use of noble-metal-based precursors such as [{Ru(*p*-cymene)I_2}$_2$] or [{Rh



Scheme 11 Preparation of chiral Knölker-type complexes through dissociative CO substitution



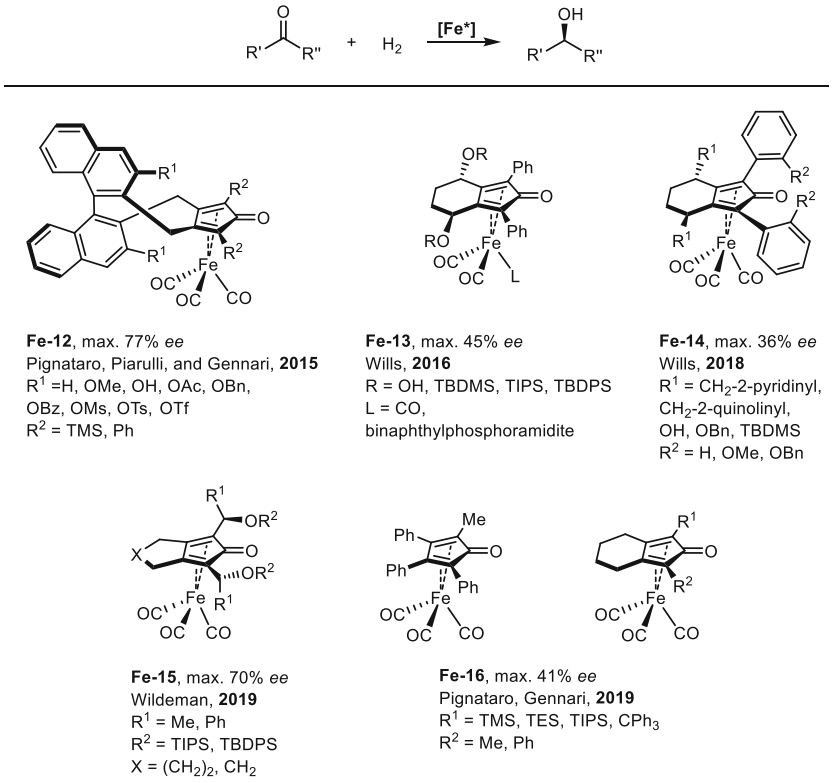
Scheme 12 Enantioselective TH of acetophenone as proposed by Wills

(COD)Cl}$_2$] increase the enantioselectivity (80% *ee*). Rather, the latter were clearly outnumbered by the base metal complex **Fe-2**. These results again emphasize the great utility of cheap and abundant iron in asymmetric hydrogenation catalysis.

A further strategy for the syntheses of enantioenriched products through iron catalysis involves the substitution of, at least, one coordinated CO in the respective tricarbonyl precursor for an optically pure ligand. In this regard, the group of Berkessel managed to prepare a series of chiral complexes upon reaction of the Knölker-type complex **Fe-10** with various BINOL-derived phosphoramidites **L*** (Scheme 11) [59]. The substitution reactions proceeded in refluxing toluene, either under photolytic conditions in the UV regime or, giving better results, by means of oxidative decarbonylation that deploys TMAO as CO-extruding reagent (vide supra). Yet, the obtained catalysts **Fe-10L*** were not self-contained but had to be activated with UV radiation in order to access the catalytic hydrogenation cycle (Fig. 2). Upon reduction of acetophenone and using this photoinduced, asymmetric hydrogenation protocol the authors finally obtained 1-phenylethanol featuring an *ee* of 31%.

Soon afterwards, Wills and coworkers succeeded in the syntheses of the diastereomeric, chiral complexes **Fe-11** and **Fe-11′** and tested them in the TH of acetophenone using a mixture of formic acid and triethylamine [60]. Yet, the obtained enantioselectivities were quite modest and the *ee* values did not exceed 25%, presumably due to the remote stereogenic center (Scheme 12). Notably, switching to noble Ru as catalytically active metal did not bring any improvement (21% *ee*).

Rewardingly, Pignataro, Piarulli, and Gennari could later show that further modification of the organic backbone through installation of a C2 symmetrical and



Scheme 13 Chiral Knölker-type precatalysts for asymmetric hydrogenation reactions

bulky BINOL-derived motif (**Fe-12**, Scheme 13) resulted in enhanced *ee* values (up to 77%) of alcohols that were obtained upon catalytic hydrogenation of ketones [61, 62]. Subsequently, Wills tested further C2 symmetrical fragments to achieve enhanced enantioselectivities but the corresponding precatalysts **Fe-13** and **Fe-14** were clearly outperformed by the BINOL-derived congener **Fe-12** (45% and 36% *ee*, respectively) [63, 64]. Wildeman then found that increasing the steric encumbrance about the cyclopentadienone carbonyl group is a proper means to ameliorate the *ee* values (70%, **Fe-15**) [65]. Finally, Pignataro and Gennari proposed the introduction of planar chirality (**Fe-16**) but this approach only led to mediocre enantioselectivities (up to 41%) [66].

To conclude, it has to be noted here that chiral cobalt cyclopentadienone-based complexes have also been described in the literature [67]. Furthermore, given its simple and flexible synthetic access [68], the cyclopentadienone motif itself functions as a versatile precursor to chiral cyclopentadienyl (Cp) ligands [69, 70]. These facts clearly show that organometallic complexes that incorporate cyclopentadienone or Cp moieties are promising candidates for the exploitation of

new reaction space, in particular with respect to enantioselective syntheses of complex molecules.

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Selective Transformations Mediated by Group 4 Metal Cyclopentadienyl Complexes

Jiří Pinkas and Martin Lamač

Contents

Abstract This chapter provides a brief overview of chemical transformations or syntheses mediated or catalysed by complexes of group 4 elements containing cyclopentadienyl and related ligands. Particular attention has been devoted to selectivity in a broad sense. While the text attempts to take a wider perspective, it focuses on selected recent trends and developments that fall approximately within the last decade (2013–2023). Covered topics comprise new approaches to the synthesis of chiral group 4 metallocenes, radical catalysis with Ti(III) species, photoredox catalysis with group 4 complexes, C–C bond formation and cleavage utilising low valent metallocenes, reactions involving hydro- and carbometallation steps, recent trends in polymerisation catalysis, and several other examples demonstrating the utility of early transition metals in organic synthesis.

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Keywords C–C bond forming · Chirality · Cp ligands · Group 4 metallocenes · Olefin polymerisation · Organic synthesis · Photocatalysis · Radical reactions · Titanium · Zirconium

Abbreviations

Bn	Benzyl
btmsa	Bis(trimethylsilylacetylene)
Bu	Butyl
Coll	Collidine, 2,4,6-trimethylpyridine
Cp	η^5-(Cyclopentadienyl)
Cp*	η^5-(Pentamethylcyclopentadienyl)
CSA	Camphorsulfonate
DFT	Density functional theory
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
dme	Dimethoxymethane
DMMS	Dimethoxymethylsilane
DPAA	Diphenyl acrylamide
dtbbpy	4,4′-Ditert-butyl-2,2′-bipyridine
ebi	η^5-{1,2-Ethylenebis(indenyl)}
ebthi	η^5-{1,2-Ethylenebis(4,5,6,7-tetrahydroindenyl)}
Et	Ethyl
HAT	Hydrogen-atom transfer
HBpin	4,4,5,5-Tetramethyl-1,3,2-dioxaborolane
Ind	η^5-(Indenyl)
LED	Light-emitting diode
Lut	2,6-Lutidine
MAO	Methylaluminoxane
Me	Methyl
MsO	Mesylate
MTG	Methyl thioglycolate
PC	Photocatalyst
Ph	Phenyl
PMHS	Polymethylhydrosiloxane
Pr	Propyl
py	Pyridine
SET	Single-electron transfer
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
TfO	Trifluoromethanesulfonate
TMS	Trimethylsilyl
ZACA	Zr-catalysed asymmetric carboalumination

1 Introduction

Early transition elements of the fourth group of periodical system, especially Ti and Zr, play important roles in chemistry, especially for their numerous applications in organic synthesis and catalytic transformations. As additional benefits, these elements are relatively cheap, abundant, and benign to the environment and human health. Unique properties of these electropositive oxophilic metals provide opportunities of developing new strategies for chemical transformations utilising their substantial reactivity, which is often orthogonal compared to late elements [1–3].

In this chapter, we discuss examples of recent developments in this field of organometallic chemistry, which fall approximately within the last 10 years. Our selection of topics should reflect the broad scope of possible applications of group 4 metal complexes containing the Cp or related η^5-ligands (the bent metallocene or half-sandwich type) in transformations, which can be classified as chemo-, regio-, or stereoselective, or simply cases, where the use of these compounds allows syntheses, which would otherwise be difficult to perform. This overview does not claim to be exhaustive, but it attempts to highlight interesting topics that have been the focus of researchers over the last couple of years. We also included a brief summary of novel synthetic approaches to chiral group 4 metallocenes, which are the necessary prerequisites for stereoselective catalysis. The reader is kindly advised to refer also to a number of excellent reviews available on the discussed topics, which are cited in the following sub-chapters.

2 Chiral Group 4 Cp Complexes

Efficient access to chiral complexes of group 4 metals is necessary for their applications in stereoselective transformations. As early as in the 1970s the potential of such reactions has been recognised and first examples of bent titanocene complexes with Cp-appended or -annulated chiral moieties, typically derived from naturally occurring terpenoids such as menthol or camphor, were prepared and subsequently utilised in enantioselective hydrogenation catalysis [4–7]. As evident from these examples, chirality is commonly introduced to the complexes during the ligand synthesis, i.e. prior or during the complexation of the Cp-derived ligands to metal fragments [7–9]. Chiral Cp derivatives prepared by an elegant copper-catalysed asymmetric carbozincation of pentafulvenes were in the same manner used to synthesise a series of biologically active enantiopure titanocene dichlorides of the type **1** (Scheme 1) [10]. The presence of annulated rings and bulkier substituents was recognised to increase conformational stability, which is crucial for the stereoselective performance. The search for readily available building blocks possessing chirality and allowing easy modifications continues. For example, an easily accessible chiral C_2-symmetric tetrahydropentalenyl ligand also has homotopic Cp ligand faces, which allows relatively easy preparation of optically pure chiral titanocenes **2** and **3** (Chart 1) [11].

Scheme 1 Cu-catalysed asymmetric carbozincation of pentafulvenes for the synthesis of chiral Cp ligands and their corresponding titanocene complexes

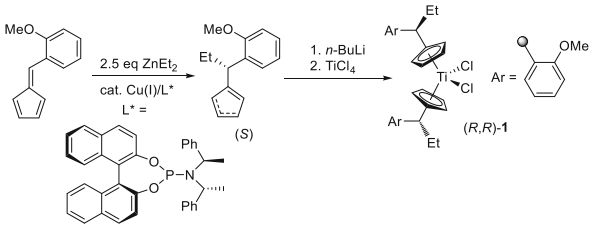
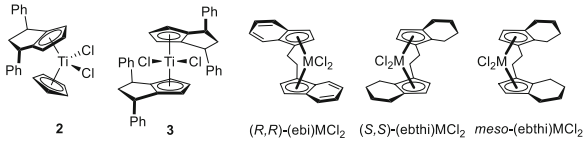
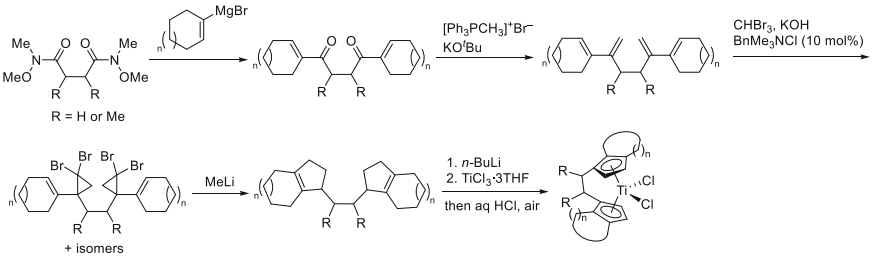


Chart 1 Selected chiral group 4 metallocenes



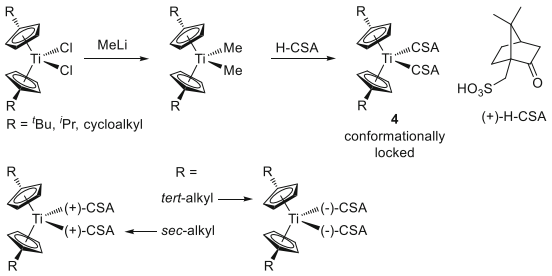
Another viable route apart from using ligands with inherent chirality is to create planar chirality by linking the two substituted cyclopentadienyl rings of the metallocene. This is most commonly achieved by the use of variously linked and substituted bis(cyclopentadienyls) – namely, bis(indenyls) and bis(4,5,6,7-tetrahydroinden-1-yls) with an ethylene bridge (ebi and ebthi ligands) being prominent examples of achiral enantiotopic chelating ligands, which means that they give rise to planar chiral *ansa*-metallocenes (Chart 1, a mixture of *rac* and *meso* isomers) upon coordination of both η^5-ligand moieties. These materials can be isolated or converted by photoinduced isomerisation to the desired *rac* isomers and the racemates can be divided into pure enantiomers, e.g., via conjugation with chiral diols, forming separable diastereomers. This approach also originated back to the early 1980s [12, 13] and has started a highly successful line of research comprising a large portfolio of *ansa*-metallocene complexes [14–16] applied particularly in the stereocontrolled olefin polymerisation catalysis, often referred to as homogeneous Ziegler-Natta catalysis (see Sect. 7). Chiral *ansa*-metallocenes were also successfully utilised in enantioselective catalysis exemplified by, e.g., olefin [17] or imine [18] hydrogenations and hydrosilylations (imines [19], ketones [20]), carbometallations (see Sect. 6) and other reactions [21, 22]. A recent detailed review article by Streuff et al. provides an overview of chiral group 4 *ansa*-metallocene syntheses [23]. The same authors also contributed to the topic by introducing a modular approach to ebthi-type metallocenes with customisable *ansa*-bridge as well as size of the annulated ring (Scheme 2) [24]. The ligand synthesis was based on a double Grignard addition to a bis-Weinreb amide, a methylenation of the dienedione, and a cyclopropanation/Skattebøl rearrangement. The obtained free ligand was directly deprotonated and used for the reactions with metal sources forming the corresponding racemic *ansa*-metallocene dichlorides [24].

A valuable contribution has been recently made by Gansäuer et al., who described a new approach to enantiopure non-bridged titanocene derivatives with achiral Cp ligands bearing metal-bound chiral camphorsulfonate moieties [25]. By using optically pure camphorsulfonic acid and non-bridged titanocenes with bulky alkyl-



Scheme 2 Modular synthesis of chiral *ansa*-titanocenes

Scheme 3
Conformationally locked chiral titanocenes



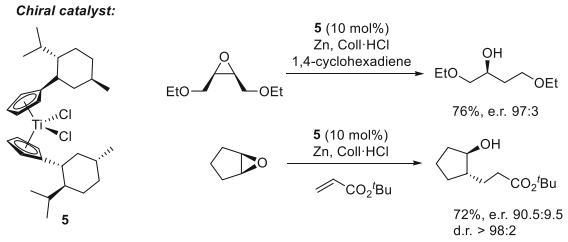
substituted Cp ligands it was possible to prepare conformationally locked complexes **4** with high enantio- and diastereoselectivity in just two steps (Scheme 3). Interestingly, *tert*-alkyl and *sec*-alkyl substitutions resulted in opposite absolute configuration at the titanocene fragment, which the authors attributed to different mechanisms of minimisation of steric interactions between the cyclopentadienyl and CSA ligands based on DFT analysis [25].

It shall be finally pointed out that in contrast to the strategies of ligand synthesis, synthetic post-modification of early transition metal complexes often represents an uneasy task due to a limited range of methods compatible with the reactive organometallic core, although many suitable methodologies involving functional group chemistry on the assembled metallocenes have been also developed and the introduction of chirality might be in principle accomplished in this way [26–29].

3 Radical Reactions Mediated by Ti(III) Species

The titanium-catalysed radical redox chemistry is certainly one of the most diverse and developed areas of selective organic synthesis utilising group 4 metal complexes [30–35]. This class of reactions employs Ti(III) species, possessing a mild reducing character due to their unpaired d electron, as single-electron transfer (SET) agents. Oxophilicity, Lewis acidity of Ti, and the presence of a coordination vacancy determine their affinity towards heteroatom-containing functional groups in organic

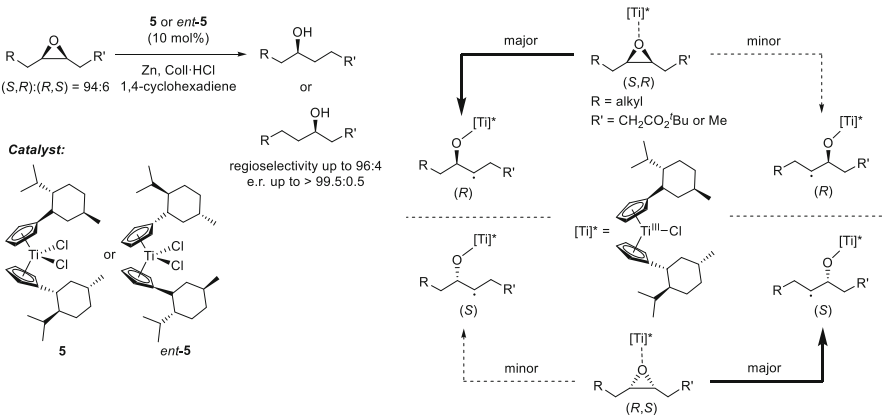
Scheme 4
Desymmetrisation of *meso*-epoxides by chiral titanocene catalysis



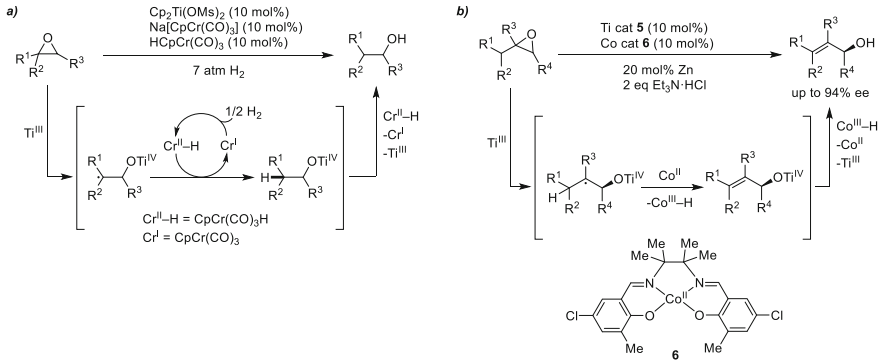
substrates such as carbonyls, epoxides, imines, etc. Seminal works of RajanBabu and Nugent on the utilisation of the prototypical Ti(III) bent metallocene complex Cp_2TiCl in the stoichiometric intramolecular cyclisation of epoxy olefins, intermolecular addition of epoxides to α,β-unsaturated carbonyl compounds, and reductive epoxide opening [36–39] created the basis for future development. Especially the titanocene-mediated cyclisations have been continuously developed as indispensable tools in natural product syntheses, where they facilitate, e.g., diastereoselective protocols for the preparation of various fused polycyclic frameworks [40–46].

Catalytic versions of the radical reactions were realised subsequently [35, 47, 48], which opened pathways to a variety of applications in organic synthesis [31, 32, 49, 50]. Importantly, regio- and stereoselectivity can be achieved in these reactions due to the reagent (or catalyst)-controlled formation of the radical intermediates, which contrasts with the traditional free-radical reactions [35]. The Ti species serves as an active electron transfer agent at the same time. As it is typical in catalysis with metal complexes, electronic and steric properties of the catalyst can be tuned through the modification of the ligand system [51]. In this manner, titanocenes with chiral ligands were applied (such as the Kagan's complex **5** in Scheme 4) in order to achieve enantioselectivity, such as in the desymmetrisation of *meso*-epoxides depicted in Scheme 4 [52, 53]. The regioselectivity of epoxide opening is determined by the absolute configuration of titanocene **5**, resulting in an efficient desymmetrisation and high enantioselectivity of the product formation. Coordination of the epoxide to the catalyst weakens one enantiotopic C–O bond through steric interactions, favouring homolytic cleavage, while an inverted selectivity can be achieved by employing the other enantiomer of the catalyst.

An important concept was subsequently coined by Gansäuer et al. in a report describing a reductive opening of sterically and electronically unbiased pseudo (*cis*-1,2-disubstituted) *meso*-epoxides as depicted in Scheme 5 [54]. The reaction has been termed "regiodivergent" emphasising the fact that the regioselective reaction involving chiral starting materials (either racemic or optically enriched) in such case leads to the formation of two distinct constitutional isomers, which are, however, obtained with high enantioselectivity when using the chiral titanocene catalyst [53, 55–57]. Such an approach, yielding diastereo- and enantiomerically pure 1,3- and 1,4- difunctionalised products, is highly desirable for generating functional and structural diversity in a single reaction (diversity-oriented synthesis).



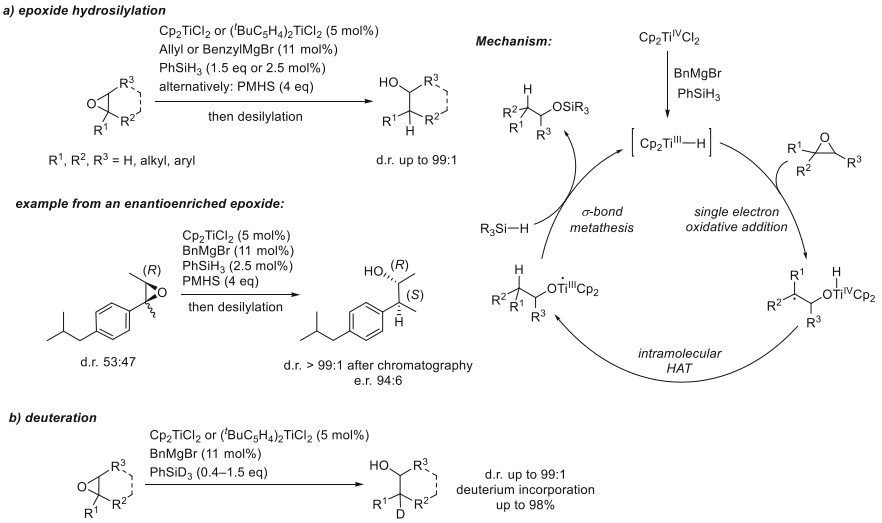
Scheme 5 Regiodivergent epoxide opening



Scheme 6 (**a**) Ti/Cr-bimetallic catalytic reductive epoxide opening, (**b**) Ti/Co-bimetallic enantioselective epoxide isomerisation

Recent development of the regioselective reductive opening of epoxides forming *anti*-Markovnikov alcohols led to cooperative bifunctional catalytic systems utilising the Ti(III) radical organometallic template and chromium species Na[$CpCr(CO)_3$]/$HCpCr(CO)_3$. The latter are capable of H_2 activation and a consecutive transfer of hydrogen atom, proton, and one-electron reduction necessary for the Ti (III) species recovery, rendering the overall process atom-economical [58] (Scheme 6a). In a related work, the authors utilised a BH_4^- anion in an unusual way as a stoichiometric H-atom donor for the discussed radical reactions, including the regiodivergent variant [59].

Lin et al. have demonstrated a regio- and stereoselective method for isomerisation of epoxides to allylic alcohols through a radical redox relay catalysed by a bimetallic Ti/Co system [60]. The titanocene catalyst was again responsible for the epoxide



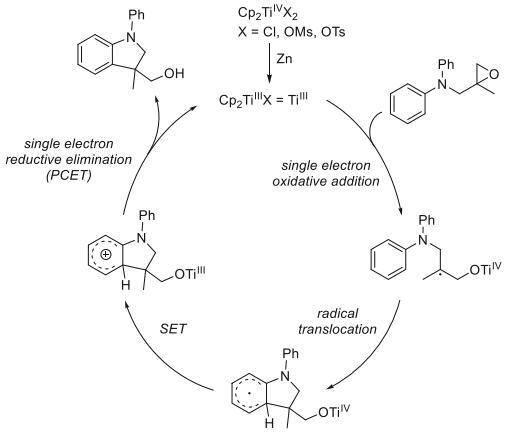
Scheme 7 Ti-catalysed epoxide (**a**) hydrosilylation, (**b**) deuterosilylation

opening initiation, while the Co complex **6** with a salen-type ligand mediated the hydrogen-atom transfer (HAT) process and regeneration of the Ti(III) species. The use of chiral titanocene allowed performing an enantioselective isomerisation of *meso*-epoxides (Scheme 6b). Similarly, this methodology can be utilised for an isomerisation of analogous *N*-benzoyl aziridines to allylic amides [61].

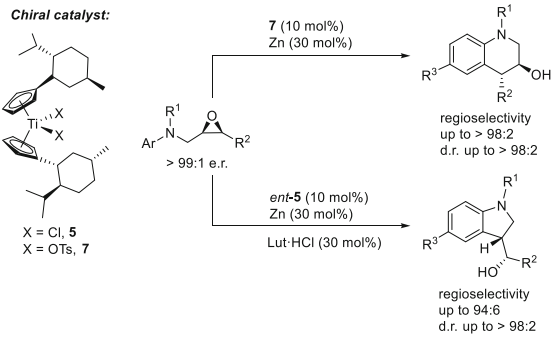
A combination of titanocene-catalysed epoxide ring-opening with hydrosilylation was developed into another facile route to *anti*-Markovnikov alcohols [62, 63]. The anticipated active species in this process has been identified as titanocene hydride Cp_2TiH, which can be conveniently generated in situ from Cp_2TiCl_2 and Grignard reagents such as allyl- [64] or BnMgBr [65] (Scheme 7). The possible use of PMHS as a cheap terminal HAT reagent makes this procedure even more attractive and sustainable. The epoxide hydrosilylation was successfully combined with a preceding enantioselective organocatalytic *syn*-specific Shi-epoxidation of a mixture of diastereomeric olefins. Thus, a formal *anti*-Markovnikov addition of H_2O to a C=C double bond was performed, which resulted in stereochemically convergent alcohol products with excellent enantio- and diastereoselectivity due to a directional isomerisation of the radical intermediates [66]. The hydrosilylation methodology was also very successfully applied for a highly regio- and diastereoselective catalytic deuterosilylation of epoxides providing β-deuterated alcohols (Scheme 7b) [67].

By combining the radical epoxide opening with a subsequent C–C bond forming reaction the radical arylation of epoxides has been developed by Gansäuer et al. (Scheme 8) [68–72]. This reaction sequence eliminated the necessity of using stoichiometric amounts of additives compared to the reductive opening. Detailed mechanistic investigations and optimisations of reaction conditions, including the catalyst structure, particularly the role of sigma-bonded ligands in the Cp_2TiX

Scheme 8 General mechanism of the Ti-catalysed radical arylation of epoxides

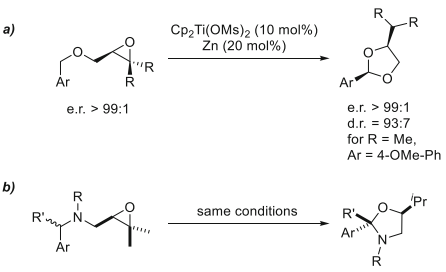


Scheme 9 Stereoselective synthesis of indolines or tetrahydroquinolines

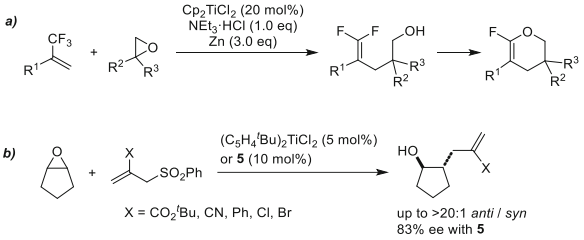


complexes, were performed [73]. The scope of this reaction spans pharmaceutically important heterocyclic products such as indolines and tetrahydroquinolines, and also related dihydropyrrolizines, tetrahydroindolizines, and others [74, 75]. In specific cases when secondary radicals are involved in the mechanism, a good control of diastereoselectivity can be exerted. Regiodivergent versions of these transformations, using the chiral titanocene catalyst, followed soon as a stereoselective and atom-economical alternative to classical Friedel-Crafts alkylations, e.g., for the synthesis of selected chiral indolines or tetrahydroquinolines (Scheme 9) [76]. The products are obtained as two heterocyclic constitutional isomers, which are readily separable and the respective regioselectivity is controlled by using a particular optical isomer of the chiral catalyst. The method also tolerates a wide range of functional groups, particularly on the arene moiety (carbonyl, halogens, etc.).

The radical translocation step by a HAT process, which is key to the above described cyclisations is also operable in reactions leading to acetals or hemiaminals starting from benzylic ethers or amines with appended epoxy groups (Scheme 10) [77]. Interestingly, the formal oxidation of the benzylic centre proceeds under reducing conditions in these reactions.



Scheme 10 Preparation of (**a**) acetals from epoxy-substituted benzylic ethers or (**b**) hemiaminals from epoxy-derived amines

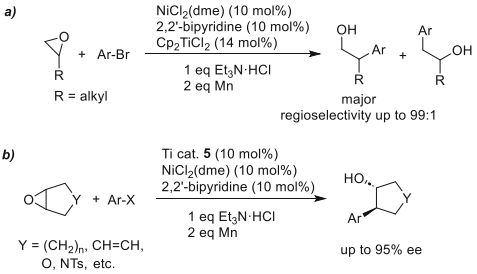


Scheme 11 Ti-catalysed reductive domino cross-coupling of epoxides with (**a**) trifluoromethyl-substituted alkenes, (**b**) with allyl sulfones

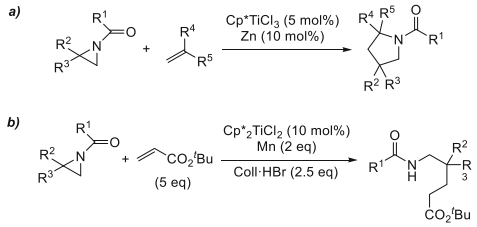
The opening of an epoxide ring can be also coupled with an intermolecular reaction of the formed radical intermediate, such as in the titanocene-catalysed reductive domino cross-coupling reaction of epoxides with trifluoromethyl-substituted alkenes [78]. This regioselective reaction is associated with a β-fluorine elimination and can also serve as a convenient route to 6-fluoro-3,4-dihydro-2*H*-pyrans (Scheme 11a). Similarly, variously substituted allyl sulfones were successfully coupled with epoxides upon their catalytic radical opening by a titanocene [79]. Due to the regioselectivity of this reaction, quaternary carbon centres were readily formed and the potential for diastereo- and even enantioselective variants of this transformation was demonstrated by using a chiral catalyst (Scheme 11b).

An intermolecular cross-coupling of aryl halides with epoxides using dual Ni/Ti catalysis was reported by Weix and co-worker [80]. In this protocol, the titanocene is again responsible for the regioselectivity of the epoxide opening at the sterically more hindered side, while the Ni-catalysed cross-coupling of the radical with the aryl fragment under reductive conditions leads preferentially to the product of internal addition (Scheme 12a). The concept was subsequently extended to an enantioselective version of cross-coupling of *meso*-epoxides with aryl halides using a chiral titanocene catalyst together with $NiCl_2$(dme) (Scheme 12b) [81].

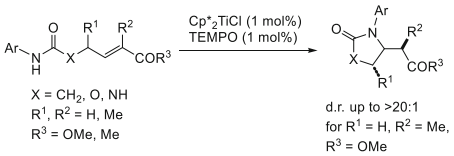
The epoxide moiety is not an exceptional prerequisite for performing radical reactions initiated by Ti(III) species. *N*-acyl aziridines were used by Lin et al. as substrates for a formal [3 + 2] cycloaddition with alkenes in a radical relay reaction catalysed by titanium half-sandwich complex Cp*$TiCl_3$ under reducing conditions [82]. Substituted pyrrolidines were thus obtained with complete regioselectivity in high yields (Scheme 13a). In a related work, Gansäuer et al. described $Cp^*_2TiCl_2$/Mn-catalysed radical opening of *N*-acylated aziridines and their subsequent application, e.g., in conjugate additions (Scheme 13b) [83].



Scheme 12 Ni- and Ti-catalysed cross-coupling of aryl halides with epoxides (**a**) using Cp_2TiCl_2, (**b**) with a chiral titanocene **5** allowing enantioselective coupling of *meso*-epoxides



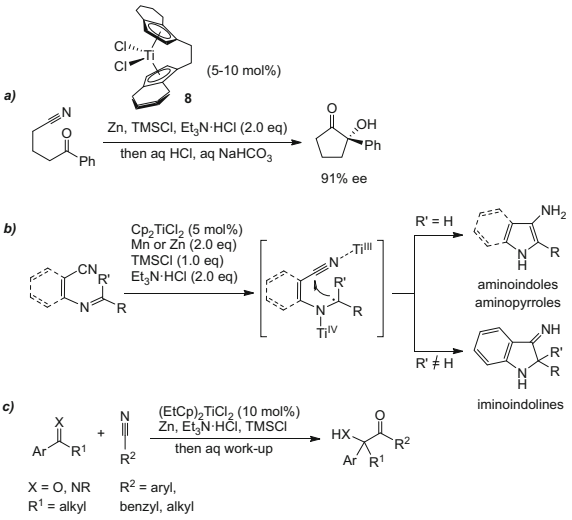
Scheme 13 (**a**) [3 + 2] cycloaddition of *N*-acylaziridines and alkenes, (**b**) reductive opening of *N*-acylaziridines

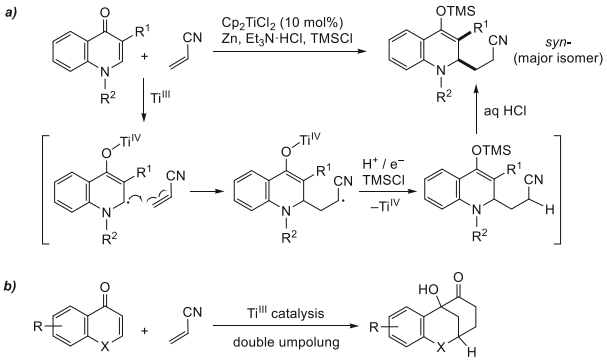


Scheme 14 Conjugate amination enabled by a homolytic N–H bond weakening

The capability of the Cp^*_2TiCl organometallic fragment of coordination to oxygen atoms of polar functional groups and consequent weakening of adjacent bonds was noted by Knowles and co-workers, who developed an intramolecular conjugate amination protocol using carbamate as a starting material [84]. This reaction was enabled by a homolytic weakening of the N–H bond in the substrate and subsequent H-atom abstraction by a TEMPO radical. The cyclisation is able to proceed with high diastereoselectivity (Scheme 14).

Ti(III)-catalysed activation of substrates containing electron-withdrawing groups such as ketones, imines, nitriles, and Michael acceptors was exploited by the group of Streuff, who developed the concept of cross-selective reductive umpolung reactions [85]. The potential of these methods can be exemplified by the enantioselective ketonitrile cyclisation leading to cyclic α-hydroxyketones (acyloins) (Scheme 15a) [86]. The Brintzinger's *ansa*-titanocene (ebthi)$TiCl_2$ **8** was the chiral catalyst of choice for this reaction. The intramolecular cyclisation could be performed also using nitriles with imines – as a formal [4 + 1] cycloaddition [87]. The methodology of radical cyclisation was further extended to preparation of various *N*-heterocyclic products, such as 3-aminoindoles, 3-aminopyrroles, or 3-iminoindolines (Scheme 15b) [88, 89]. Attempts were made to perform some of the nitrile-imine cyclisations enantioselectively using chiral titanocene catalysts, but only with a limited success [89]. Moreover, intermolecular variants of the ketone-nitrile and imine-nitrile cross-



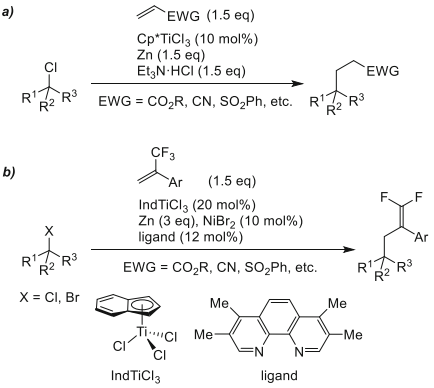


Scheme 15 Reductive umpolung reactions: (**a**) enantioselective ketonitrile cyclisation, (**b**) imine-nitrile cyclisation, (**c**) intermolecular cross-selective couplings

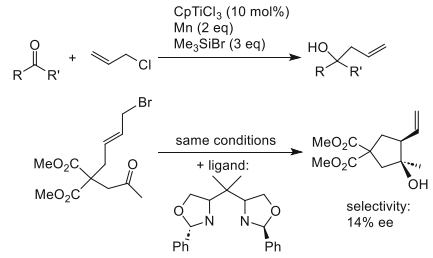
Scheme 16 Reductive umpolung of Michael acceptors: (**a**) conjugate alkylation of enones, (**b**) double umpolung with ketone-nitrile cyclisation

selective couplings were described, giving direct access to α-hydroxylated and α-aminated ketones (Scheme 15c) [90, 91].

A reductive umpolung of Michael acceptors is represented by a conjugate alkylation of α,β-unsaturated carbonyls, which allows the cross-selective preparation of 1,6- and 1,4-difunctionalised building blocks without the need of stoichiometric organometallic reagents [92, 93]. Diastereoselectivity of the coupling can be exploited in specific cases (Scheme 16a). A double umpolung combining the coupling of Michael acceptors with the ketone-nitrile cyclisation led to valuable tricyclic motifs (Scheme 16b) [94]. Mechanistic studies explaining the role of catalysts, precise reaction conditions, and additives in umpolung reactions were



Scheme 17 Radical additions of tertiary alkyl groups (**a**) to electron-deficient alkenes, (**b**) as a reductive allylic defluorinative cross-coupling with CF_3-substituted alkenes under Ni catalysis



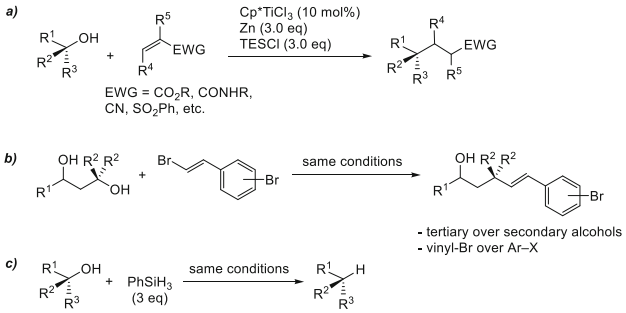
Scheme 18 Barbier allylation of ketones

performed using a combination of experimental and computational approaches [95–97].

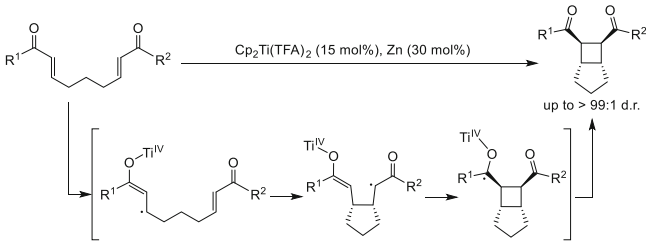
C-halogen bonds can also be homolytically cleaved utilising the Ti(III) catalysis, namely employing the Cp*$TiCl_3$ precatalyst, as has been demonstrated by Lin et al. [98]. The challenging tertiary alkyl chlorides were used as substrates for radical addition to electron-deficient alkenes (Scheme 17a). In a similar manner, tertiary alkyl radicals were generated using the (indenyl)$TiCl_3$/Zn system and used for a reductive allylic defluorinative cross-coupling with trifluoromethyl alkenes catalysed by a Ni(II) complex (Scheme 17b) [99].

A Barbier-type propargylation and allylation of ketones was described by Oltra et al. using a Cp$TiCl_3$/Mn catalytic system [100]. Intramolecular versions of this reaction can be performed in the presence of a chiral ligand, albeit with low enantioselectivity (Scheme 18).

Activation of the C–O bond in tertiary alcohols is viable through the radical mechanism employing a Cp*$TiCl_3$/Zn catalytic system. Wang and Shu reported on the dehydroxylative alkylation of tertiary alcohols using activated alkenes (Scheme 19a) [101]. In a related work, the authors utilised the tertiary alcohols for reductive dehydroxylative vinylation with various vinyl halides (Scheme 19b) [102]. Both the methods, which are also chemoselective and tolerant to a range of functional groups, represent a convenient route to the construction of all-carbon quarternary centres. The utility of this approach was extended to dehydroxylation of tertiary alcohols using $PhSiH_3$ as the hydrogen-atom source (Scheme 19c) [103]. Principially related



Scheme 19 Ti-catalysed dehydroxylative reactions: (**a**) dehydroxylative alkylation of tertiary alcohols by activated alkenes, (**b**) reductive dehydroxylative vinylation of tertiary alcohols, (**c**) reductive dehydroxylation by silanes



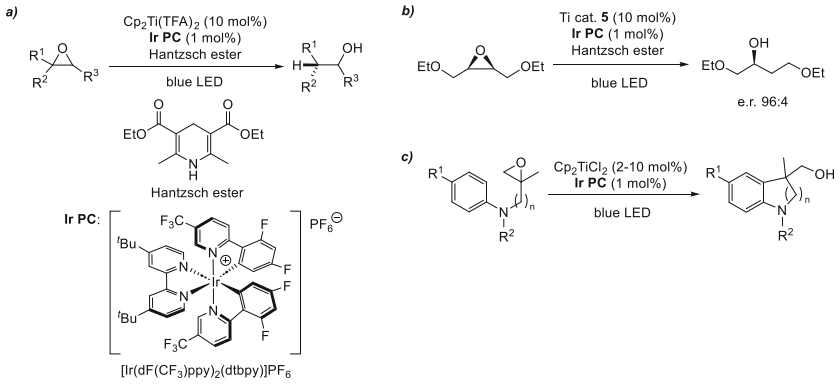
Scheme 20 Intramolecular [2 + 2] cycloaddition of bis(enones) by a radical mechanism with a titanocene catalyst

reactions reported by Streuff et al. also make use of the homolytic bond scission (C–S or C–C, respectively): Ti(III)-catalysed reductive desulfonylation of α-sulfonyl nitriles [104] and reductive decyanation of geminal dinitriles [105].

A formal intramolecular [2 + 2] cycloaddition of bis(enones) was also performed by a radical pathway using $Cp_2Ti(TFA)_2$ catalyst with a high diastereoselectivity, a broad substrate scope, and under sustainable conditions compared to previously established methods (Scheme 20) [106].

4 Photoredox Catalysis with Group 4 Metallocenes

Photoredox catalysis gained much attention recently as a discipline allowing efficient chemical transformations by utilising the energy of light. One important direction of current research is devoted to combining the power of photoredox catalysis with additional catalytic cycles mediated by transition metals [107–110]. Group 4 metal complexes seem perfectly suitable for this approach and there

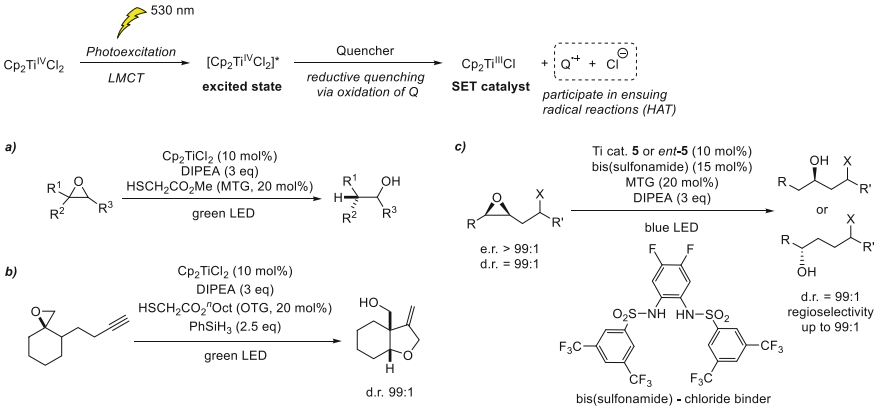


Scheme 21 Merging photoredox catalysis with titanocene-mediated radical reactions: (**a**) reductive epoxide opening, (**b**) desymmetrisation of *meso*-epoxides, (**c**) reductive intramolecular arylation of epoxides

are already relevant examples of their successful utilisation [111, 112], most of them based on the radical catalysis discussed in the previous sub-chapter. In this context, it is appealing to enhance sustainability of the established reactions, featuring the Ti (III)/Ti(IV) redox chemistry in single-electron transfer (SET) steps, by avoiding stoichiometric metal reductants. Merging these protocols with photoredox catalysis allows the use of simple organic electron donors as sacrificial reductants. This strategy also overcomes the limited oxidising capability of the Ti(IV) radical intermediate, which might hinder the desired reductive elimination. As a drawback, many processes feature an additional photocatalyst, sometimes based on a precious metal complex, which is necessary for the actual light energy harvesting and a subsequent reductive ET from its excited state generating the active titanium species.

Gansäuer et al. reported the first such example in 2019, describing a catalytic system comprising Cp_2TiX_2 (X = Cl or TFA), Hantzsch ester as a sacrificial hydrogen-atom donor and an iridium-based photocatalyst (Scheme 21) [113]. The latter PC produces the Ti(III) species by ET and its corresponding radical cation $[PC]^{\cdot+}$ is able to oxidise the radical Hantzsch ester intermediate to the corresponding acidic pyridinium ion, which mediates the release of the product from the Ti (IV) centre. Reductive epoxide opening was thus possible with the above system and, in addition, a chiral titanocene was also employed to promote an enantioselective epoxide opening with good results (Scheme 21b). An example of radical cyclisation reaction – arylation of epoxides – proceeded smoothly without the necessity of additives (Scheme 21c).

An important improvement was introduced by Gansäuer and Flowers in a subsequent paper, which marked the first utilisation of titanocene dichloride as a photocatalyst in reductive epoxide opening (Scheme 22) [114]. Green light irradiation of the complex yields an LMCT excited state [115], which is successfully reduced to the active Ti(III) species by $^{i}Pr_2NEt$ (DIPEA). A carbon-centred radical



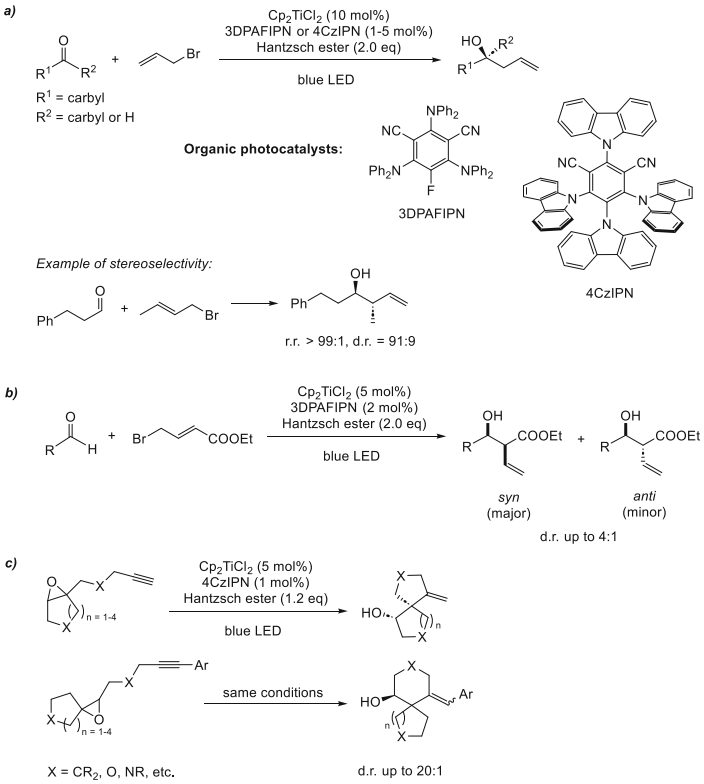
Scheme 22 Cp_2TiCl_2 as a photocatalyst: (**a**) reductive epoxide opening, (**b**) 5-*exo*-cyclisation, (**c**) regiodivergent opening of chiral epoxides

formed in this process undergoes HAT with methyl thioglycolate (MTG), resulting in the corresponding Ti(IV)-alkoxy species. The HAT cycle is sustained by the radical cation $DIPEA^{\cdot+}$, and the titanocene redox cycle is closed by interacting with the iminium ion of DIPEA, which serves as a scavenger for the Ti(IV) species. The authors suggest the initial formation of a hemiaminal, which, after hydrolysis, yields the corresponding alcohol. The generality of this process was demonstrated also in several examples of 5-*exo*-cyclisations (Scheme 22b). The concept of the titanocene-enabled photoredox catalysis was recently extended to a regiodivergent reductive epoxide ring-opening yielding monoprotected 1,3- or 1,4-diols with high enantio- and regioselectivity, depending on the configuration of the chiral catalyst **5** used (Scheme 22c) [116].

Other researchers focused on combining the Ti-based radical catalysis with organic photocatalysts. A Barbier-type allylation of aldehydes was described by Cozzi et al. using visible-light irradiation and Hantzsch ester stoichiometric reductant and Ti scavenger (Scheme 23a) [117]. An analogous methodology can be applied also to the preparation of α-vinyl-β-hydroxy esters from aldehydes with exclusive regioselectivity (Scheme 23b) [118]. Similar results were reported also by Shi et al., who employed a range of aldehydes, ketones, and alkyl halides for the Barbier-type coupling reactions [119]. The same catalytic system was applied also for spirocyclisations (5-exo and 6-exo cyclisations) of epoxy alkynes, which proceeded in some cases with excellent diastereoselectivity (Scheme 23c) [120].

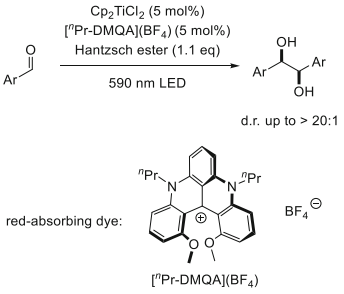
A highly diastereoselective pinacol coupling of aromatic aldehydes, yielding preferably the *syn*- isomer, was developed using the Cp_2TiCl_2 catalyst in combination with a red-absorbing organic dye (Scheme 24) [121].

A Ti-mediated alkylation of ketones by carbon-centred radicals formed via sp^3 C–H bond activation by organic photocatalysis combined with HAT catalysis was reported by Kanai and Mitsunuma (Scheme 25) [122]. A possibility of combining



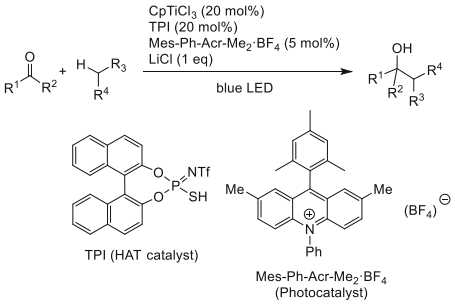
Scheme 23 Titanocene radical catalysis with organic photocatalysts: (**a**) Barbier allylation of aldehydes or ketones, (**b**) preparation of α-vinyl-β-hydroxy esters from aldehydes, (**c**) spirocyclisations of epoxy alkynes

Scheme 24 Ti-catalysed pinacol coupling of aromatic aldehydes

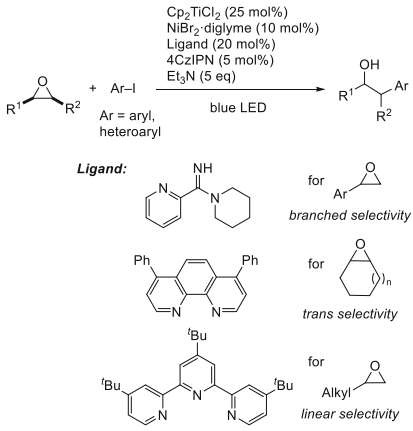


two transition metal catalysts (Ti and Ni) with the organic photoredox catalysis was demonstrated by Doyle et al. in a paper describing a cross-electrophile coupling of three different classes of epoxides with (hetero)aryl iodides (Scheme 26)

Scheme 25 Radical alkylation of ketones

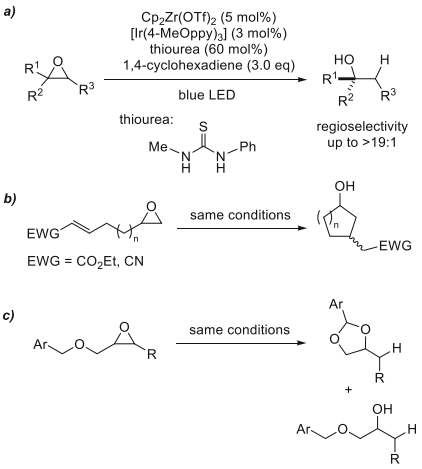


Scheme 26 Ti- and Ni-catalysed cross-coupling of epoxides with aryl iodides



[123]. Titanocene catalyst was responsible for epoxide opening, while the cross-coupling proceeded on Ni with regioselectivity depending on the ligand used.

A unique example of photoredox processes utilising zirconocene complexes for radical catalysis was reported by Yamaguchi and Ota [124]. Using the strongly reducing photocatalyst Ir(4-MeOppy)$_3$, $Cp_2Zr(OTf)_2$, and 1,4-cyclohexadiene as the hydrogen source, reductive epoxide opening was successfully performed. Remarkably, the alcohol products were obtained with an opposite regioselectivity compared to titanocene-based protocols (Scheme 27a). The scope of this method also comprised intramolecular cyclisations of epoxy olefins and the formation of acetals from epoxy ethers (Scheme 27b, c, respectively). The use of zirconium cyclopentadienyl complexes as the sole photocatalysts, similarly as titanocenes, remains to be developed, but there is a clear evidence that Zr complexes with different ligand systems can act as photoredox catalysts in both reduction and oxidation processes [125, 126]. Photophysical properties of some zirconocenes suggest that they might become another viable alternative for precious metal-based photocatalysts [127].



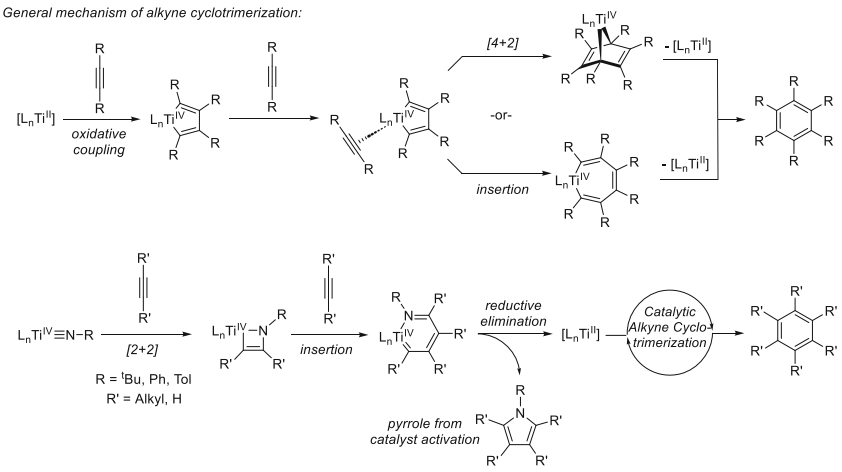
Scheme 27 Zirconocene-catalysed photoredox reactions: (**a**) reductive epoxide opening, (**b**) intramolecular cyclisations of epoxy olefins, (**c**) acetals from epoxy ethers

5 Low-Valent Metallocenes for C–C Bond Forming or Cleavage

In contrast to radical reactions discussed in previous chapters, another large group of transformations is based on metal centres alternating between the M(II) and M (IV) oxidation states in oxidative addition and reductive elimination steps [1, 128]. Utility of these processes, especially for C–C bond forming reactions, either stoichiometric or catalytic, has been widely recognised after decades of systematic explorations [2, 129]. The capability of low-valent group 4 metals to undergo oxidative addition of unsaturated molecules in a [2 + 2] cycloaddition process giving rise to metalacyclic products has been frequently exploited for the construction of various cyclic moieties [130–136]. Among the studied complexes, metallocenes of the type "$Cp_2M(II)$" dominate as active species, typically generated in situ by reduction using metals, alkyl lithium, or Grignard reagents, or employed as preformed complexes stabilised by weakly coordinated alkyne or other ligands [137, 138]. Okamoto et al. reported an efficient use of half-sandwich precatalysts $CpTiX_3$ (X = Cl, O^{i}Pr) in combination with Me_3SiCl and Zn or Mg for the [2 + 2 + 2] cyclotrimerisation of alkynes [139].

Tonks et al. reported an alternative method for the generation of Ti(II) active species for alkyne cyclotrimerisation catalysis [140]. In contrast to typical reduction of Ti(IV) halides with (organo)metallic reductants, titanium imido complexes (with various ligands including Cp) were employed as precatalysts, which were activated just by the alkyne substrate, liberating a pyrrole molecule by reductive elimination (Scheme 28).

Utility of the stoichiometric zirconocene-mediated [2 + 2] cycloaddition of alkynes for the construction of various complex molecules with interesting physical properties, such as large polycyclic aromatic hydrocarbons, was clearly demonstrated in a series of works by Tilley et al. (Scheme 29) [141, 142]. Rosenthal's



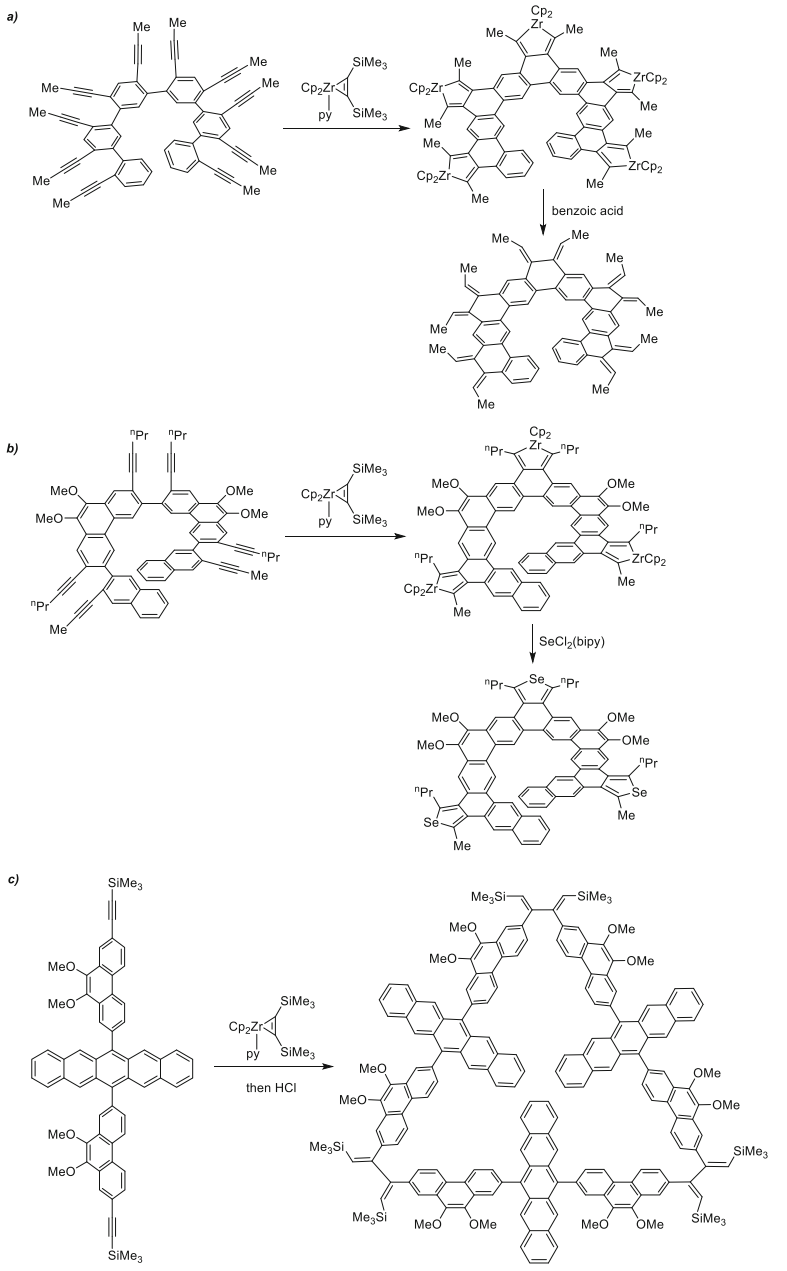
Scheme 28 Ti-catalysed alkyne cyclotrimerisation – general mechanism and reactivity of titanocene imido complexes

complex $Cp_2Zr(py)(Me_3SiC \equiv CSiMe_3)$ was used as the reagent of choice, while the obtained zirconacyclopentadiene moieties can be converted to open dienes by protolysis or to selenophenes by the reaction with $SeCl_2$ (Scheme 29b). A similar strategy was also applied by Rivard et al. for the synthesis of phosphorescent heteroacenes containing Te atoms [143] and by Hissler and Staubitz for the preparation of stannoles [144].

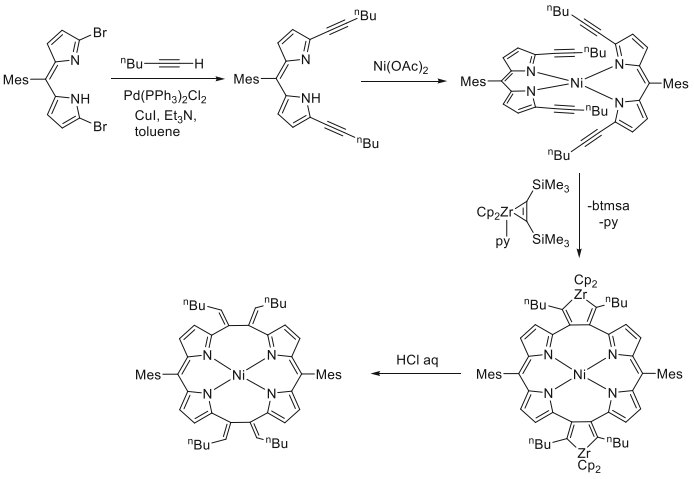
Even separate large molecular fragments can be connected by the same approach into macrocyclic molecules as shown in the preparation of pentacene-containing macrocycles or carbon nanobelts, both constructed from alkynyl-terminated polyaromatic building blocks (Scheme 29c) [145–147]. The method has been also applied for the synthesis of porphyrins(2.1.2.1) by Song et al., directly connecting two bis(alkynyl)-substituted ligands coordinated to a Ni(II) centre in a single step (Scheme 30) [148].

Also the titanocene source $Cp_2Ti(Me_3SiC \equiv CSiMe_3)$ was used for the synthesis of polycyclic aromatic molecules, this time mediating dinitrile-coupling steps giving diimine moieties, which were directly transformed into *o*-quinone, diazole, or pyrazine units (Scheme 31) [149].

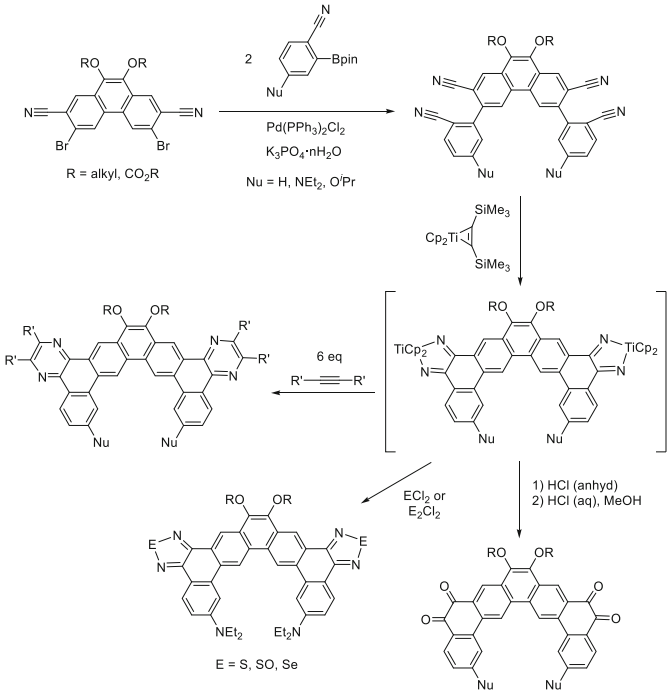
In general, reactivity of the in situ generated "$Cp_2M(II)$" gives the possibility to prepare an enormous variety of unusual metallacycles by connecting different unsaturated moieties – both pure hydrocarbon-based or heteroatom-containing [130, 131, 134, 136, 150–152]. There still seems to be room for further development in this area, mainly of new synthetic methods featuring good regiocontrol and allowing also catalytic processes to be realised. Some recent examples suggesting this possibility have already been realised. A seven-membered zirconacyclocumulene **9**, prepared by coupling of two diyne molecules, reacted with benzonitrile at elevated temperature to release a pyrimidine derivative **10**



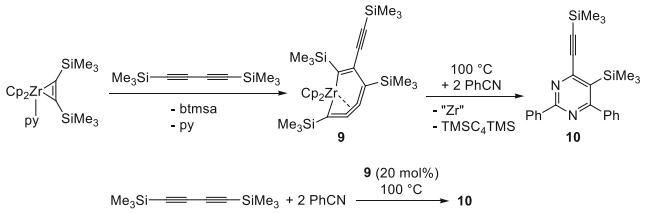
Scheme 29 Application of zirconocene alkyne complexes for the construction of supramolecular architectures



Scheme 30 Assembly of a porphyrin molecule using a low-valent zirconocene

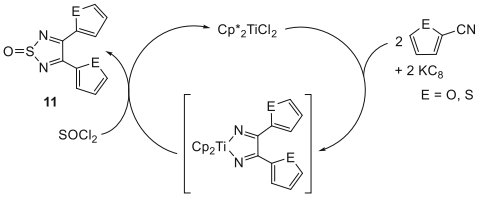


Scheme 31 Coupling of pendant nitrile groups by a low-valent titanocene for the preparation of polycyclic heteroaromatic molecules

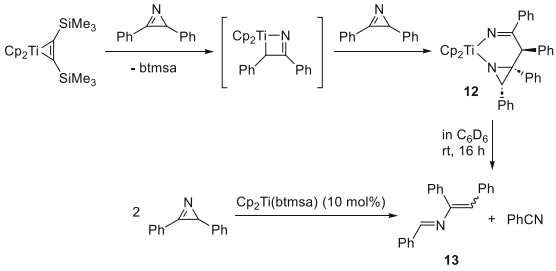


Scheme 32 Reactivity of a seven-membered zirconacyclocumulene **9** and a potential catalytic pyrimidine derivative **10** formation

Scheme 33 Ti-mediated preparation of furan- and thiophene-substituted thiadiazole oxides



Scheme 34 Ti-mediated coupling of *2H*-azirines and a potentially catalytic release of azabutadiene

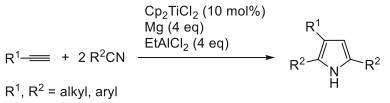


(Scheme 32). This reaction can be performed starting with a diyne and with only a catalytic amount of the independently prepared metallacycle [153]. As discussed above, titanocenes mediate the coupling of nitriles and various diazole derivatives can thus be prepared. As demonstrated by Beweries et al. a furan- or thiophene-substituted thiadiazole oxide **11** can be obtained from the corresponding nitriles and $SOCl_2$ in a synthetic cycle using $Cp^*_2TiCl_2$ and KC_8 as a reductant (Scheme 33) [154].

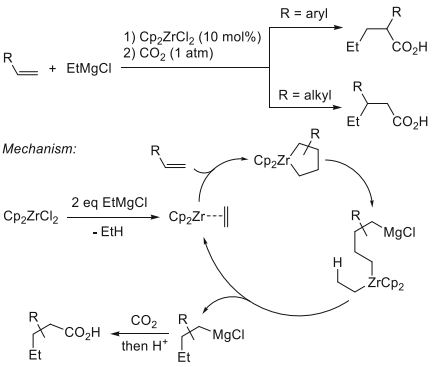
Tonks et al. reported the coupling of 2*H*-azirines on a titanocene fragment to form a diazatitanacyclohexene **12**, which decomposes in solution to an azabutadiene **13** and a nitrile. The process is catalytic in the presence of excess *2H*-azirine (Scheme 34) [155].

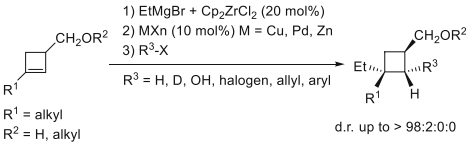
A catalytic preparation of 2,3,5-substituted 1*H*-pyrroles from nitriles and alkynes using Cp_2TiCl_2/Mg was published by Khafizova and co-workers [156]. The reaction utilised a stoichiometric amount of $EtAlCl_2$ for removal of the coupled product from Ti (Scheme 35).

Scheme 35 Ti-catalysed synthesis of 2,3,5-substituted 1*H*-pyrroles



Scheme 36 Zr-catalysed ethylcarboxylation of alkenes

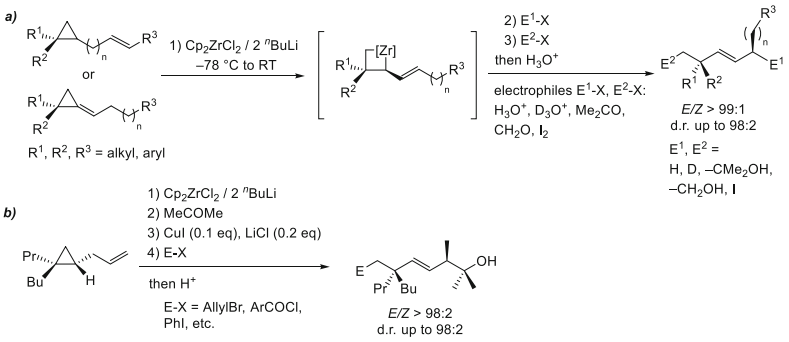




Scheme 37 Carbomagnesiation of cyclobutenes and a subsequent metal-catalysed coupling with electrophiles

A zirconocene-catalysed sequential ethylcarboxylation of alkenes reported by Xi et al. also featured an oxidative addition onto a Zr(II) centre as one of the key steps in the mechanism (Scheme 36) [157]. EtMgBr generated the active species and then likely also entered the catalytic cycle in a transmetallation step. The final carboxylation of the liberated organomagnesium species led to the product after hydrolysis. The same catalytic system was also used for a regio- and diastereoselective carbomagnesiation of cyclobutenes by Marek and co-workers (Scheme 37) [158]. The obtained configurationally stable cyclobutylmagnesium species can subsequently react with a variety of electrophiles under Cu or Pd co-catalysis to give polysubstituted cyclobutane derivatives with high diastereoselectivity.

A synthetically important approach utilising a low-valent zirconocene reagent for stereoselective transformations and derivatisations of hydrocarbon molecules by a combination of C–C and C–H bond activations was developed by the group of Marek [159–161]. They have shown that cyclopropane molecules with a distant double bond, like ω-ene-cyclopropanes or alkylidene cyclopropanes, could be turned into acyclic fragments with two stereogenic centres, including a challenging all-carbon quaternary stereocenter (Scheme 38a) [162].



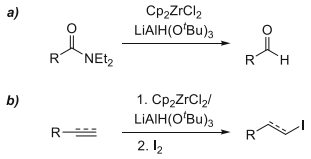
Scheme 38 Selective C–C and C–H bond activations by low-valent zirconocenes: (**a**) stereoselective cleavage of the cyclopropane moiety with a concomitant allylic C–H activation leading to acyclic molecules with defined stereochemistry, (**b**) stereoselective remote functionalisation

This transformation was mediated by a low-valent zirconocene generated from the Negishi reagent $Cp_2Zr(^nBu)_2$ and it involved an allylic C–H activation followed by a highly selective C–C bond activation or fragmentation. The resulting bifunctional nucleophilic species were further modified with two different electrophiles, leading to more complex molecular structures with a defined stereochemistry. The reaction could be further extended by a transmetallation of the alkylzirconium species to Cu, which can undergo further C–C bond forming process enabling a stereoselective route to remote functionalisation (Scheme 38b) [163]. In general, the cleavage of three-membered ring carbocycles such as ω-ene polysubstituted cyclopropanes, alkylidene cyclopropanes, ω-ene spiro[2.2]pentanes, and ω-ene cyclopropyl methyl ethers leads through stereodefined organometallic intermediates to finally provide acyclic scaffolds with excellent stereocontrol as demonstrated by the same authors on a number of examples [164].

6 Reactions Involving Hydrometallation and Related Processes

Group 4 metal cyclopentadienyl complexes are crucial also for reactions involving addition of M–H or M–X (X = C, B, etc.) bonds to alkynes or olefins leading to organometallic reagents useful, above all, for various selective C–C bond formations. This area of synthetic organic chemistry is vast and has been developed over more than five decades. Due to obvious limitations of this chapter, we encourage the reader to refer for further information to several excellent review articles covering recent developments in the utilisation of organozirconium and partially also organotitanium reagents in organic synthesis [165–168].

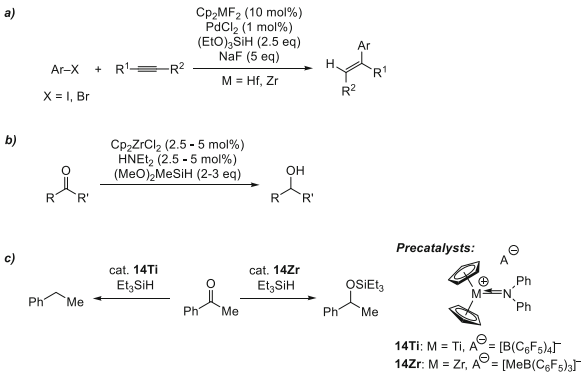
Among the known methods, hydrozirconation is the most robust and broadly applied procedure, which generates alkenyl- or alkylzirconium species that are mild



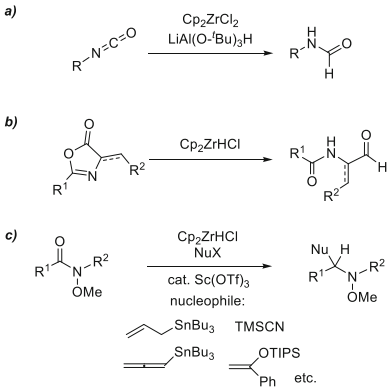
Scheme 39 (**a**) Zr-mediated reduction of amides to aldehydes and (**b**) regioselective hydrozirconation/iodination of alkenes and alkynes

nucleophiles (comparable, e.g., to organotin reagents, but exerting larger sterical hindrance around the M–C bond), exhibiting a good functional group tolerance and, consequently, favourable selectivity. Organozirconium reagents can subsequently undergo facile transmetallation to a variety of metals [169], allowing thus to perform other transformations, cross-couplings catalysed by nickel or palladium complexes being typical examples [170]. A prototypical starting material for the organozirconium chemistry is the Schwartz's reagent, Cp_2ZrHCl, first reported in 1969 [171], the hydrozirconation reactivity of which has been explored since early 1970s [172–174]. Although this compound is commercially available, its air-sensitivity, limited stability, problematic solubility, and high cost motivated researchers to look for more convenient alternatives. Several methods for the in situ preparation of Schwartz's reagent were described using, e.g., $LiAlH_4$, DIBAL-H, $LiBHEt_3$, or ^{t}BuMgCl. The method reported by Snieckus et al. using Cp_2ZrCl_2/$LiAlH(O^tBu)_3$ seems to be an advantageous protocol . The in situ generated Cp_2ZrHCl was used for a chemoselective reduction of amides to aldehydes (Scheme 39a) and a regioselective hydrozirconation/iodination of alkenes and alkynes (Scheme 39b) [175].

Other strategies for the generation of M–H bonds utilise hydrosilanes as the hydride source, where the formation of very strong Si–O or Si–F bonds is the reaction driving force. In this manner, it is possible to run the reactions catalytically. Sakai and co-workers reported a bimetallic catalysis for the reductive cross-coupling of alkynes with aryl halides based on zirconocene or hafnocene difluorides combined with palladium, to which the intermediate alkenylmetallocene species was transmetallated (Scheme 40a) [176]. $(EtO)_3SiH$ was the hydrosilane of choice for the active M-H species generation and NaF was used for regeneration of the difluoride necessary for an efficient catalytic cycle. Another approach was described in the work of Bayeh-Romero et al., who used Cp_2ZrCl_2 in combination with $HNEt_2$ and excess of $(MeO)_2MeSiH$ (DMMS) for a chemoselective carbonyl reduction (Scheme 40b) [177]. In this case, traces of moisture together with the amine were responsible for the formation of an oxo-bridged dimer [$(Cp_2ZrCl)_2$-μ-O], which was converted to the active Zr-H species by the hydrosilane likely via a classical σ-bond metathesis route. Simple metallocene dihalides are not the only possible precatalysts for reductive reactions. Group 4 cationic amidometallocene complexes **14** were used for hydrosilylation/reductive deoxygenation of carbonyl compounds with Et_3SiH (Scheme 40c), while a $[Cp_2M^{IV}H]^+$ active species was proposed to facilitate this



Scheme 40 (**a**) Zr- or Hf- and Ni-catalysed reductive cross-coupling of alkynes with aryl halides, (**b**) Zr-catalysed carbonyl reduction, and (**c**) catalytic hydrosilylation/deoxygenation of a ketone using cationic amidometallocene complexes

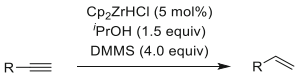


Scheme 41 Reductive reactions using the Schwartz's reagent: (**a**) reduction of isocyanates, (**b**) reduction of azlactones to α-aminoaldehydes, (**c**) reduction/nucleophilic addition to *N*-methoxyamides

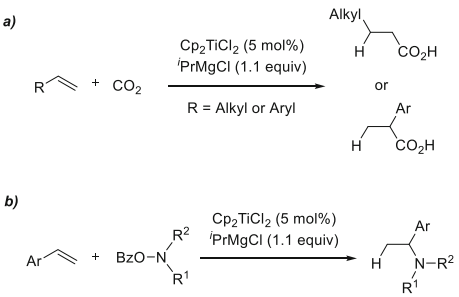
process [178]. The preferred reaction pathway as well as the catalytic activity depended on the central metal.

As evident from the previous examples, the Schwartz's reagent can be used for mild and chemoselective reductions of various carbonyl groups and other moieties by a hydrozirconation mechanism [179]. Such useful stoichiometric reactions include transformations of isocyanates to formamides (Scheme 41a) [180] and azlactones to α-aminoaldehydes (Scheme 41b) [181]. A reduction of *N*-methoxyamides by Cp_2ZrHCl was coupled with a nucleophilic addition (Scheme 41c). The method exhibited excellent tolerance towards various electrophilic functional groups and was successfully applied in natural product synthesis [182].

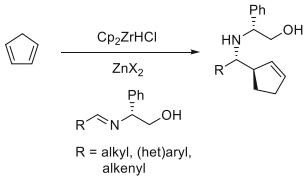
Higher reactivity of the M–H bond (M = Ti, Zr) towards alkynes in comparison with alkenes was repeatedly utilised also for selective hydrogenations of both internal and terminal alkynes into alkenes. A preferential *syn*-insertion of alkynes into the M–H bond could be further promoted by the formation of agostic interactions with the metal, as it was experimentally demonstrated for the products of internal alkyne insertion into the Ti–H bond in the complex Cp^*_2TiH [183]. Recently, a catalytic semi-hydrogenation of various terminal alkynes utilising Cp_2ZrCl_2/DMMS/^{i}PrOH was reported (Scheme 42) [184]. Importantly, the



Scheme 42 Catalytic semi-hydrogenation of terminal alkynes



Scheme 43 (**a**) Titanocene-catalysed hydrocarboxylation of alkenes and (**b**) hydroamination of styrene derivatives with *O*-benzoylhydroxylamines



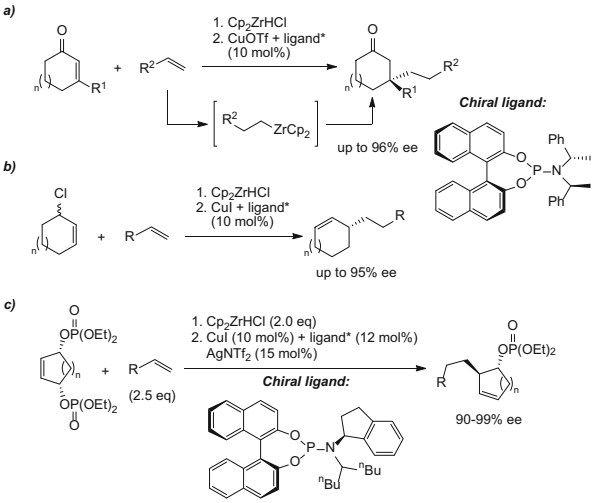
Scheme 44 Zr-mediated diastereoselective allylzincation of chiral imines

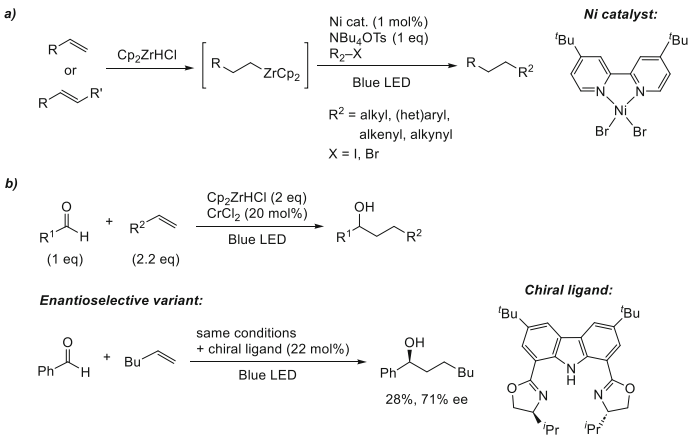
discussed system tolerated many functional groups present in the substrates (hydroxyl, esters, epoxy, amino, nitrile, halido, and sulfido).

Generation of the reactive titanocene hydride species by Grignard reagents is the crucial step in catalytic hydrocarboxylation of alkenes developed by Xi and co-workers (Scheme 43a) [185]. In this protocol, a transient organotitanium intermediate generated by hydrometallation is transmetallated to magnesium and the resulting Grignard species reacts with CO_2. Notably, the reaction proceeds with different regioselectivity depending on the alkene substituent nature. A related catalytic hydroamination of styrene derivatives with *O*-benzoylhydroxylamines was developed later by the same group (Scheme 43b) [186]. This highly regioselective reaction proceeds under same conditions as the previous one with a catalytic amount of Cp_2TiCl_2 and stoichiometric ^{i}PrMgCl.

Transmetallation of organozirconocene reagents to other metals can be beneficial for stereoselective outcome of subsequent reactions as it was exemplified in a diastereoselective allylzincation of chiral imines (Scheme 44) [187]. An important recent application of organozirconiums was coined by Fletcher et al. in a series of contributions describing dynamic kinetic asymmetric transformations based on copper-catalysed C–C bond formations [188]. These reactions are generally capable of converting widely available racemic chiral starting materials into enantiopure products with a near quantitative conversion. An example is the asymmetric conjugate addition of in situ prepared alkylzirconium reagents catalysed by Cu(I) in the

Scheme 45 Dynamic kinetic asymmetric transformations using Cu catalysis: (**a**) asymmetric conjugate addition, (**b**) asymmetric allylic alkylation (AAA) with racemic allyl chlorides, (**c**) desymmetrisation of *meso*-bis(phosphates)



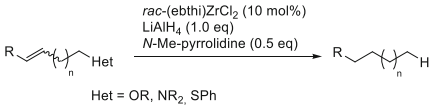


Scheme 46 Visible-light-promoted reactions with organozirconiums: (**a**) Ni-catalysed cross-coupling of alkenes with organohalides, (**b**) Cr-catalysed alkylation of aldehydes

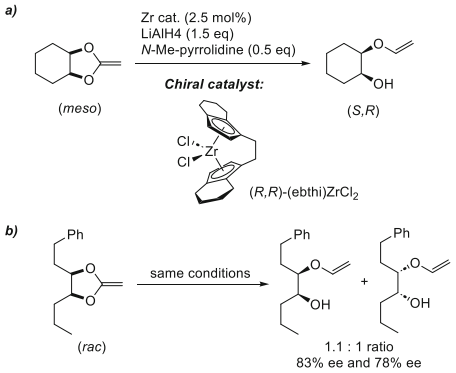
presence of a chiral ligand (Scheme 45a) [189]. Later, an even more attractive asymmetric allylic alkylation with racemic allyl chlorides was introduced (Scheme 45b) [190, 191] and the methodology was then extended also to allylphosphates or bisphosphates (Scheme 45c) [192].

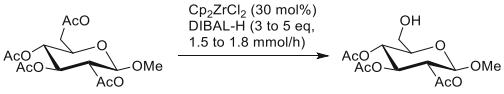
Another interesting feature of organozirconium reagents – their photochemical reactivity – was exploited independently by two research groups. A Ni-catalysed cross-coupling of alkylzirconocenes with organohalides (various alkyl, alkenyl, alkynyl, aryl, heteroaryl) was introduced as a general method of a broad scope, where the irradiation with blue light is responsible for Zr-C homolytic cleavage and formation of organic radicals that are transferred to the Ni catalyst (Scheme 46a)

Scheme 47 Remote defunctionalisation of alkenes



Scheme 48 Asymmetric opening of ketene acetals: (**a**) *meso*-substrate, (**b**) racemic chiral substrate – regiodivergent reactivity





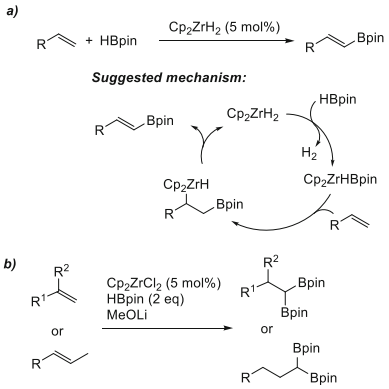
Scheme 49 Selective catalytic deprotection of acetylated carbohydrates

[193]. A similar approach was applied to a Cr-catalysed alkylation of aldehydes with alkenes assisted by a visible-light irradiation (Scheme 46b) [194]. An attempt to perform the reaction enantioselectively was made with promising results. Notably, in both protocols, also internal olefins can be used that readily undergo isomerisation upon hydrozirconation to give exclusively linear products after the cross-coupling.

The hydrozirconation reactivity was utilised also in several defunctionalisation protocols. Streuff et al. reported on a catalytic remote defunctionalisation of alkenes by an in situ generated zirconocene hydride (Scheme 47) [195]. Ether, thioether, or amine groups were removed with an excellent site selectivity by a combination of zirconium chain-walking with a β-heteroatom elimination. The same group described also an enantioselective β-oxygen-elimination, which is a key step in a catalytic asymmetric opening of *meso*-ketene acetals (Scheme 48a) [196]. Using chiral racemic substrates led to a regiodivergent reactivity giving a mixture of enantioenriched regioisomers (Scheme 48b).

The combination of a catalytic amount of Cp_2ZrCl_2 with DIBAL-H was efficient in a site-selective deprotection of peracetylated compounds, typically carbohydrates, as demonstrated by Lecourt and co-workers (Scheme 49) [197]. The reaction proceeds likely via a zirconium-catalysed hydroalumination of carbonyl moieties likely involving bimetallic Zr-Al intermediates.

Reactivity of zirconocene hydrides towards organoboron species is relatively specific and allows formation of many useful organoboron compounds typically



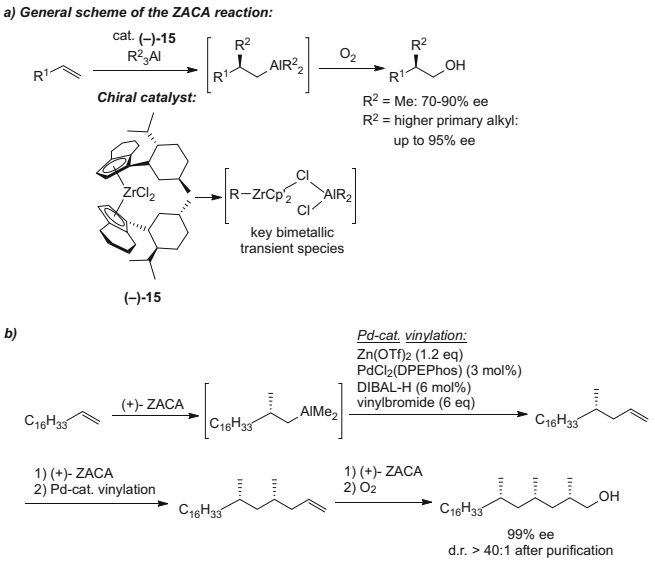
Scheme 50 (**a**) Dehydrogenative borylation of alkenes catalysed by Cp_2ZrH_2, (**b**) Zr-catalysed 1,1-diborylation of terminal or internal alkenes

by metal-mediated hydroboration reactions. This chemistry has been recently reviewed [198] and we will focus on two examples of interesting dehydrogenative borylation reactions introduced by Wu and co-workers. In the first case, terminal alkenes reacted with HBpin under catalysis by Cp_2ZrH_2 leading to a regioselective formation of *E*-alkenyl boronates (Scheme 50a) [199]. The authors proposed insertion of alkene into the Zr–B bond of the [Cp_2Zr(H)Bpin] intermediate as the key step. The methodology was subsequently extended to the preparation of 1,1-diborylalkanes from terminal and internal alkenes and HBpin using Cp_2ZrCl_2/alkali metal methanolates as the catalytic system (Scheme 50b) [200].

Reactions involving a carbozirconation step are also well established. Especially the work of E. Negishi and his group was a landmark in organic chemistry using transition metals [129, 201–203]. Concerning selective catalysis, the Zr-catalysed asymmetric carboalumination protocol (ZACA) is the most relevant example, which is using chiral zirconocene dichlorides (such as **15** in Scheme 51a) to form new C–C bonds in a stereodefined manner. This reaction features a key bimetallic Zr-Al active species, which facilitates the carbometallation process. One of the more recent examples of utility of this approach is depicted in Scheme 51b, showing a convenient stereoselective route to natural products containing the deoxypropionate motif. In this case, a combination of repetitive ZACA reaction with Pd-catalysed vinylation of the intermediate organoaluminium species allowed a facile one-step homologation leading to desired products [204].

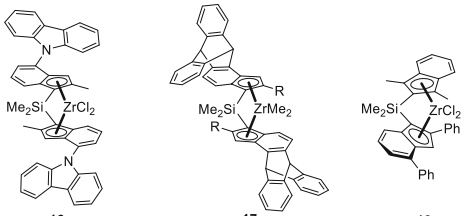
7 Polymerisation Catalysis

Olefin polymerisation catalysis is undoubtedly one of the milestones of early transition metal chemistry and has indeed become a source of great economic success, which stimulated research in this area for several decades [205, 206]. The discovery of homogeneous single-site catalysts, based initially on metallocene complexes, was followed by their subsequent evolution since the 1980s until the



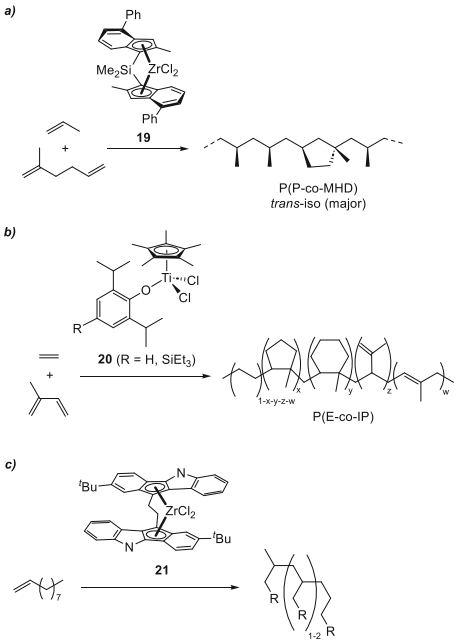
Scheme 51 (**a**) Zirconocene-catalysed asymmetric carboalumination – general scheme, (**b**) application of ZACA to the synthesis of a natural product intermediate

Chart 2 Zirconocene complexes for iPP production at high temperature or for ethylene/α-olefin co-polymerisations



present days [207–212]. It is clearly beyond the scope of this text to cover all the recent developments in this field. However, several examples of recent trends related to the main topic of this contribution – selective reactivity – will be discussed.

In general, the development is focused on modifications of catalytic systems in order to exert control over specific parameters of the polymerisation process, each of which may have significant effect on various physical properties of the resulting polymer. Stereochemical control in the polymerisation of propylene and other higher olefin monomers is one of the key factors [213]. Tailored zirconocene complexes, often with *ansa*-bridged Cp and larger polyaromatic ligands dominate this area. Voskoboynikov, Cipullo, Ehm, Uborsky, and co-workers developed highly selective catalysts with *ansa*-bis(indenyl)-derived ligands for isotactic PP production at high temperatures (**16** and **17** in Chart 2) [214–216]. These studies were also aided by high-throughput methods of catalytic screening [217, 218]. In addition, recent theoretical studies are increasingly precise in the description of quantitative

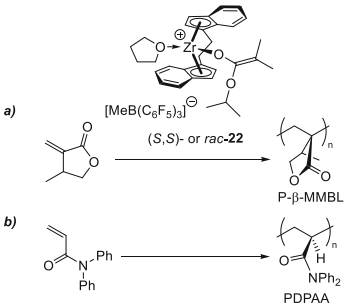


Scheme 52 Co-polymerisation or oligomerisation of various co-monomers. (**a**) Propylene and 2-methyl-1,5-hexadiene, (**b**) ethylene with isoprene, (**c**) linear α-olefin oligomerisation

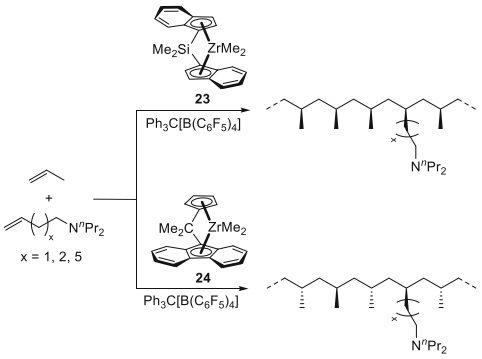
parameters influencing the catalyst performance and in explaining or predicting reaction pathways [219–222]. Other types of zirconocenes, such as those with *ansa*-bridged 1- and 2-indenyl ligands (**18**), were successfully used for ethylene/α-olefin copolymerisation with a high co-monomer incorporation (Chart 2) [223]. Utilisation of different co-monomers was studied by several groups, for example in the case of propylene and 2-methyl-1,5-hexadiene co-polymerisation, which led to the occurrence of cycloalkane units in the polymer with perfect *trans*-stereoselectivity (Scheme 52a) [224]. Preparation of ethylene copolymers with isoprene with superior properties compared to previously known systems was reported by Nomura and co-workers [225]. In this case, half-sandwich Ti complexes (**20** in Scheme 52b) were employed and polymers with a high content of cycloalkane units were obtained. Nifant'ev et al. focused on an efficient preparation of low viscosity oils based on linear α-olefin oligomers using various *ansa*-zirconocene catalysts [226–228]. One of the best performing catalysts for this purpose turned out to be the ethylene-bridged *ansa*-complexes containing fused *N*-heterocyclic ligands (**21**), giving the highest yields of the most valuable trimer and tetramer fractions of 1-decene (Scheme 52c).

A growing importance of a precise preparation of macromolecules with defined properties and of adding a functionality to simple polyolefin materials stimulated a significant research effort. Various functional polar monomers became a desirable feedstock for polymerisation catalysis [229–231]. The question of stereoselectivity in zirconocene-catalysed coordination polymerisation of methylene butyrolactones as a renewable monomer feedstock was studied by Chen et al., who described a

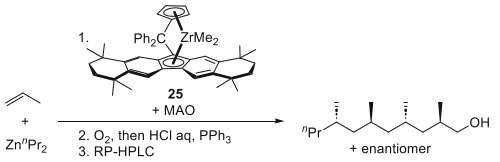
Scheme 53 Chiral zirconocene-catalysed polymerisation of polar monomers: (**a**) methylene butyrolactones, (**b**) diphenyl acrylamide



Scheme 54 Co-polymerisation of propylene and aminoolefins



Scheme 55 Syndiospecific propylene oligomerisation for the preparation of chiral natural compounds



dependence of the selectivity on the particular catalyst structure as well as the structure of the employed monomer (Scheme 53a) [232]. The scope of polar vinyl monomers was further studied and using an optically pure chiral *ansa*-zirconocene **22**, enantioselective polymerisation of diphenyl acrylamide (DPAA) was achieved (Scheme 53b) [233]. The same methodology was also utilised for the preparation of more complex brush-type polymeric architectures intended for photovoltaic applications [234]. A co-polymerisation of propylene and aminoolefins was reported by Marks et al. to proceed without any masking reagents in a highly stereospecific manner, either using *syndio*- or *iso*-specific *ansa*-zirconocene catalysts (**23** and **24**, respectively, Scheme 54) [235].

An interesting overlap of the industrially important polymerisation of olefins with natural products synthesis was demonstrated by Nozaki et al. in the preparation of a chiral alcohol with the deoxypropionate motif by syndiospecific propylene oligomerisation using an *ansa*-zirconocene catalyst **25** (Scheme 55) [236].

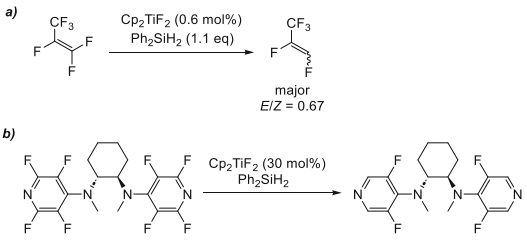
Another important aspect of polymerisation catalysis is the possibility of heterogenisation of well-defined molecular single-site catalysts onto solid supports [237, 238]. As an interesting contribution to this topic, Marks et al. reported a surface-bound $[Cp^*ZrMe_2]^+$ active centre on sulphated alumina capable of isotactic polypropylene and poly-1-hexene production [239].

8 Miscellaneous Reactions

The last part of this chapter contains several examples of selective transformations involving group 4 metallocene complexes, which do not fit into the previous sections. An important example is the dehalogenative catalysis by group 4 metallocene complexes, which can proceed via several possible reaction mechanisms [240, 241]. Titanocene(III) hydride was proposed as an active species by Lentz et al. when generated by the reaction of Cp_2TiF_2 with Ph_2SiH_2. This system catalysed preferably defluorination of sp^2-C–F bonds in hexafluoropropene and other vinylic and allylic C–F bonds (Scheme 56a) [242, 243]. The possible involvement of both the insertion/elimination and σ-bond metathesis of the Ti–H bond was proposed. Application of the same methodology for a selective removal of heteroaromatic C–F bonds in pyridine derivatives was reported later (Scheme 56b) [244].

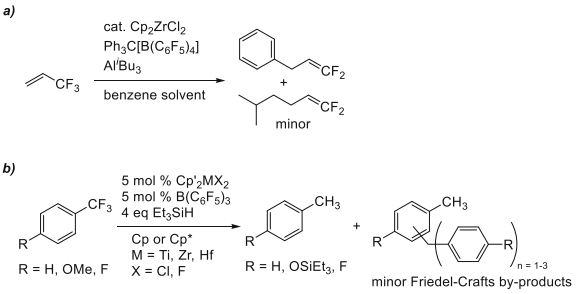
Defluorination of 3,3,3-trifluoropropene was studied by Rieger et al. using a cationic zirconocene catalyst generated from Cp_2ZrCl_2 by a combination of trityl borate and Al, a commonly used activator in polymerisation catalysis [245]. The alkyl aluminium species is used in excess and serves also as an acceptor for the fluorine atom. Importantly, in the presence of benzene, the intermediate carbocation performs a Friedel-Crafts alkylation of the aromatic system (Scheme 57a). A series of group 4 metallocene complexes were studied in catalytic dehalogenations of trifluorotoluenes using the $Et_3SiH/B(C_6F_5)_3$ system for the active cationic species generation [246]. Aliphatic C–F bonds were efficiently converted, while the aromatic bonds remained intact (Scheme 57b). Interestingly, the formation of Friedel-Crafts products was suppressed using the titanocene catalysis.

In contrast to the previous study, Crimmin et al. obtained a preferential removal of aromatic C–F bonds in the presence of a CF_3 group with a catalytic system based

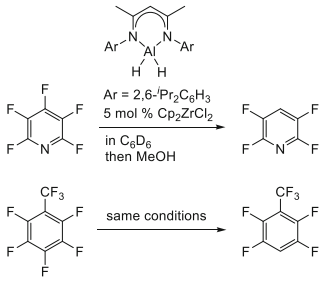


Scheme 56 Ti-catalysed defluorination with Ph_2SiH_2

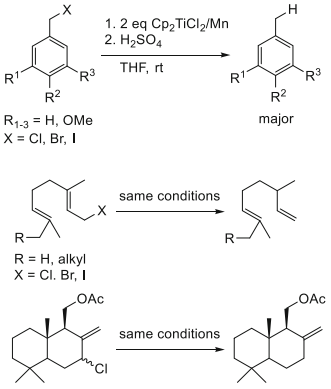
Scheme 57 Group 4 metallocene-catalysed defluorinations



Scheme 58 Removal of aromatic C–F bonds by aluminium hydride complexes under Zr catalysis



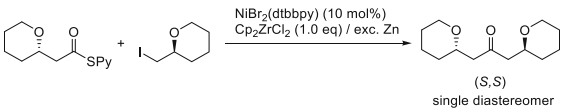
Scheme 59 Ti-mediated reductive dehalogenation



on Cp_2ZrCl_2 and a stoichiometric aluminium hydride complex with a β-diketiminate ligand (Scheme 58) [247].

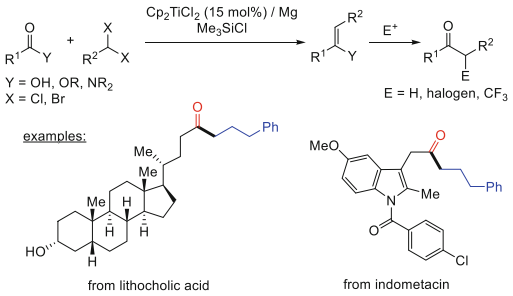
A mechanistically different approach using a stoichiometric amount of Cp_2TiCl_2 under reducing conditions led to the development of a versatile reductive dehalogenation protocol for a range of benzyl-, allyl-, and even primary alkyl halides with a good functional group tolerance (Scheme 59) [248].

A one-pot method for ketone synthesis from alkyl iodide and a thiopyridine ester was reported by Kishi et al. using a Zr/Ni-mediated protocol [249]. A dual role of the reduced zirconocene is expected in the activation of both substrates, which is followed by a transmetallation to Ni. The method is tolerant to functional groups and proceeds stereoselectively (Scheme 60).

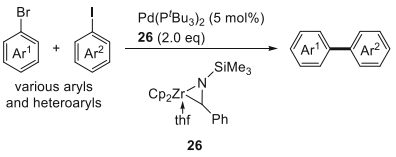


Scheme 60 Zr-mediated Ni-catalysed diastereoselective ketone synthesis

Scheme 61 Titanocene-catalysed ketone synthesis from carboxylic derivatives



Scheme 62 Pd-catalysed Zr-mediated cross-selective coupling of aryl halides



Yet, another modular protocol for the synthesis of ketones from carboxylic derivatives and *gem*-dihaloalkanes was recently described by Wang and co-workers [250]. These reactions are catalysed by Cp_2TiCl_2/Mg, which is supposed to give in situ the divalent titanocene, likely interacting with the *gem*-dihalide to produce an alkylidene complex or a binuclear species, which then reacts with the carbonyl substrate. The released titanocene oxo-species is regenerated by Me_3SiCl and enters again the catalytic cycle. The method can convert widely available carboxylic acids, esters, lactones, or amides and can be used for a range of functionalised molecules (Scheme 61).

A cross-selective electrophile coupling of (hetero)aryl halides combining Pd catalysis with a zirconocene-mediated reductive transmetallation step was described as a highly versatile method for the preparation of biaryl molecules [251]. A zirconaaziridine complex **26** is used as a redox shuttle, which is responsible for a high selectivity towards the heterocoupling products (Scheme 62).

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Naturally Occurring Cyclopentadienes and Cyclopentadienyl Anions

Josef Hájíček, David Nečas, and Martin Kotora

Contents

Abstract The history of cyclopentdienyl complexes (or cyclopentadienyl salts) has been spanning already for more then 70 years and they have been always considered as typical representatives of truly manmade molecules. Although compounds possessing the cyclopentadiene scaffold have been isolated and characterized, those possessing the cyclopentadienyl anion have been avoiding discovery for a long period of time. Nonetheless, since the isolation of juglorubin in 1993, the family of naturally occurring compounds possessing the cyclopentadienyl anion is steadily growing. This review aims to give an overview of the current state of the art in this area.

Keywords Cyclopentadiene · Cyclopentadienyl anion · Natural compounds · Synthesis

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1 Introduction

The discovery of ferrocene in 1951 [1], cyclopentadienyl (Cp) or pentamethylcyclopentadienyl (Cp*) anions, opened a pathway to a new class of anionic ancillary ligands for a broad range of various transition metals [2]. There have been several reasons for such a situation. First, the robust nature of the metal complexes expressed by oxidation stability and ligand non-transferability stimulated their application in the field of catalysis. Comparatively easy synthesis of chiral cyclopentadienyl ligands [3, 4] and their exploitation in enantioselective synthesis is a second reason. Given the long history of cyclopentadienyl complexes (or cyclopentadienyl salts) that has been spanning already for almost 70 years, these compounds have been always considered as typical examples of truly man-made molecules. Or are they? Although it is quite reasonable to assume that compounds possessing the cyclopentadiene scaffold might exist in nature, the same question regarding cyclopentadienyl anions (salts) sounds rather provocative and challenging. Yet, against all the odds, these intriguing compounds have been found, isolated, fully characterized and some of them even synthesized in the last two decades. The aim of this rather short review, because of few and far between examples, is to give an overview of the current state of the art in this area. Note that natural diazocyclopentadienes are treated in a separate chapter under the name kinamycins.

2 Natural Compounds with Cyclopentadiene or Cyclopentadienyl Anion Scaffold

The first-ever isolated compound possessing the cyclopentadienyl anion moiety was juglorubin (Fig. 1). It was isolated by Lackner et al. in 1993 from cultures of *Streptomyces spp.* [5, 6] and exists in the form of its sodium salt. Its unusual structure bearing benzindenylid-quinone scaffold was elucidated by using NMR techniques and confirmed by a single crystal X-ray diffraction analysis of its derivative. It confirmed the existence of the planar pentasubstituted cyclopentadienyl anion fragment having C–C bond lengths very similar (1.42 ± 0.08 Å). The metabolite shows orange-red fluorescence.

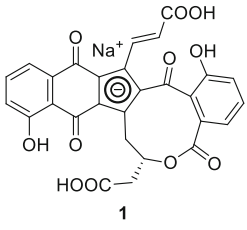

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Fig. 1 Structure of juglorubin (**1**)

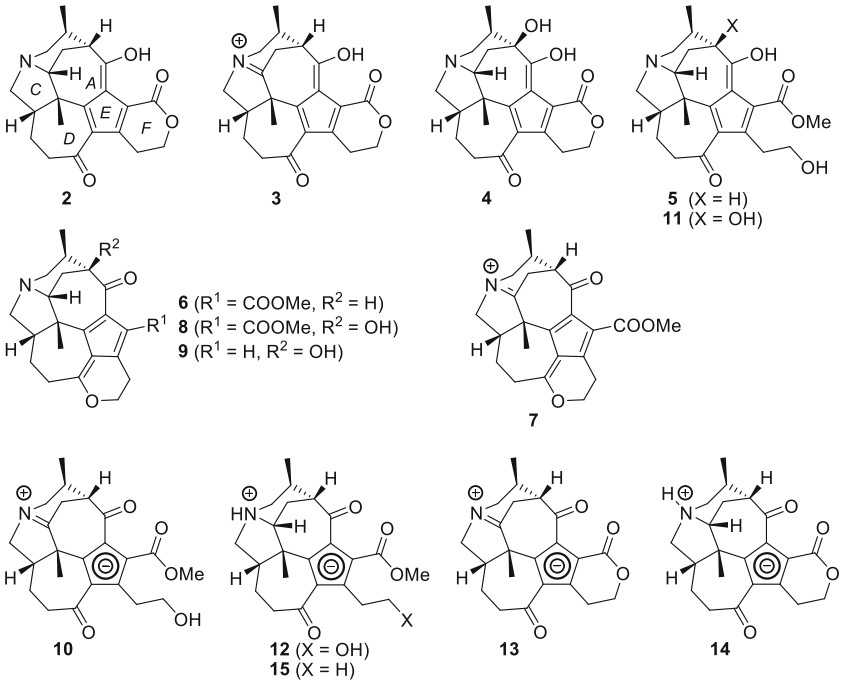


Fig. 2 *Daphniphyllum* alkaloids of the daphnicyclidin type

By far the richest source of natural compounds featuring cyclopentadiene and/or cyclopentadienyl anion moiety are two related skeleton types (Fig. 2) from the alkaloid-rich evergreen trees and shrubs of the genus *Daphniphyllum*, which are native to central and southern Japan [7–10]. The first members were reported in 2001 by Kobayashi et al. [11] from the stems of *Daphniphyllum humil*e and *D. teijsmanni* and belonged to a group of daphnicyclidins, alkaloids with unprecedented fused hexa- and pentacyclic skeletons. Owing to the presence of the enolizable carbonyl group attached to the cyclopentadiene moiety, daphnicyclidins A (**2**), B (**3**), C (**4**), and H (**5**) exist as enol tautomers and hence have conjugated π-system of three double bonds with the fulvene framework. However, tautomerization is in principle possible to pentasubstituted cyclopentadienes/fulvenes. The structure of daphnicyclidin A (**2**) was confirmed by using a single crystal X-ray diffraction analysis. Other members of the group such as daphnicyclidins D (**6**), E (**7**), F (**8**), and G (**9**) cannot undergo tautomerization and exist as fulvenes due to their structural features.

Five years later, in 2006 Guo et al. reported on isolation of macropodumine B (**10**) and C (**11**) from the stems of *Daphniphyllum macropodum* [12]. Structural analysis of the former revealed this compound to be intramolecular iminium salt (zwitterion) possessing the cyclopentadienyl anion. Its structure was confirmed by a single crystal X-ray diffraction analysis. The C–C bond lengths in the

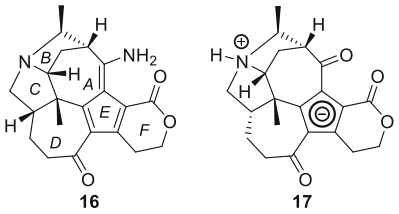


Fig. 3 *Daphniphyllum* alkaloids of the daphnipaxinin type

cyclopentadienylium anion are all very similar (1.417 ± 0.023 Å) providing clear-cut evidence for the presence of the cyclopentadienyl anion. On the other hand, the latter, macropodumine C (**11**), was in its enol form and is the 2β-hydroxy derivative of daphnicyclidin H (**5**).

In the same year Hu et al. reported isolation and characterization of daphnicyclidin L (**12**). It is also an internal salt, but ammonium one in this instance (wrongly claimed to be the iminium salt in the original paper) [13]. Once again, its structural elucidation including a single-crystal X-ray diffraction analysis revealed the presence of the pentasubstituted cyclopentadienyl anion. Daphnicyclidin L must be an internal salt of daphnicyclidin H (**5**) taking into the account their identical structural features. In 2013, Hao et al. reported isolation of another two intramolecular salts possessing the cyclopentadienyl anion: daphmacrodins A (**13**) and B (**14**). They were isolated from *Daphniphyllum macropodum* [14]. The former is an iminium salt whereas the latter is an ammonium one. The latest entry into isolation and characterization of naturally occurring cyclopentadienyl anion alkaloids was done by Zhang in 2018, who obtained [15] daphnicyclidin M (**15**), a desoxy analogue of daphnicyclidin L (**12**), from the stems and leaves of *D. paxianum*. This caused rather confusing situation in that the same name, daphnicyclidin M was given [16] already in 2014 to an alkaloid with different skeleton from *D. macropodum*.

Daphnipaxinin (**16**), the first representative of the eponymous sub-group, and also the first-ever *Daphniphyllum* alkaloid featuring two nitrogen atoms, was reported [17] in 2004 from the stems of *D. paxianum* (Fig. 3). It features the 5-membered ring *B* which is believed to originate from the piperidine ring *B* of daphnicyclidin skeleton by an oxidative (Hofmann-type) degradation. Further investigation of *Daphniphyllum* plants alkaloid composition resulted in a discovery of a new intramolecular salt possessing the cyclopentadienyl anion in 2008 by Hao et al. [18] Oldhamine A (**17**), an inner ammonium salt, was isolated from the dried twigs of *D. oldhamii*. X-ray diffraction analysis revealed very similar C–C bond lengths of the cyclopentadienyl fragment (1.424 ± 0.026 Å) confirming its anionic character. It was also demonstrated that the inter-conversion between the conjugated cyclopentadiene moiety and the cyclopentadienyl anion can be conducted in a pH dependent chemical environment.

Artabsin (**17**), a sesquiterpenoid lactone (Fig. 4), was isolated in 1953 from wormwood *Artemisia absinthium* [19]; its correct structure (without stereochemistry) [20], the correct stereochemistry except C-10 [21], and absolute configuration were reported later [22]. Achillicin, the major proazulene (prochamazulene) of

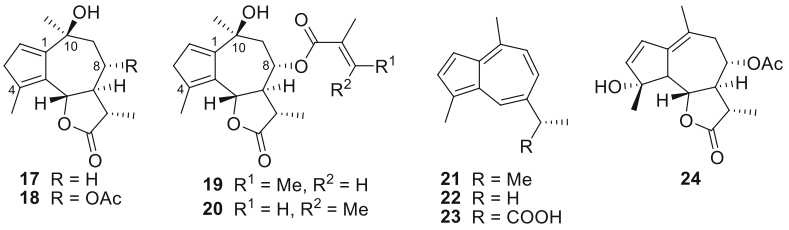


Fig. 4 Naturally occurring sesquiterpenic cyclopentadienes

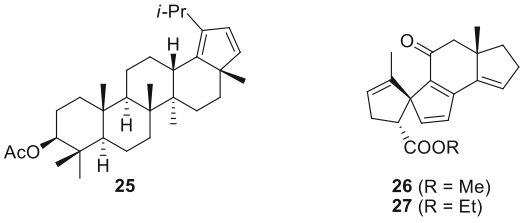
yarrow *Achillea millefolium* ssp. *Collina*, was first isolated in 1979 and its structure determined as 10-*epi*-**18** on the basis of spectral arguments [23]. The stereochemistry was finally corrected as 8α-acetoxyartabsin (**18**) on the basis of 2D-NMR experiments [24]. Further two acyloxy derivatives were isolated from the same plant source [25]; their absolute configuration was finally fixed as 8α-tigloyloxyartabsin (**19**) and 8α-angeloxyartabsin (**20**), respectively, based on the same NMR arguments as with **18** [24].

Note that azulenic compounds, like guaiazulene (**21**), and the long-known chamazulene (**22**) [26, 27], that is produced, probably via chamazulene carboxylic acid (**23**), by processing of chamomile blossoms from another sesquiterpenoid lactone matricine (**24**) [26], are not included in this article.

3 Other Cyclopentadienes

Another class of naturally occurring cyclopentadienes are compounds bearing the geminal substituted carbon atom within the cyclopentadiene moiety and hence cannot form the corresponding cyclopentadienyl anions (Fig. 5). Two examples of such compounds were reported. The first example is lupa-18,21-dien-3ß-yl acetate (**25**) that has been isolated from the dried roots of *Taraxacum officinale* (dandelion) [28]. Other examples are urceoloids A (**26**) and B (**27**) that were isolated from dried powder of the plant *Urceola quintaretii* [29].

Fig. 5 Naturally occurring compounds possessing the geminally substituted carbon atom within the cyclopentadiene fragment



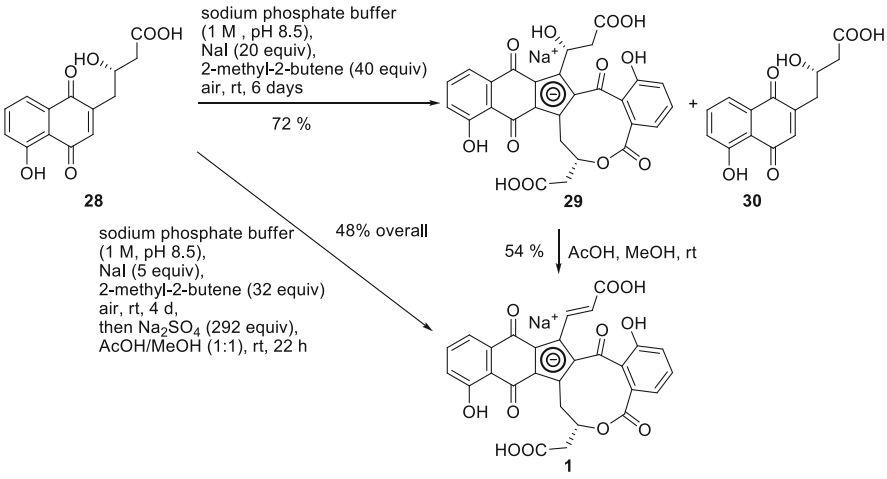
4 Syntheses of Compounds Possessing the Cyclopentadiene Fragment

4.1 Total Syntheses

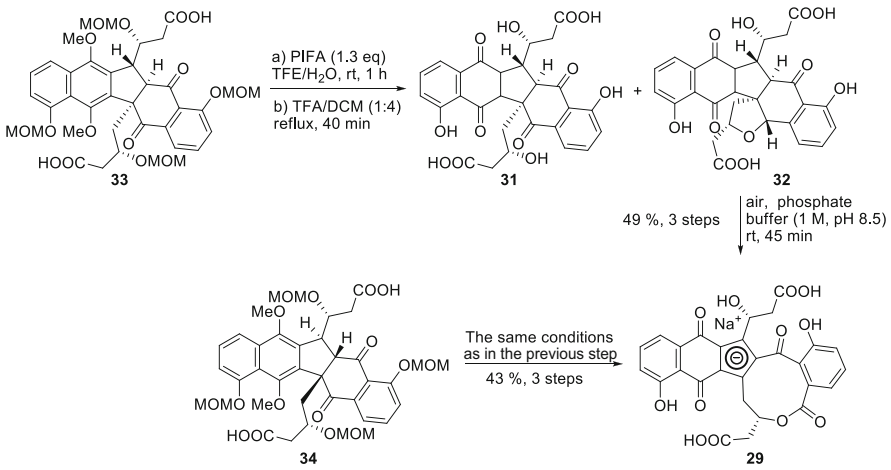
Attempts at syntheses of the previously mentioned compounds are rather scarce, which is not so surprising taking into account their complex molecular structures. Only recently, an elegant total synthesis of juglorubin (**1**) has been accomplished [30] by Kuramochi et al. from juglomycin C (**28**) (Scheme 1). The route was inspired by a biogenetic proposal of Lackner [5, 6]. Thus, a dimerization of juglomycin C (**28**) under aerobic condition provided **29** (43%) together with **30** (41%), which is also natural compound juglomycin D [31]. However, in the presence of hydrogen peroxide scavengers (NaI and 2-methyl-2-butene) a yield of crucial intermediate **29** as high as 72% could be achieved, whose dehydration then afforded juglorubin (**1**). One pot variant of the process provided 48% yield of the target molecule.

Juglocombins A (**31**) and B (**32**) were obtained as an equilibrium mixture from **33** by total synthesis [32], and subjected to the above-described aerobic dimerization conditions (Scheme 2) [30]. It afforded the compound **29** in 49% yield, supporting thus the postulated intermediacy [5, 6] of **31** and **32** in biogenesis of juglorubin. The process involved a fragmentation in **32** facilitated by a stabilization of the cyclopentadienyl anion by the three adjacent carbonyl groups. Later on, Kuramochi et al. have shown [33] that diastereoisomeric diacid **34** is also transformable into lactone **29**.

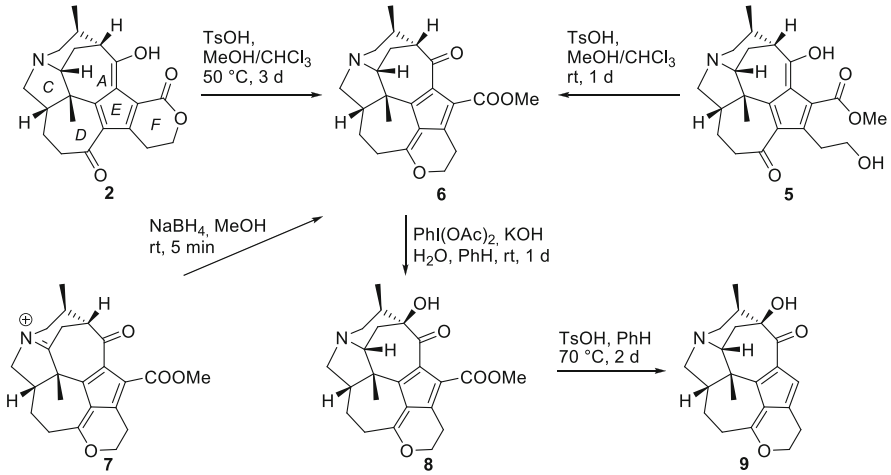
Synthetic endeavours in the field of daphnicyclidin type of *Daphniphyllum* alkaloids are currently at the stage of model studies, a fact not surprising given by the alkaloid complexity [7–10]. At first, transformations within the alkaloids are



Scheme 1 Biomimetic synthesis of juglorubin (**1**) from juglomycin C (**28**)



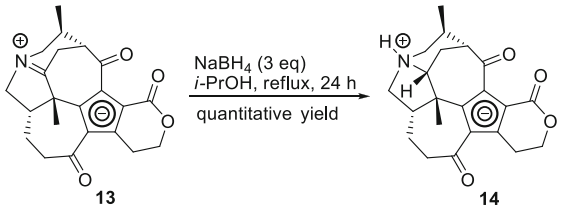
Scheme 2 Synthesis of intermediate **29** by Kuramochi



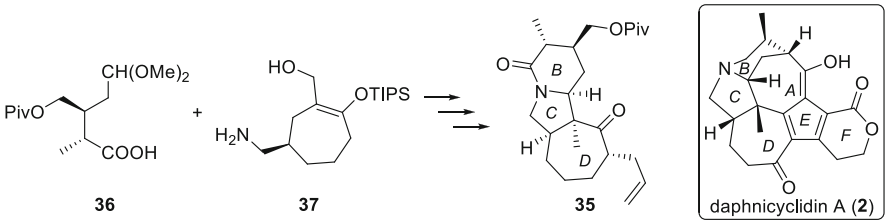
Scheme 3 Interconversions of alkaloids within the daphnicyclidin group

shown [11] here that originally served in structure elucidation, but can also be seen as partial syntheses (Scheme 3). Both daphnicyclidin A (**2**) and daphnicyclidin H (**5**) afford by a treatment with tosylic acid daphnicyclidin D (**6**), which indicates higher stability of the latter fulvene. Daphnicyclidin D (**6**) leads by hydroxylation with iodosobenzene diacetate to daphnicyclidin F (**8**), which can be decarboxylated further into daphnicyclidin G (**9**) with tosylic acid at elevated temperature. On the other hand, reduction of the iminium moiety in daphnicyclidin E (**7**) with sodium borohydride gives daphnicyclidin D (**6**).

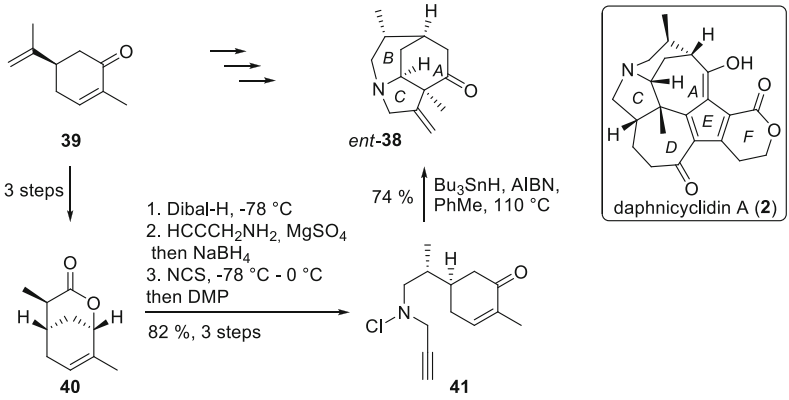
Likewise, daphmacrodin A (**13**) was transformed to daphmacrodin B (**14**) by $NaBH_4$ reduction of the iminium moiety (Scheme 4) [14].



Scheme 4 Reduction of daphmacrodin A (**13**) to daphmacrodin B (**14**)



Scheme 5 Synthesis of *ent*-BCD fragment **35** of daphnicyclidin A (**2**) by Iwabuchi

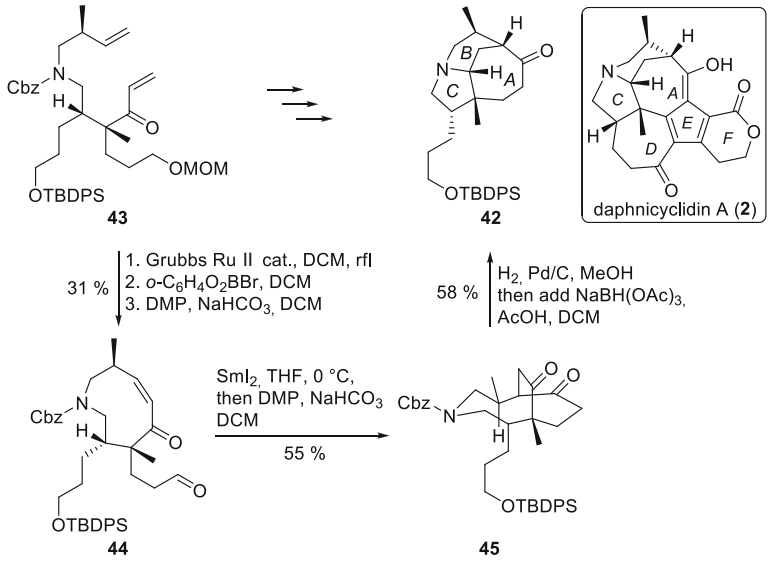


Scheme 6 Synthesis of *ent*-ABC ring model **38** by Stockdill

4.2 Model Studies

Iwabuchi et al. have described [34] in 2009 a synthesis of BCD fragment **35** with the opposite configuration as compared with daphnicyclidin A (**2**) (Scheme 5). The compound was secured in five steps from intermediary acid **36** and amine **37**, themselves prepared from *D*-mannitol and cycloheptanone, respectively.

Stockdill et al. have reported [35] on synthesis of a tricyclic compound **38**, possible intermediate for synthesis of *ent*-daphnicyclidin A (**2**) and other *Daphniphyllum* alkaloids (Scheme 6). (−)-(*R*)-Carvone (**39**) was converted in



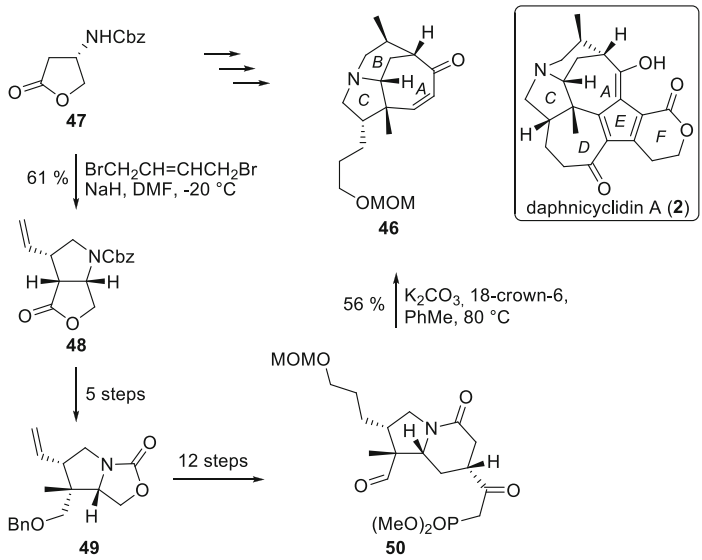
Scheme 7 Synthesis of ABC ring model **42** by Williams

three steps into bicyclic lactone **40** and then, in another 3 steps, into *N*-chloro propargylamine **41** in 82% yield over 3 steps. After some experimentation, crucial radical cascade cyclization, triggered by aminyl radical, was shown to be best induced by Bu_3SnH/AIBN, which at reflux in toluene provided tricycle *ent*-**29** in a yield as high as 74%.

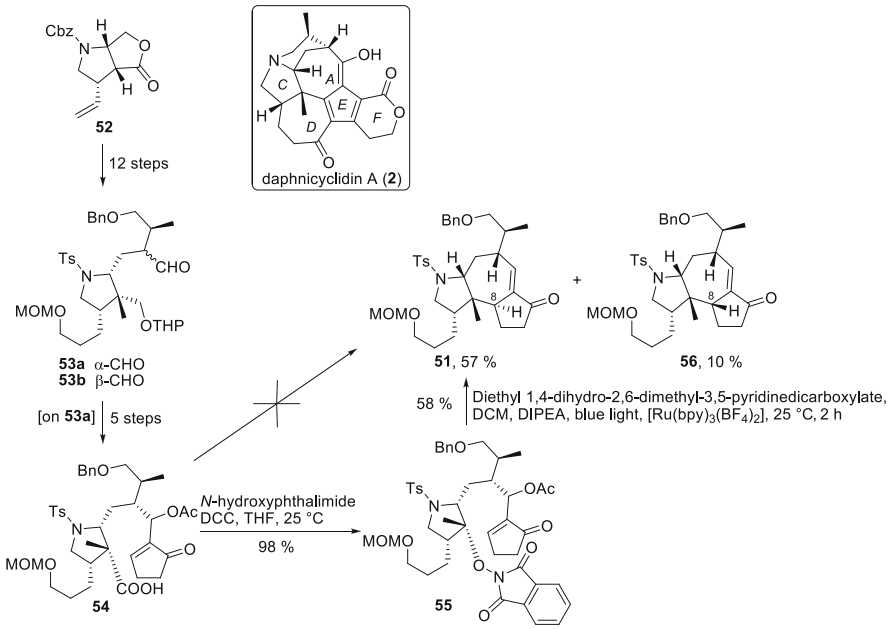
Williams et al. have described [36] an enantioselective synthesis of tricyclic ABC fragment **42**. Scheme 7 shows just final stages of the route: The advanced intermediate **43** was converted in three steps including RCM into an unusual (*Z*)-azocine **44** which afforded by a treatment with samarium iodide followed by oxidation with DMP the bicyclic dione **45**. Hydrogenolysis of Cbz derivative set the stage for the final reductive amination with $NaBH(OAc)_3$ to give the target tricycle **42**.

Yang et al. have reported [37] on enantioselective synthesis of tricyclic fragment **46**, a close relative of compound **42** (Scheme 8). The synthesis started with alkylation of (*S*)-butyrolactone **47** with *trans*-1,4-dibromo-2-butene (NaH in DMF); the reaction run on 50 g-scale afforded stereoselectively the *cis*,*cis*-bicycle **48** in 61% yield. Compound **48** was transformed into phosphonate **50** via bicyclic oxazolidinone **49**. Finally, intramolecular Horner-Wadsworth-Emmons reaction induced a closure of cycloheptenone ring in **50** to give the target molecule **46**.

Synthesis of a tricyclic compound **51**, representing a CAE model of daphnicyclidin A (**2**), was recently reported by Yang et al. [38] (Scheme 9). Bicycle **52** was converted in 12 steps into epimeric mixture of aldehydes; fortunately, unwanted epimer **53b** could be recycled by base epimerization. The desired aldehyde **53a** then afforded in 5 steps the carboxylic acid **54**, which failed to undergo decarboxylation/radical conjugate addition using McMillan's condition with iridium



Scheme 8 Synthesis of ABC ring model **46** by Yang

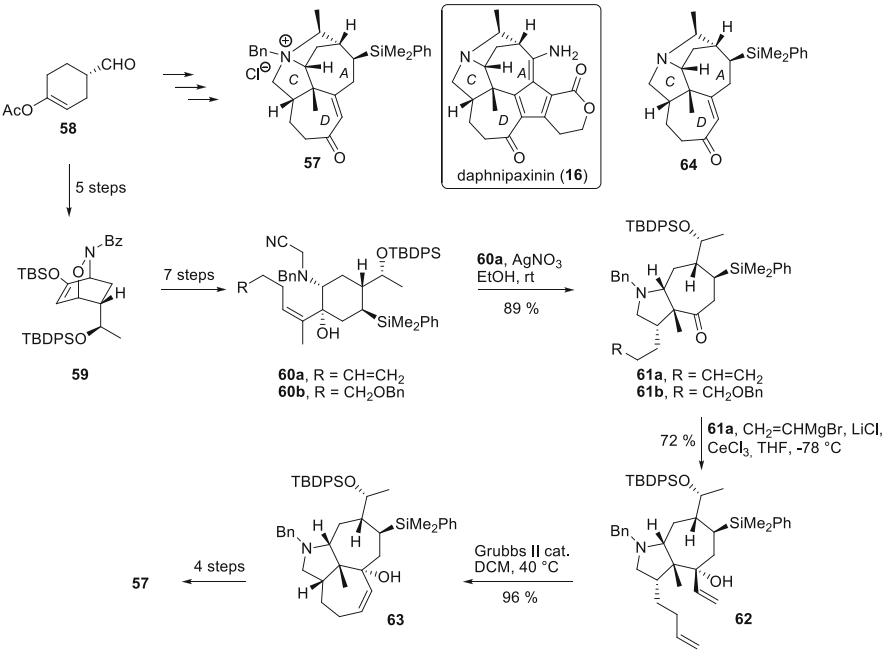


Scheme 9 Synthesis of an advanced CAE model **53** by Yang

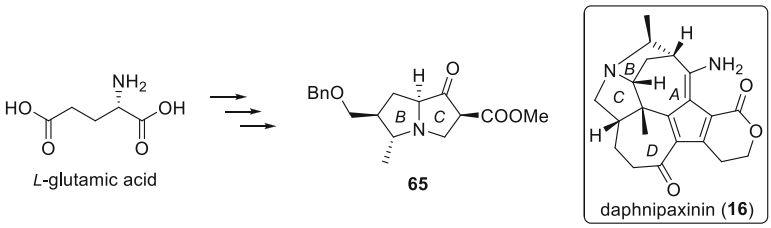
catalyst [Ir(dF(CF_3)ppy)$_2$(dtbbpy)PF_6]. However, the corresponding phthalimido ester **55** when subjected to Overman's procedure ([Ru(bpy)$_3$](BF_4)$_2$ as catalyst, diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate as photoelectron transfer agent, DIPEA as a base, irradiation by blue light) gave rise to tricycle **51** (57%) and 8-epimer **56** (10%).

Overman et al. were the first to report on synthesis of daphnipaxinin type skeleton of *Daphniphyllum* alkaloids [39]. They published a synthesis of advanced ABCD fragment **57** (and **64**) containing all of the stereocenters of the alkaloid **16** (Scheme 10). The route started with the preparation of (*S*)-aldehyde **58** (91% ee) by organocatalytic [4 + 2] cycloaddition of acrolein to 2-acetoxybutadiene. The conversion of **58** into **60** in 12 steps set the stage for the crucial cascade transformation: exposure of cyanoamine **60a** to silver nitrate released an iminium and thus triggered [3,3]-azonia-Cope rearrangement followed by an immediate transannular Mannich reaction. The AC bicycle **61a**, which was obtained as a single stereoisomer in 89% yield, was then transformed into the target tetracycle **57** by a six-step process which involved a closure of the ring D by RCM (**62** → **63**). Likewise, tetracycle **64** was secured from the bicycle **61b**.

Another report by Trauner et al. encompassed enantioselective synthesis of the bicyclic pyrrolizidine moiety **65** [40], which represents structural *ent*-BC fragment of daphnipaxinin (**16**), from a simple starting material (glutamic acid) (Scheme 11).



Scheme 10 Synthesis of the advanced ABCD fragment **57** (and **64**) of daphnipaxinin (**16**) by Overman



Scheme 11 Synthesis of the *ent*-pyrrolizidine BC fragment **65** of daphnipaxinin by Trauner

5 Summary

During the past approximately 30 years, several natural compounds possessing the cyclopentadiene and/or cyclopentadienyl anion fragments have been isolated from different natural sources. Especially in the latter case, the use of various spectroscopic techniques provided clear-cut evidence that cyclopentadienyl anion really does exist in nature. The results collected so far indicate, on the one hand, that search for elusive compounds with "unusual structures" makes sense and could be fruitful. On the other hand, at the same time it indicates that such compounds are rare and it is difficult to predict where to look for them. In this respect, any success is the result of hard work, perseverance and, without any doubt, a great deal of luck. Despite that this area is young we can surely anticipate future significant findings and isolation of new natural compounds.

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Naturally Occurring Diazofluorenes

Josef Hájíček and Martin Kotora

Contents

Abstract The chapter deals with yet another type of natural compounds incorporating diazo cyclopentadienyl moiety. Natural diazofluorenes involving monomeric kinamycins as well as dimeric lomaiviticins count a few dozen members only, yet their stucture elucidation and synthesis reads like a thriller. Significant structure corrections that were enforced by discrepancies in properties of the natural and synthesized compounds have had a great impact on their total synthesis. This review covers the synthesis of the compounds in the period 2011–2021.

Keywords Diazofluorene · Kinamycin · Lomaiviticin · Natural compounds · Total synthesis

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1 Introduction

It was not before 1994 that diazo-compounds were recognized as natural products. Bacterial metabolites that contain in the skeleton the diazocyclopentadiene moiety (**1**), Fig. 1, are often referred to as the diazo-fluorenes or -tetrahydrobenzo[b] fluorenes. Complex molecules with the tetracyclic framework of the general formula **2** exist both as monomeric and dimeric and feature powerful antimicrobial and anticancer activities.

The metabolites were repeatedly reviewed [1–4], this overview covers the synthesis of the compounds in the period 2011–2021 and can thus be considered as an update of the last major review [5].

2 Isolation of Natural Products

2.1 Monomeric Natural Compounds

The first isolated compounds possessing the diazotetrahydrofluorene moiety were kinamycins A–D, isolated in the early 1970s from the strain of *Streptomyces murayamaensis* [6–9], Fig. 2. The metabolites were originally believed to be cyclic

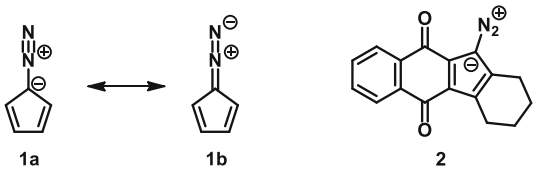
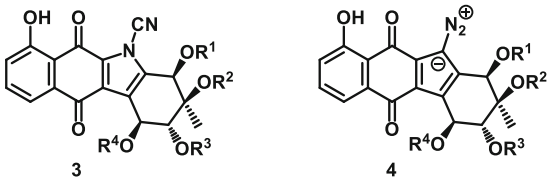
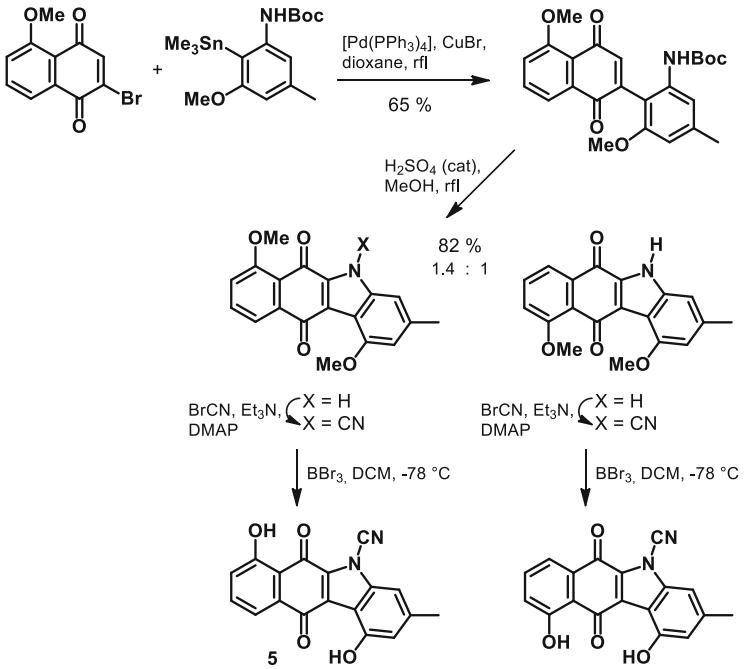


Fig. 1 Structural features of diazofluorene metabolites



a Kinamycin A $R^1 = H, R^2 = R^3 = R^4 = H$
b Kinamycin B $R^1 = R^3 = R^4 = H, R^2 = Ac$
c Kinamycin C $R^1 = R^3 = R^4 = Ac, R^2 = H$
d Kinamycin D $R^1 = R^3 = Ac, R^2 = R^4 = H$
e Kinamycin E $R^1 = Ac, R^2 = R^3 = R^4 = H$
f Kinamycin F $R^1 = R^2 = R^3 = R^4 = H$
g Kinamycin G $R^1 = R^3 = R^4 = Ac, R^2 = CO$*i*-Pr
h Kinamycin H $R^1 = CO$*i*-Pr, $R^2 = H, R^3 = R^4 = Ac$
i Kinamycin I $R^1 = R^3 = CO$*i*-Pr, $R^2 = H, R^4 = Ac$
j Kinamycin J $R^1 = R^2 = R^3 = R^4 = Ac$

Fig. 2 Original **3** and revised **4** structure of kinamycins A–J



Scheme 1 Synthesis of the cyanamide **5** by Echavarren

cyanocarbazoles **3**; the studies included an X-ray analysis of kinamycin C *p*-bromobenzoate, which established absolute stereochemistry [10]. However, during years, uncertainties about the structures have been increasing, including the total synthesis of prekinamycin, the NMR spectra of which were considerably different from those of the natural product (vide infra) [11]. There had to pass more than two decades from the original isolation until Gould [12] and Dmitrienko [13] independently revised structures as the diazotetrahydrofluorenes **4** on the basis of both the spectral and the synthetic arguments, Fig. 2.

Prekinamycin, itself a biosynthetic intermediate to kinamycins, was isolated from *S. murayamaensis* and originally formulated as cyanocarbazole **5** [14]. The compound was synthesized as illustrated in Scheme 15 and shown to be different from the natural product [11], (see also [12]) (Scheme 1).

Among others, considerable differences in ^{1}H-NMR spectra have been noticed, in addition, the cyano group carbon of **5** resonated in ^{13}C-NMR spectrum at δ 112 ppm as compared with natural prekinamycin (δ 83.7 ppm) [14]. Likewise, the cyano-group carbon in ^{13}C-NMR spectrum of bicyclic model **7** was observed at δ 104.7 ppm [15]. These and other observations have led to revision of the structure, not only of this compound, to the diazo-compound **6**, Fig. 3.

Three more metabolites isolated from the same source included keto-anhydrokinamycin [14], an obvious biosynthetic precursor of kinamycin C (**3c**),

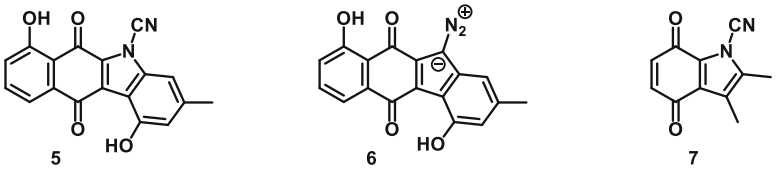
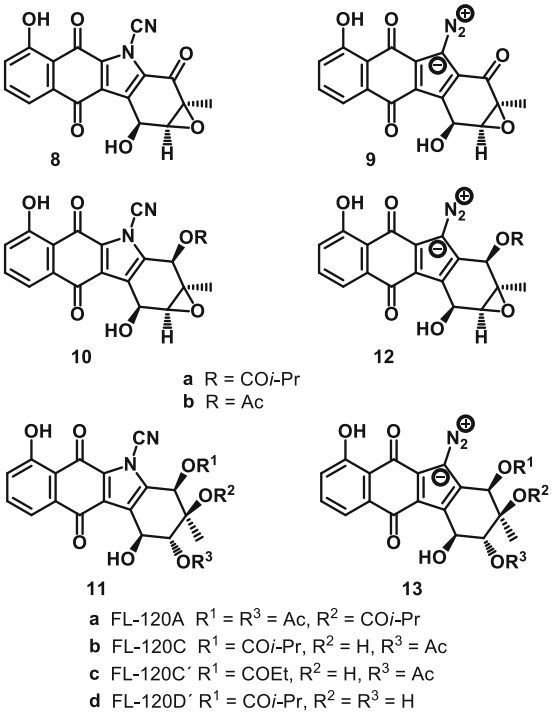


Fig. 3 Original **5** and revised **6** structure of prekinamycin

Fig. 4 Original and revised structures of further monomeric metabolites



whose structure has been corrected from **8** to **9**, Fig. 4. Two more oxirane moiety-containing compounds have been obtained in 1994 from *Streptomyces chattanoogensis* subsp. *taitungensis* [16, 17], and named FL-120B (**10a**) and FL-120B´ (**10b**). Four kinamycin-related metabolites FL-120 (**11**) were isolated from the same source. Similarly as above, their originally assigned structures were changed to the diazo-compounds **12** and **13**, respectively, Fig. 4.

2.2 Dimeric Compounds

There have been five dimeric genotoxic metabolites isolated to date. They were formulated as diazofluorene derivatives since their isolation, yet the story of their

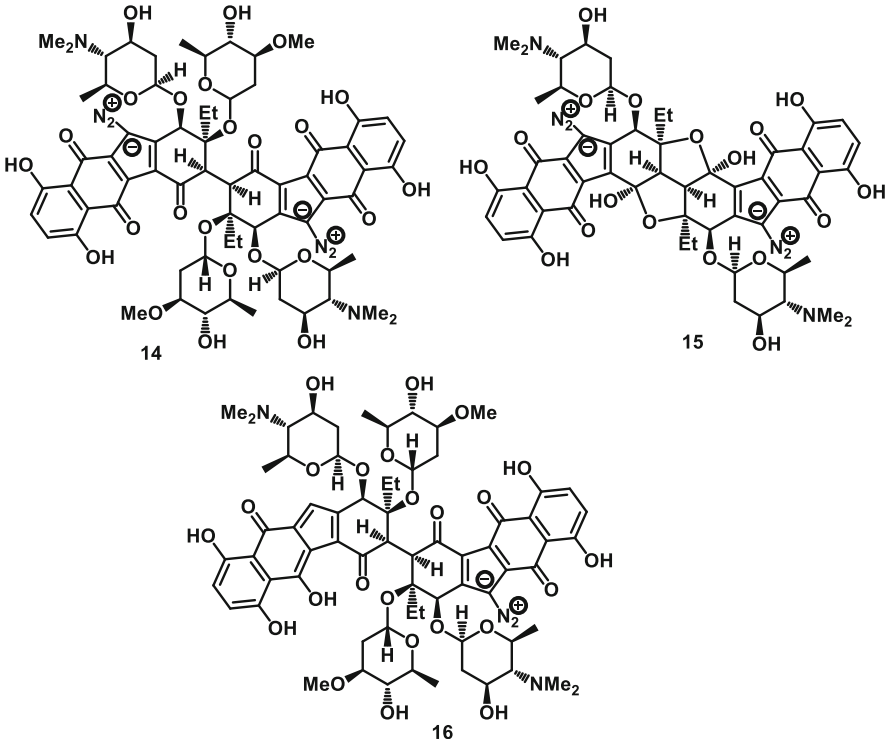


Fig. 5 Several dimeric lomaiviticins and their originally assigned structures

structure elucidation is as interesting as the one with monomers. 2001 saw the isolation of C_2-symmetric lomaiviticin A (**14**) and lomaiviticin B (**15**), potent antitumor antibiotics from the actinomycete *Micromonospora lomaivitiensis* [18], Fig. 5. Lomaiviticin C (**16**), D, and E were obtained in 2012 from *Salinispora pacifica* strain DPJ-0019 [19].

In 2021, however, with the help of the cryo-electron microscopy technique known as the microcrystal electron diffraction (microED), lomaiviticin C was shown to contain 4,6-dihydroxycyclohex-2-ene-1-one moiety rather than 4,5-dihydroxycyclohex-2-ene-1-one and the connecting bond located at C-5 [20]. These and other findings have led to the structure revision, see e.g. the structures **17** and **18** for lomaiviticin A and C, respectively, Fig. 6.

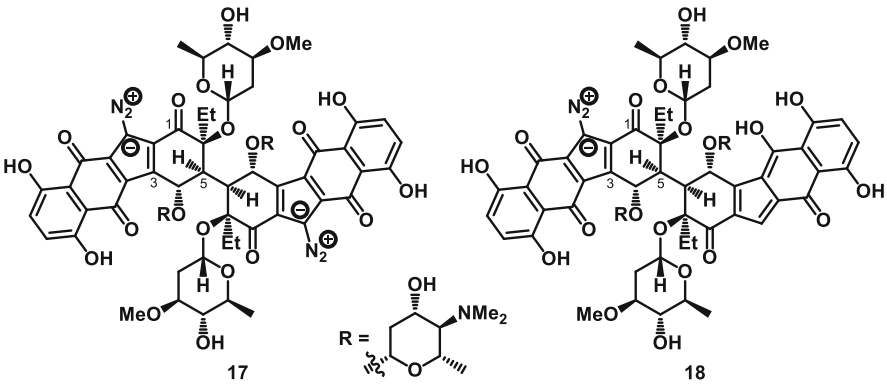


Fig. 6 Examples of revised structures of the dimeric lomaiviticins from 2021

3 Syntheses of Compounds Possessing the Diazocyclopentadiene Fragment

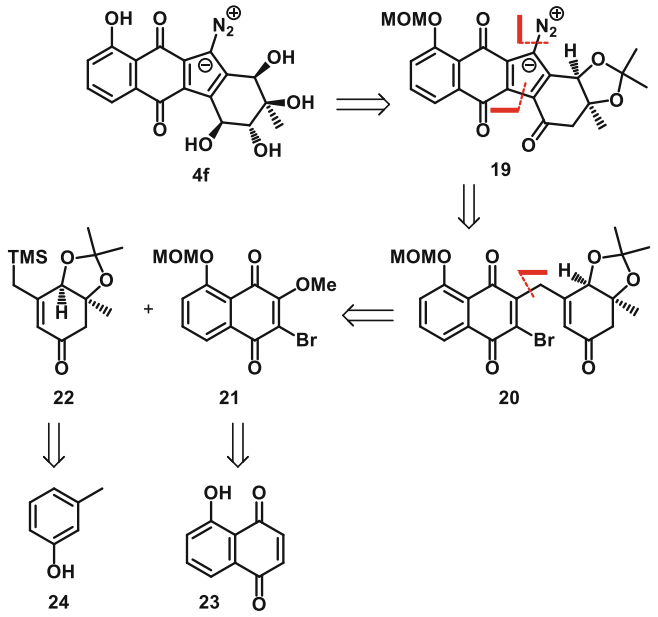
3.1 Synthesis of Monomers

3.1.1 Total Synthesis of Monomers

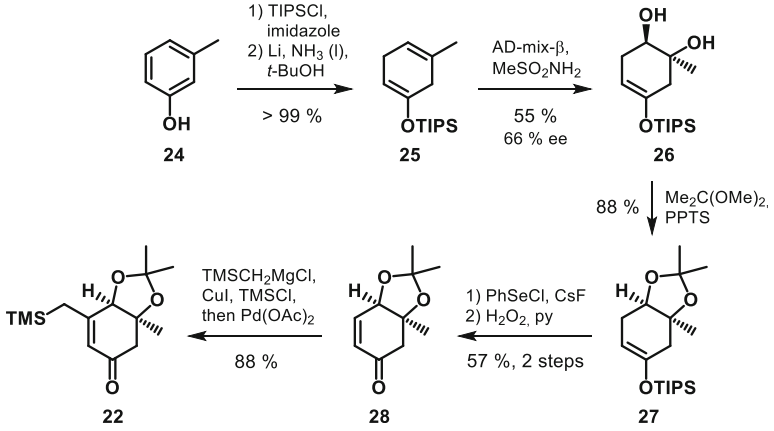
Herzon has discussed their total synthesis of (−)-kinamycin F (**4f**) from 2010 [21] also in the *synpacts* article in 2011 [22], and the full paper was published [23] in 2012, see also [24]. This enantioselective total synthesis is shown retrosynthetically in Scheme 2. It was envisioned that kinamycin F could be obtained from the diazo compound **19**, which would originate from enone **20** by way of cyclization followed by a diazo transfer. The enone **20** could be secured by a coupling of bromonaphthoquinone **21** with cyclohexenone **22**, and the synthesis could start from juglone (**23**) and *meta*-cresol (**24**).

Scheme 3 discloses the steps leading to cyclohexenone **22**. Thus, 3-methylphenol (**24**) was *O*-protected and subjected to the Birch reduction. The resulting cyclohexadiene **25** was treated with AD-mix-β affording the *cis*-diol **26** with 66% ee (55%) which was protected (→ **27**, 88%). The latter compound was converted to cyclohexenone **28** by a two-step protocol consisting of α-phenylselenenylation followed by oxidation and elimination, 57% over 2 steps, which could be recrystallized to >95% ee. Finally, the silane **22** was obtained by the Cu-catalyzed addition of Grignard reagent, trapping an enol by silylation and reoxidation with palladium acetate (88%).

The optically active trimethylsilane **22** was coupled with quinone **21** biased toward subsequent addition at C-3, which was secured from juglone (**23**) in 3 steps (48% overall), Scheme 4. The coupling was mediated by fluoride (tris-(diethylamino)sulfonium trimethyldifluorosilicate, TASF(Et)) and provided quinone **20** with complete regioselectivity in 79% yield. The following cyclization was

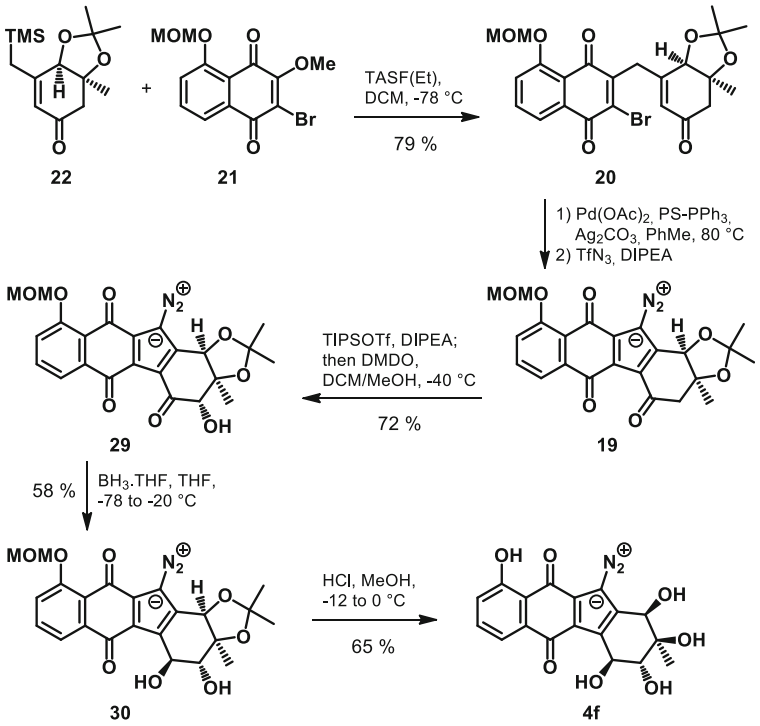


Scheme 2 Retrosynthetic scheme for kinamycin F (**4f**) by Herzon



Scheme 3 Synthesis of the cyclohexenone **22** by Herzon

catalyzed by palladium acetate and polymer-supported Ph_3P with silver carbonate as the base (66%), and the thus generated hydroxyfulvene was subjected to the diazo transfer with trifluoromethanesulfonyl azide TfN_3 and DIPEA (*N,N*-diisopropylethylamine) to provide diazo compound **19** (65% over 2 steps). Given the sensitivity of diazo compounds toward reducing agents, the following

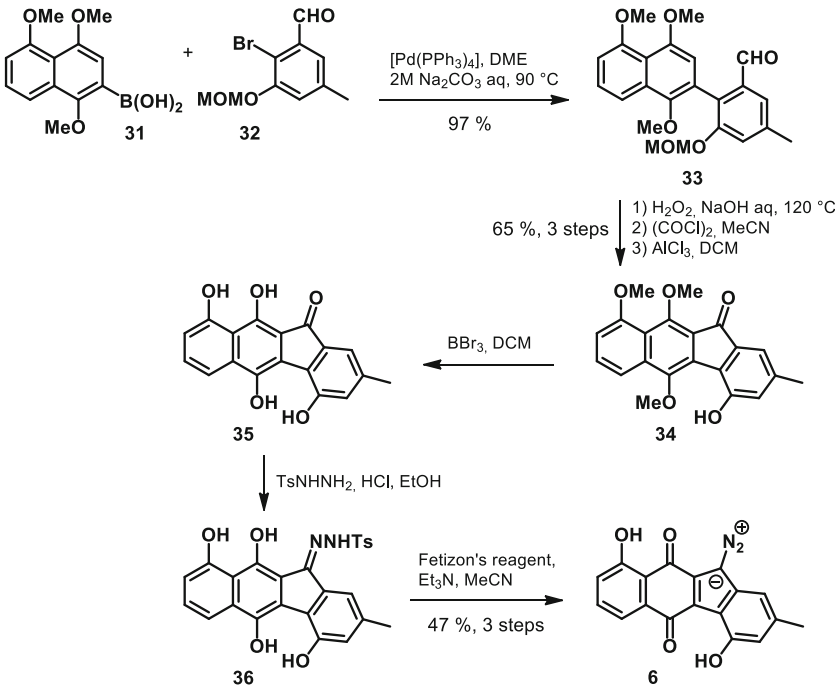


Scheme 4 Enantioselective synthesis of (−)-kinamycin F (**4f**) by Herzon

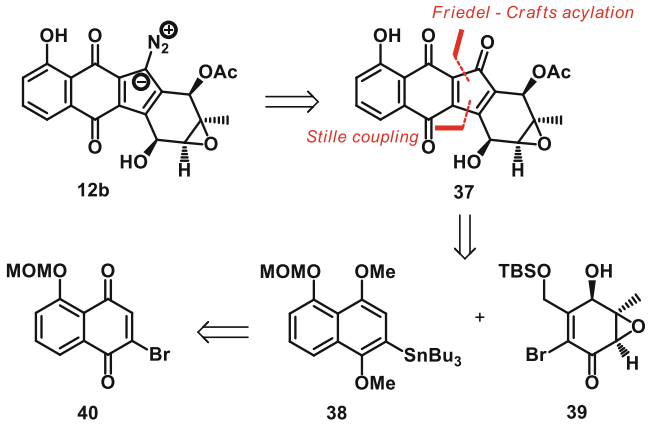
conversion of ketone to *trans*-1,2-diol was all but trivial. Thus, the silylated enol of the ketone **19** was epoxidized by DMDO from the convex, less sterically branched face to provide, after methanolysis, the desired α–alcohol **29** (76%), which was used as a handle to pursue the following reduction of the ketone by borane in a pseudointramolecular manner (→**30**, 58%). Complete deprotection by HCl in methanol afforded finally the target (−)-kinamycin F (**4f**).

Kumamoto et al. have reported on total synthesis of prekinamycin (**6**) in 2011, Scheme 5 [25]. Bromoaldehyde **32**, obtained in 4 steps from 3,5-dimethylphenol, and boronic acid **31** underwent the high-yielding Suzuki coupling (97%). Biaryl aldehyde **33** thus obtained was cyclized by the Friedel–Crafts acylation of the intermediary acid chloride to afford tetracycle **34**, possessing the complete carbon skeleton of the metabolite. Deprotection then gave tetraol **35**, the carbonyl group of which was then used to complete the synthesis via the corresponding tosylhydrazone **36**, and its final oxidative transformation by silver carbonate on celite (Fetizon's reagent) into the target prekinamycin (**6**), 47% from **34**.

Synthesis of epoxykinamycin FL-120B´ (**12b**) was described by Porco, Jr. and Scully [26]. As follows from Scheme 6 the strategy of their synthesis was similar to the one they used in synthesis of kinamycin C (**4c**) [27]. It was expected that metabolite FL-120B´ (**12b**) could be elaborated by an installation of the diazo group from ketone **37**, which itself could be formed by the Stille coupling of



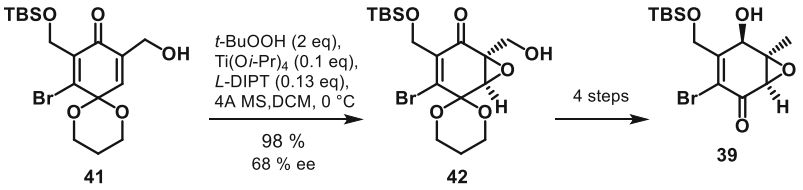
Scheme 5 Total synthesis of prekinamycin (**6**) by Kumamoto



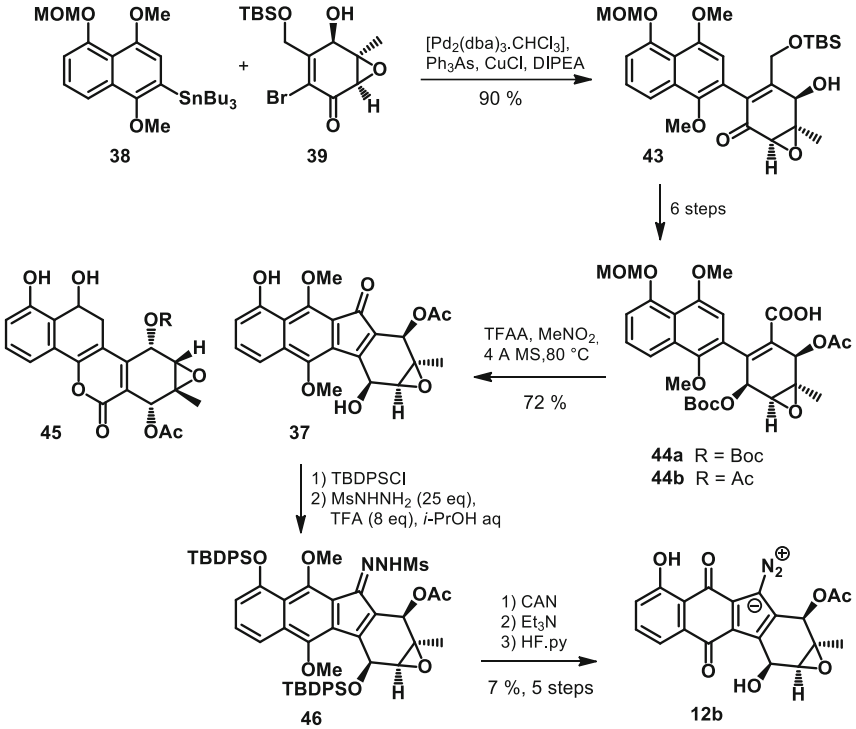
Scheme 6 Retrosynthetic analysis of epoxykinamycin FL-120B´ by Porco, Jr.

bromo enone **39** with stannane **38** followed after appropriate manipulation of functionalities by the Friedel–Crafts acylation. Stannane **38** was envisioned to originate from the bromojuglone derivative **40**.

In their original synthesis [27] of intermediate **39** from 2,5-dihydroxybenzaldehyde, Porco et al. have used an asymmetric nucleophilic



Scheme 7 Improved synthesis of the bromo epoxide **39** by Porco



Scheme 8 Total synthesis of epoxykinamycin FL-120B´ (**12b**) by Porco, Jr.

epoxidation to access optically active **39**. However, the approach suffered an erosion of enantioselectivity upon upscaling and, therefore, had to be modified as illustrated in Scheme 7. Thus, the allyl alcohol **41**, an intermediate of their original synthesis of **39**, was subjected [26] to the Sharpless epoxidation with *L*-diisopropyl tartrate, to give 98% yield of **42** with 68% ee, which could be raised to 99% ee by a single recrystallization. The compound was transformed in 4 steps into the bromide **39** (65%) as described previously [27].

The synthesis of epoxykinamycin FL-120B´ (**12b**) continued with the preparation from quinone **40** in 3 steps of stannane **38**, which underwent Stille coupling with bromide **39** and afforded compound **43** as a 1.5:1 mixture of atropisomers (90%), Scheme 8. The corresponding carboxylic acid **44a** was secured in 6 steps and

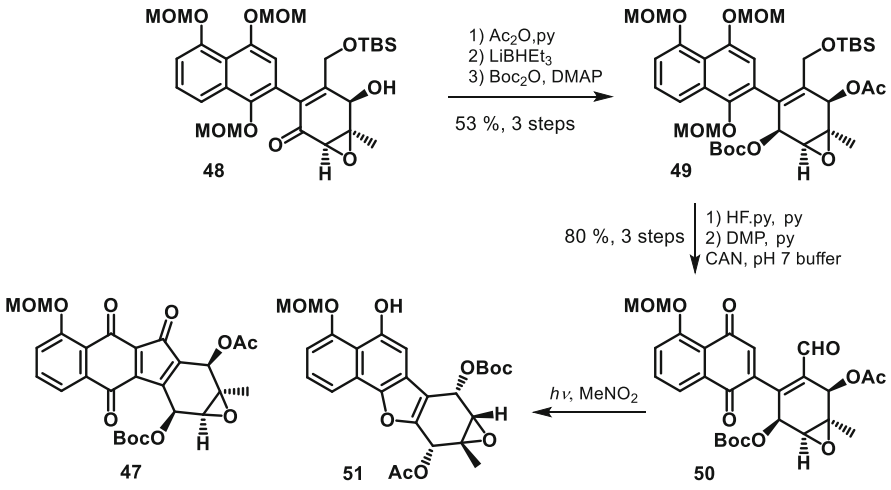
underwent Friedel–Crafts acylation with TFAA (trifluoroacetic anhydride); simultaneous deprotections provided the crucial tetracycle **37** in 72% yield. Note that with the less sterically demanding acyl groups (like in **44b**) and at lower temperature, side product lactone **45** was also formed.

The strategy of the late stages was similar as above, however, a selective formation of mesylhydrazone in the presence of a sensitive oxirane was only successful when trifluoroacetic acid was used as a non-nucleophilic Bronsted acid (→ **46**). Oxidation of naphthalene **46** with cerium(IV) ammonium nitrate (CAN) installed the desired quinone followed by partial desulfination, which was completed by a treatment with base; final deprotection afforded the target **12b** in an overall yield 7% from **37**.

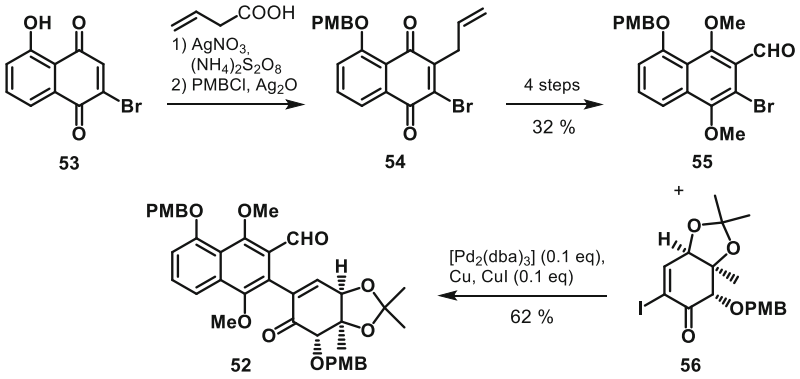
3.1.2 Model Studies on Monomers

During synthetic efforts toward epoxykinamycin FL-120B´ (**12b**), Porco Jr. and a coworker attempted [28] also an approach to tetracyclic ketone **47** by a photo-Friedel–Crafts acylation in aldehyde **50** similar to the acid **44a**, Scheme 9. Thus, the ether **48**, an intermediate in their synthesis of kinamycin C (**4c**) [27], was converted in 3 steps into the intermediate **49** and then by oxidation to the quinone-aldehyde **50** (43% from **48**). Unfortunately, tetracyclic furan **51** was obtained through a radical decarbonylative cyclization (34%) instead of ketone **47**.

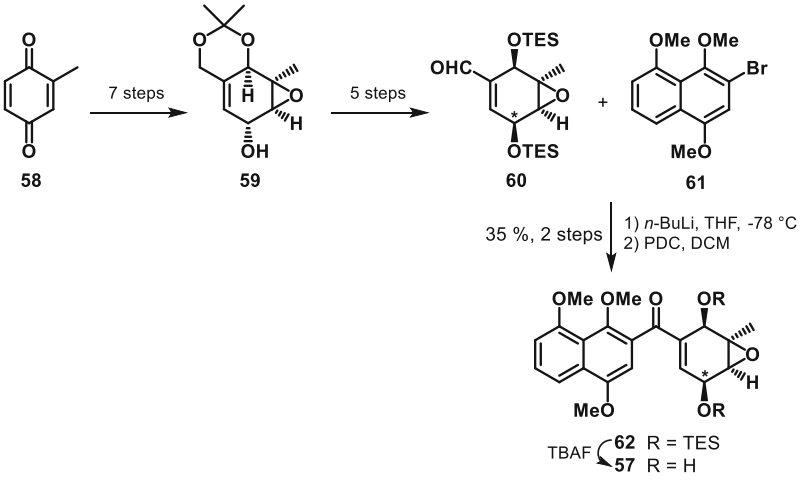
Fokas and coworker synthesized [29] compound **52** as an advanced intermediate in the projected, but not completed, approach to kinamycin F, by way of an Ullmann-type coupling reaction between naphthaldehyde **55** and vinyl iodide **56**, which afforded a 62% yield of the product, Scheme 10. Aldehyde **55** was obtained in 6 steps from quinone **53** via allylnaphthalene **54**, while the synthesis of the enone **56** from 3-methyl-2-cyclohexenone required 11 reaction steps.



Scheme 9 Cyclization of the aldehyde **50** by Porco Jr.



Scheme 10 Synthesis of the intermediate **52** by Fokas

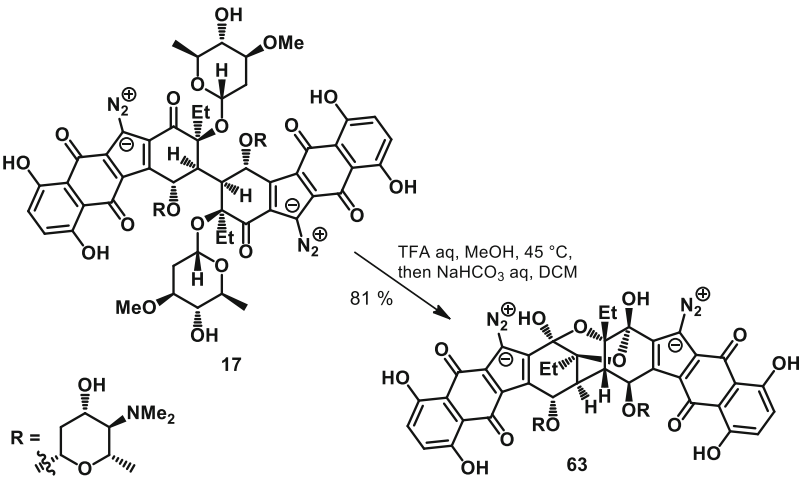


Scheme 11 Synthesis of the ketone **57** by Mehta

Mehta et al. have reported [30] on the synthesis of ketone **57**, which was obtained by a two-step protocol consisting of reacting lithiated naphthalene **61** with aldehyde **60** followed by oxidation, Scheme 11. Silylated ketone **62** was afforded in 35% yield over 2 steps, and could be desilylated to diol **57** (78%). Similarly, a diastereoisomer of **62** was secured from an epimeric aldehyde **60** (see the star in both structures).

3.2 Synthesis of Dimers

Transformation of (−)-lomaiviticin A (**17**) by a treatment with TFA (trifluoroacetic acid) in aqueous MeOH into (−)-lomaiviticin B (**63**) in 81% yield was reported [23]



Scheme 12 Partial synthesis of (−)-lomaiviticin B (**63**) by Herzon

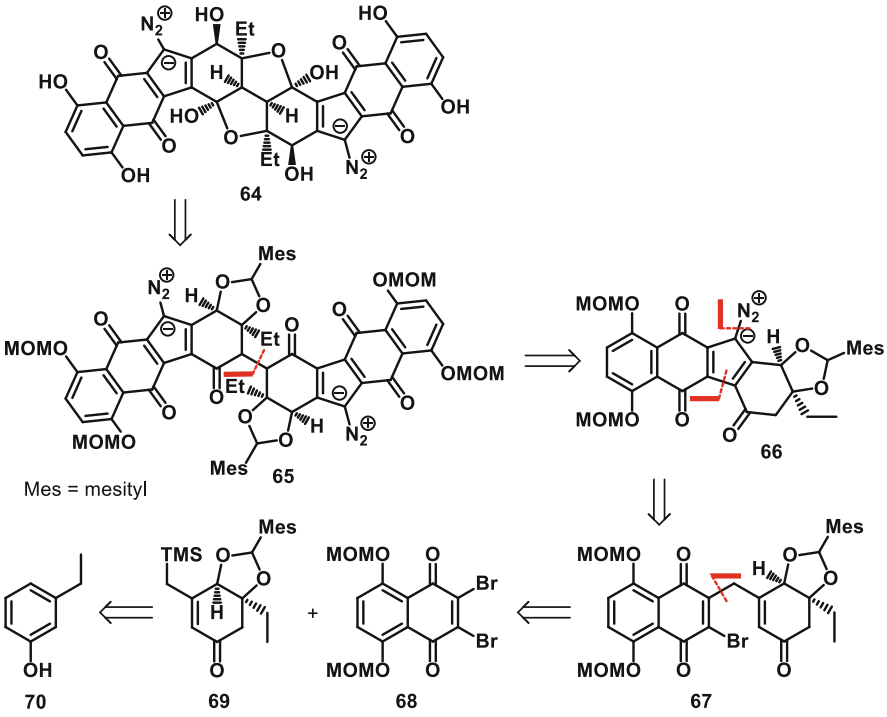
by Herzon et al. Note that Scheme 12 shows corrected structures [20] of the compounds.

It should be noted that all synthetic efforts described in this section targeted the originally assigned, but incorrect, structures only.

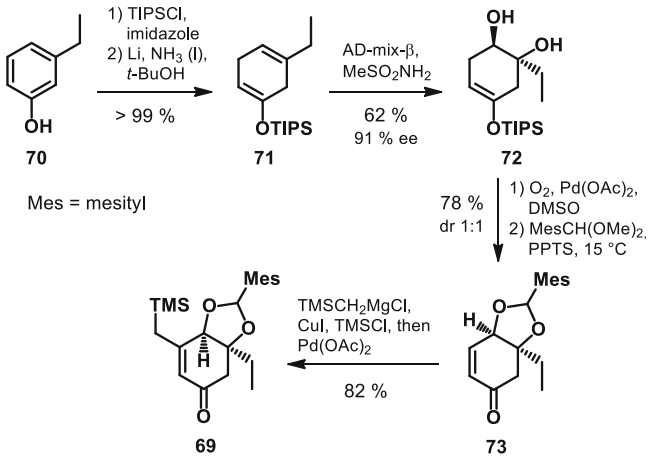
3.2.1 Total Synthesis of Dimers

Herzon et al. have described in 2011 [31] the total synthesis of a compound that was believed up to 2021 to be natural (−)-lomaiviticin B aglycon (**64**), see also Refs [22–24]. The total synthesis consisted from synthesis of the monomeric unit **66** essentially by the route developed for kinamycin F, dimerization (→ **65**) and the final deprotection accompanied by further cyclizations (→ **64**), as shown retrosynthetically in Scheme 13. The monomeric unit **66** was derived, in analogy with the synthesis of **19**, by cyclization followed by the diazo group transfer from bromo enone **67**, the building blocks for which were believed to be dibromonaphthoquinone **68** and silane **69**, itself affordable from 3-ethylphenol (**70**).

Optically active trimethylsilane **69** was synthesized [23, 31] from phenol **70** by a route paralleling in early steps synthesis of **22**, Scheme 14. Dihydroxylation of alkene **71** with AD-mix-β was more efficient compared to **26**, affording diol **72** with 91% ee (62%). The diol-enol was directly oxidized by palladium acetate in oxygen atmosphere, and the enone thus formed (92%) was treated with mesitylaldehyde acetal to protect the diol moiety. The acetal **73** was obtained as a 1:1 mixture of diastereoisomers (85%) and was transformed to silane-enone **69** by copper(I) iodide-mediated Michael addition of trimethylsilylmethylmagnesium chloride, trapping with TMSCl (trimethylsilyl chloride) and reoxidation in 82% yield.



Scheme 13 Retrosynthetic scheme for the total synthesis of lomaiviticin B aglycon **64** by Herzon

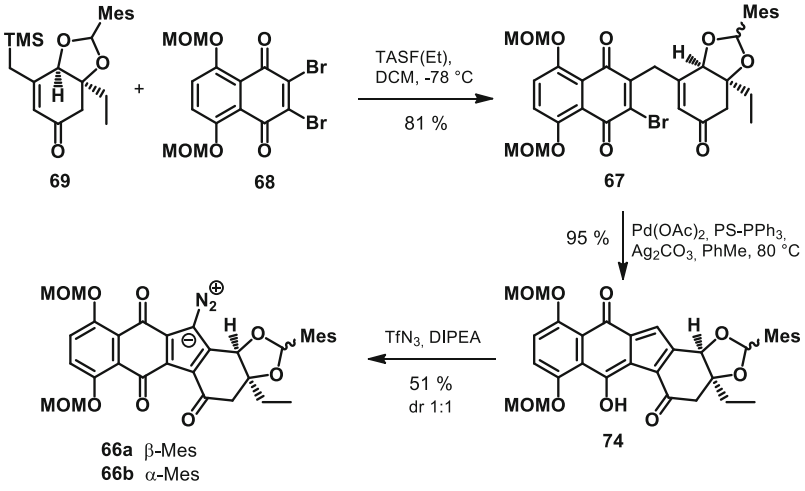


Scheme 14 Synthesis of the silane **69** by Herzon

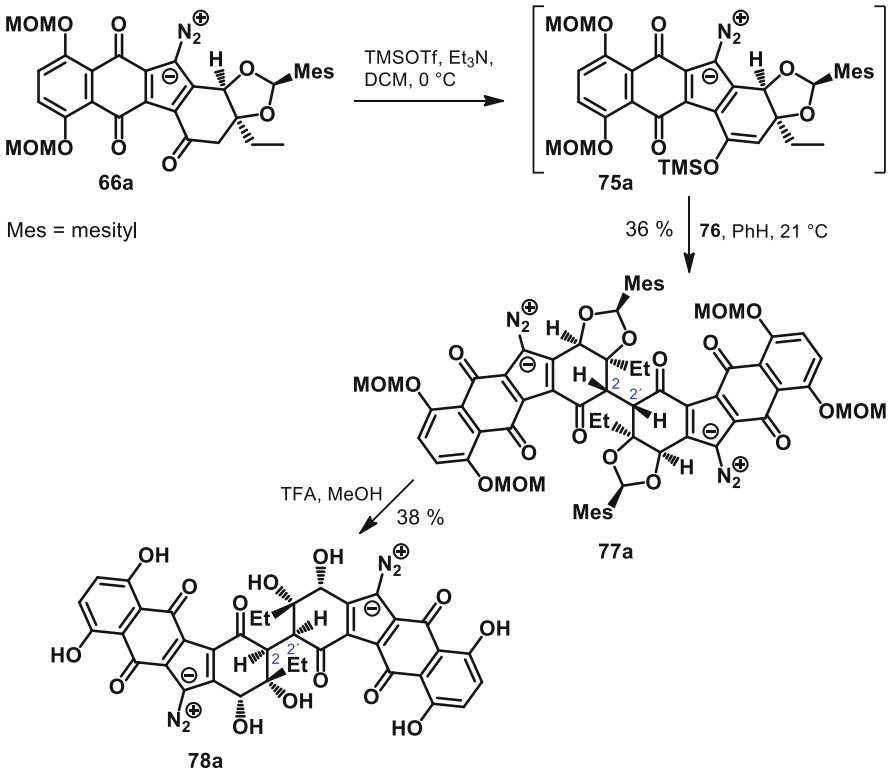
With the optically active trimethylsilane **69** at hand, the authors studied [23, 31] its coupling with quinone **68**, prepared in one step from 2,3-dibromo-5,8-dihydroxynaphthoquinone, Scheme 15. Coupling was mediated again by TASF (Et) and provided quinone **67** regioselectively in 81% yield (dr 1:1). The following cyclization was catalyzed by palladium acetate with polymer-supported Ph_3P. It was shown that lowering the ratio of Ph_3P to Pd from 2.5:1 to 1.5:1 had raised the yield to 95%; compared with analog **20**. The product with the hydroxy fulvene structure **74** was finally subjected to diazo transfer with trifluoromethanesulfonyl azide TfN_3 and DIPEA to provide diazo compound **66** as a 1:1 mixture of diastereoisomers, which were separated (51% totally).

Transformation of diazofluorenes **66** into the lomaiviticin aglycon (**64**) proved to be a real challenge [23, 29], Schemes 16 and 17. On the basis of exhaustive experimentation (> 1,500 experiments), however, a straightforward route was developed. The outcome of the oxidative dimerization, including stereoselectivity, was shown to be dependent upon diol protecting group, the enoxysilane structure (silyl group), choice of oxidant and solvent. Thus, an exposure of the so-called *endo*-diastereoisomer **66a** to trimethylsilyl triflate provided silylated enol **75a**, which was allowed to react with manganese tris(hexafluoroacetylacetonate) (**76**) to yield the (2*S*,2'*S*)-dimer **77a** (36%) exclusively, in accordance with the preferred approach of radical-cation from *exo*-face (from below) in **75a**. Note that 42% yield of **77a** was obtained with TBS (*tert*-butyldimethylsilyl) protection and cerium ammonium nitrate as oxidant [23]. The product could be deprotected by TFA in MeOH to dimer **78a** (38%), which resisted all attempts at further cyclization.

On the other hand, an exposure of the *exo*-diastereoisomer **66b** to trimethylsilyl triflate followed by the immediate treatment with manganese tris (hexafluoroacetylacetonate) (**76**) afforded [23, 29] the mixture of (2*R*,2'*R*)-dimer **77b** (26%) and (2*S*,2'*S*)-dimer **77c** (12%); 30% of **66a** was also recovered,



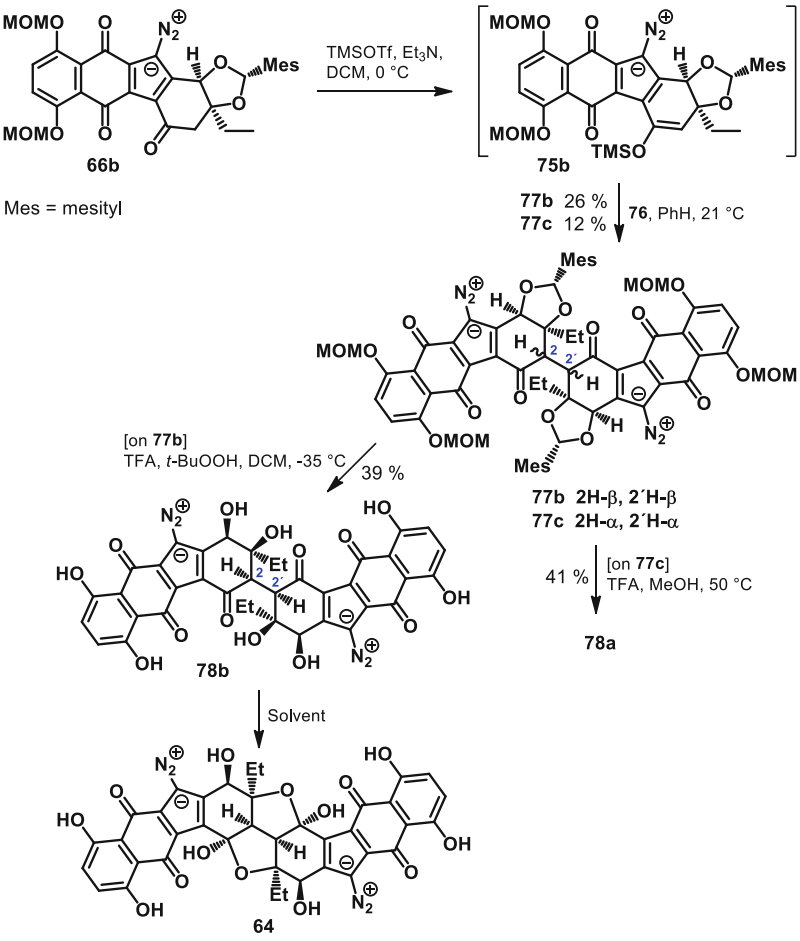
Scheme 15 Synthesis of the monomeric diazoketone **66** by Herzon



Scheme 16 Dimerization of the monomeric *endo*-mesityl diazofluorene **66a** by Herzon

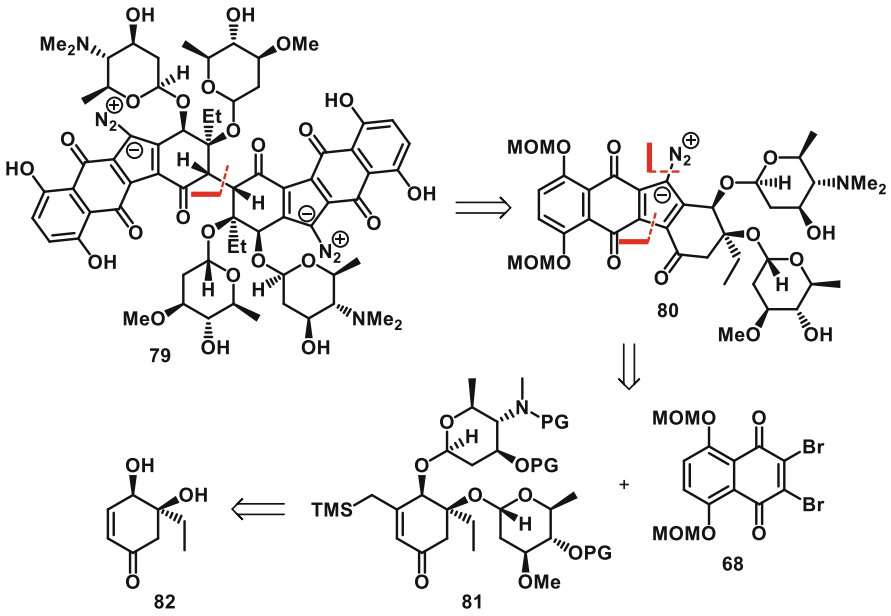
Scheme 17. Stereochemistry of the major diastereoisomer is explained by the favorable effect of *ortho*-methyl of the mesityl group which is believed to force the ethyl group to be oriented below the silyl enol ring, and thus to hinder approach from the *exo*-face. Global acidic deprotection (TFA, *t*-BuOOH) of **77b** then provided compound **78b** containing already some **64**. Full conversion of **78b** to ring isomer of lomaiviticin aglycon **64** was achieved by preparative TLC or by standing in solvent (10 min in MeOH). Unfortunately, a direct comparison sample of the aglycon could not be obtained from lomaiviticin A by hydrolysis without decomposition.

Capitalizing on their experience with this chemistry, Herzon et al. have described [32] the synthesis of unnatural (sic) (2*S*,2'*S*)-lomaiviticin A (**79**) using essentially the strategy described above. The major difference was in that the real sugar moieties (in protected form, of course) were carried through the synthesis instead of protecting groups. The strategy is shown retrosynthetically in Scheme 18. The target **79** was believed, based on gained previous experience, to be accessible from monomeric unit **80**, itself affordable from intermediates **68** and **81**, where the latter was expected to be accessible from diol **82**.



Scheme 17 Completion of the total synthesis of the presumed lomaiviticin aglycon **64** by Herzon

Heavily decorated enone **83** was prepared [32] by the six step sequence from diol **82** [23, 31] and subjected to 1,4-addition of trimethylsilylmagnesium bromide in the presence of CuI, silylation and oxidation with DDQ in the presence of 2,6-di-*t*-butylpyridine (**84**) to give silyl enone **81** (85%), Scheme 19. The latter reacted with dibromide **68** in the presence of tris(diethylamino)sulfonium trimethyldifluorosilicate, TASF-(Et), at −78°C and afforded bromo enone **85** (84% yield), which was heated with palladium bis(chloroacetate) ($Pd(ClAc)_2$) in the presence of polymer-supported triphenylphosphine ($PS-PPh_3$) and silver carbonate, and provided the hydroxyfulvene **86**. Diazo group transfer with trifluoromethanesulfonyl azide and DMAP finally afforded the monomeric bis(glycosylated) diazofluorene **80** (44% in 2 steps).

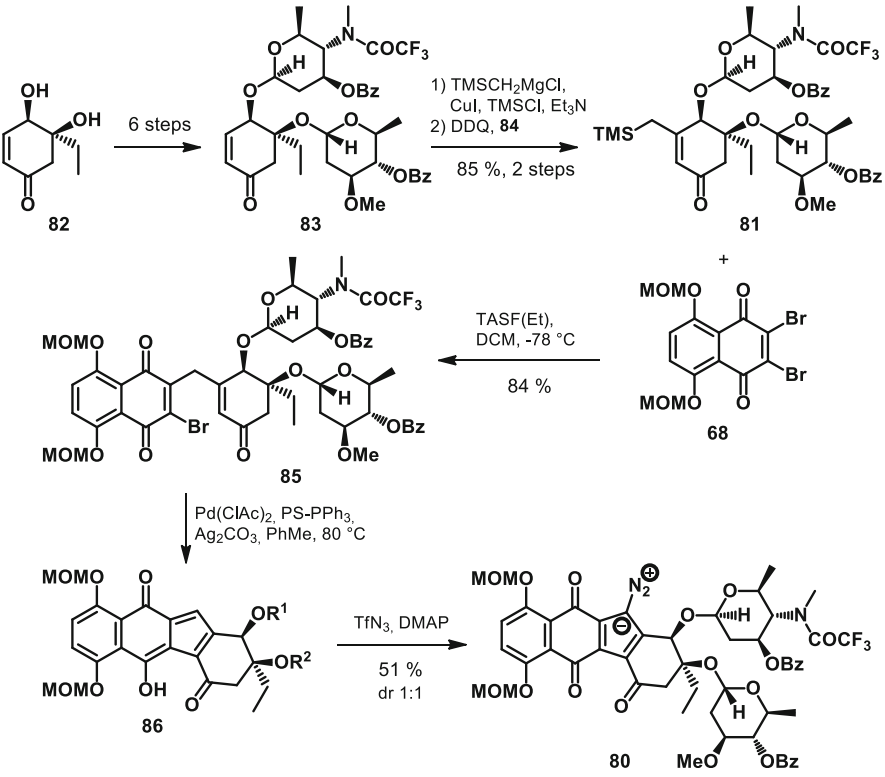


Scheme 18 Retrosynthesis of the presumed (2*S*,2'*S*)-lomaiviticin A (**79**) by Herzon

The synthesis of **79** was completed [32] in the "standard" way by converting diazoketone **80** into silyl enol followed by oxidation with cerium ammonium nitrate (CAN) in the presence of 2,6-di-*t*-butylpyridine (**84**), Scheme 20. The product consisted of two diastereoisomers (ca. 4:1). The relative stereochemistry was inferred from the successful transformation of the major one into the target (2*S*,2'*S*)-lomaiviticin A (**79**), by a treatment with $MgBr_2$ to release hydroquinone moieties (**87,** 32% from **80**), methanolysis and *N*-methylation (22% for the last 2 steps).

Total synthesis of the fully decorated monomeric unit **88** to lomaiviticin A was reported [33] by Nicolaou et al. Scheme 21 summarizes some of the milestones of the route. Repeated oxidations, formation of diazo group, and installation of pyrrolosamine β–glycosidic as well as *L*-oleandrose α–glycosidic bond would allow to trace the approach back to the tetracyclic intermediate **89**. The latter could be formed by the Pd-catalyzed coupling and allylic oxidation from bromoenone **90**, itself expected to be available by a reaction of naphthalene aldehyde **91** with vinyl iodide **92**.

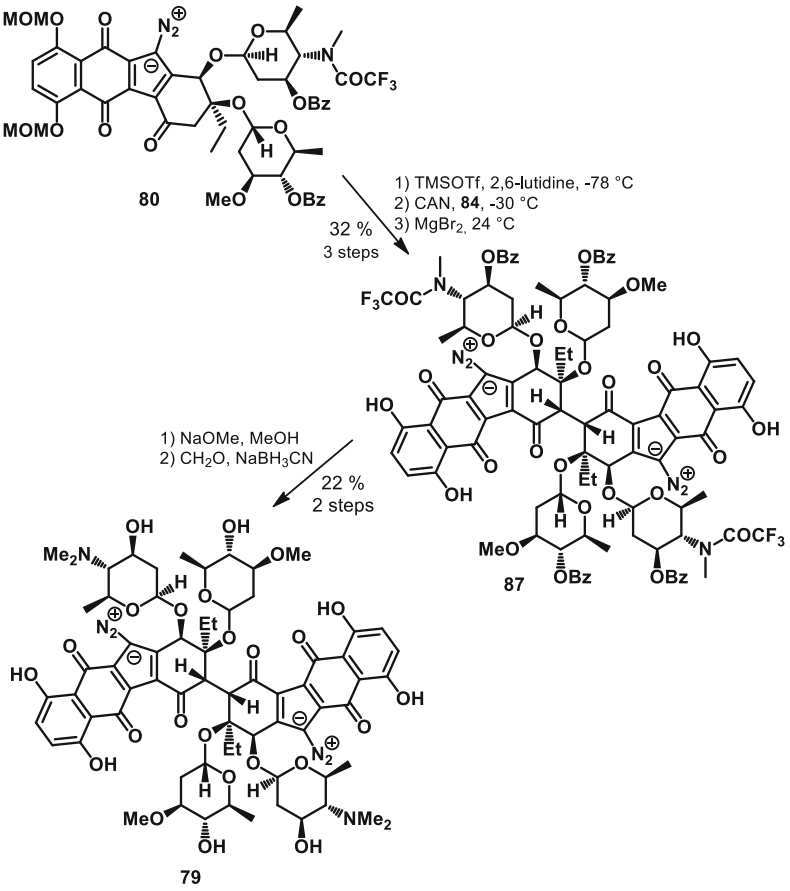
Required intermediates **91** and **92** were secured from quinone **93** and ketone **94**, respectively, compounds that were used in their synthesis of kinamycins [34], Scheme 22. Vinyl iodide **92** was metalated and reacted with aldehyde **91** to afford alcohol **95** as a mixture of diastereoisomers (73%), which was then oxidized with 4-methylmorpholine N-oxide (NMO) and tetrapropylammonium perruthenate (TPAP). The ketone (not shown) underwent ring-closure under the Herzon's



Scheme 19 Synthesis of the monomeric unit **80** by Herzon

optimized conditions ([$Pd_2(dba)_3$] (0.5 eq), K_2CO_3, BI-DIME (1 eq), dioxan at 80° C) and delivered cyclopentadienone **96** in 63% over 2 steps. Introduction of a hydroxyl in benzylic position was achieved with SiO_2-supported selenium dioxide and pyridine, followed by chloroacetylation and a liberation of diol moiety by scandium triflate. The diol **97** was obtained as a 2.3:1 mixture of diastereoisomers at C-1.

Installation of the glycosyl moieties was achieved using gold-promoted reactions with *o*-alkynylbenzoate derivatives of protected sugars, Scheme 23. Thus, the diol **97** was reacted in the presence of promoter [$Ph_3PAuNTf_2$] with ester **98** to give preferentially the β-anomer (ca. 6:1); at this stage, C-1 epimers were separated and carried through up to ketone **102** individually. The reaction with ester **99** in the presence of gold reagent [$Ph_3PAuOTf$] then delivered intermediate **100**; **100a** 14% from **97**, **100b** 32% from **97**. These were converted in three steps to triol **101a** and **101b**, 45% and 43%, resp. over 3 steps. Introduction of the diazo moiety was achieved via tosylhydrazone and its Dess–Martin periodinane (DMP) oxidation, which also installed ketone at C-1; 44% from **101a**, 28% from **101b**. The naphthalene ketone **102** afforded upon oxidation with cerium ammonium nitrate (CAN) and stepwise deprotection the target monomer **88** in 30% yield from **102**.

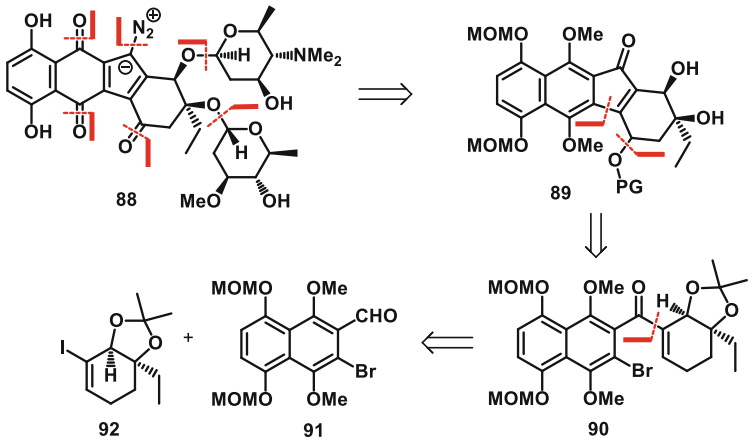


Scheme 20 Completion of the synthesis of the presumed (2*S*,2'*S*)-lomaiviticin A (**79**) by Herzon

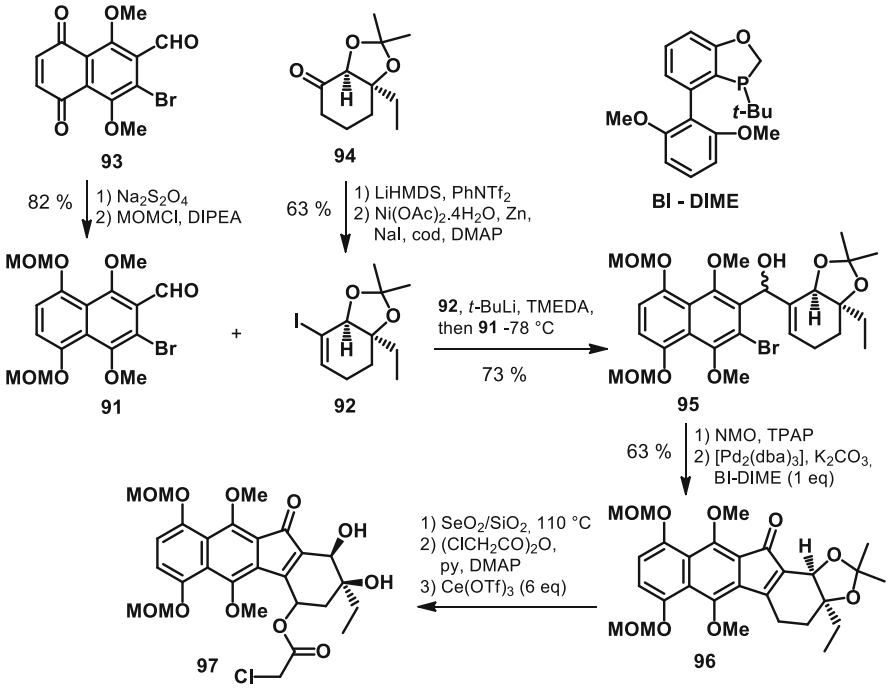
3.2.2 Model Studies Towards Dimers

Sulikowski et al. have reported [35] on a model study toward the synthesis of the so-called dideoxylomaiviticinone (**103**), Scheme 24. It was reasoned that the tetracyclic moiety in **104** could be build up by forming the bonds in red. Unfortunately, base induced addition of 3-nitromethylcyclohexenones **105** to naphthazarin (**106**) under oxidative conditions provided, instead of the desired quinones **107**, the tetracyclic heterocycles **108**.

Synthesis of enantiomeric bicyclic core of lomaiviticin A **109** was published [36, 37] by Feldman et al., Scheme 25. (*Z*,*Z*)-Diene diester **110** was secured in 3 steps from 1-phenyl-2-propyne-1-ol of 95% ee and subjected to the double Ireland–Claisen rearrangement, which proceeded with high stereoselectivity and provided, after treatment with TBAF, diacid **111** in 79% yield as a single

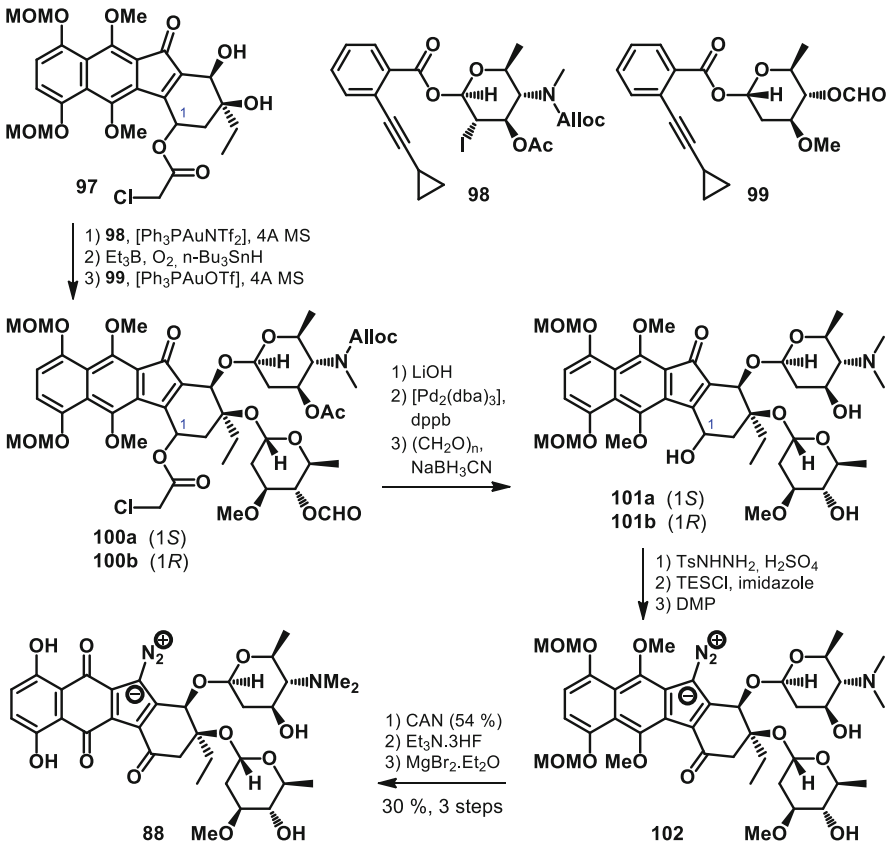


Scheme 21 Retrosynthetic summary for the total synthesis of **88** by Nicolaou



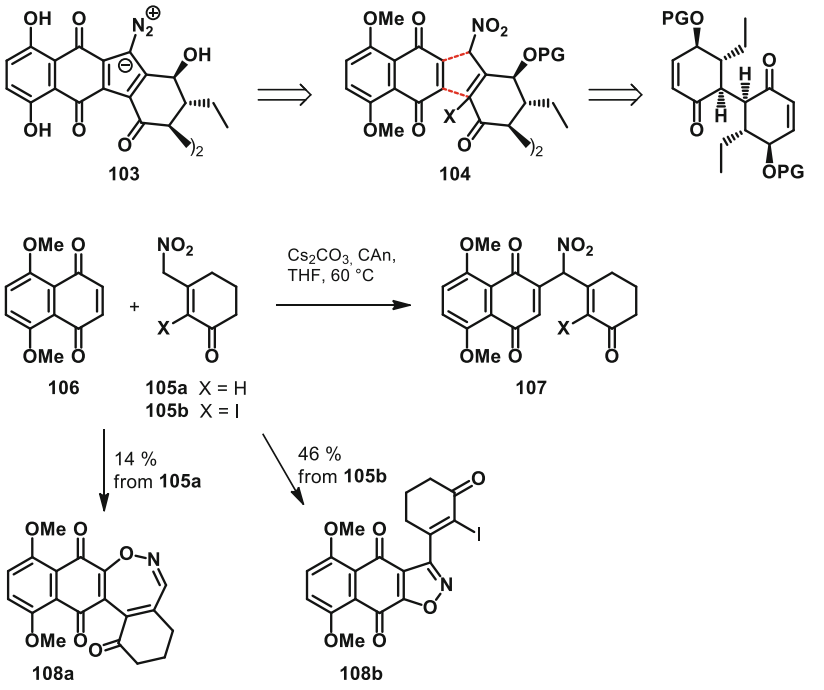
Scheme 22 Synthesis of the diol **97** by Nicolaou

stereoisomer. The compound was converted in 3 steps to the double terminal olefin **112** which afforded by double ring-closing metathesis with the Grubbs 2nd generation catalyst (G-II) the *bis*-cyclohexene **113** (64%). Conversion to cyclohexenone **109** required 4 more steps.



Scheme 23 Completion of the total synthesis of monomer **88** by Nicolaou

Synthesis of the core compounds **114** and **115** to lomaiviticin A and B, respectively, was published [38] by Shair and Lee in 2013, Scheme 26. Acrylate **116**, obtained in 10 steps from (*S*)-malic acid, provided the Diels–Alder tricycle **117**, which might well have been formed stepwise through Michael–Michael process, in 64% yield. Ester **117** was transformed into ketone **118** which underwent the stereoselective oxidative enolate dimerization with LiHMDS (lithium bis(trimethylsilyl)amide) and $[Cp_2Fe]PF_6$ as oxidant affording exclusively the *exo*-*exo*-product **119**. *O*-Debenzylation and oxidation induced formation of the ketone hydrated form **120**, 47–57% from **118**, its exposure to potassium hydroxide induced fragmentation of the oxygen bridge and gave rise to enone **121**. Note that similar process with the C-4 epimeric substrate failed, illustrating thus a subtle yet important stereoelectronic effect of the center. The latter was then dehydrated with $MgSO_4$ giving the 4-*epi*-lomaiviticin A core **114**; subsequent treatment with TsOH (*p*-toluenesulfonic acid) induced cyclization to the 4-*epi*-lomaiviticin B core **115**, 62% over last 3 steps.

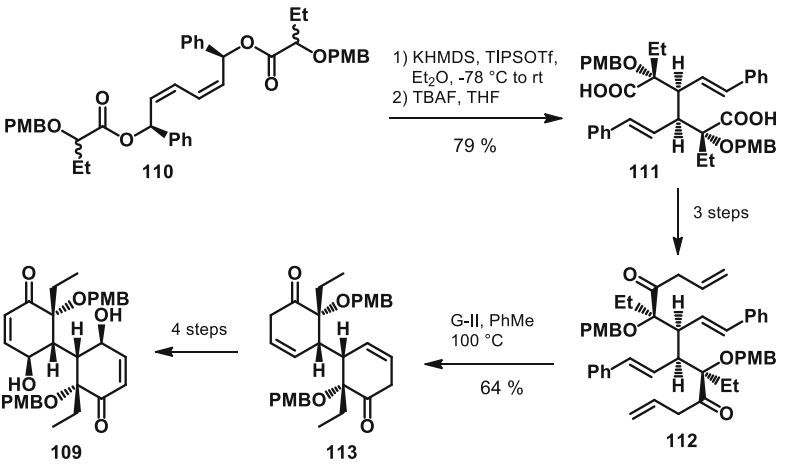


Scheme 24 Model study with the nitroenones **105** by Sulikowski

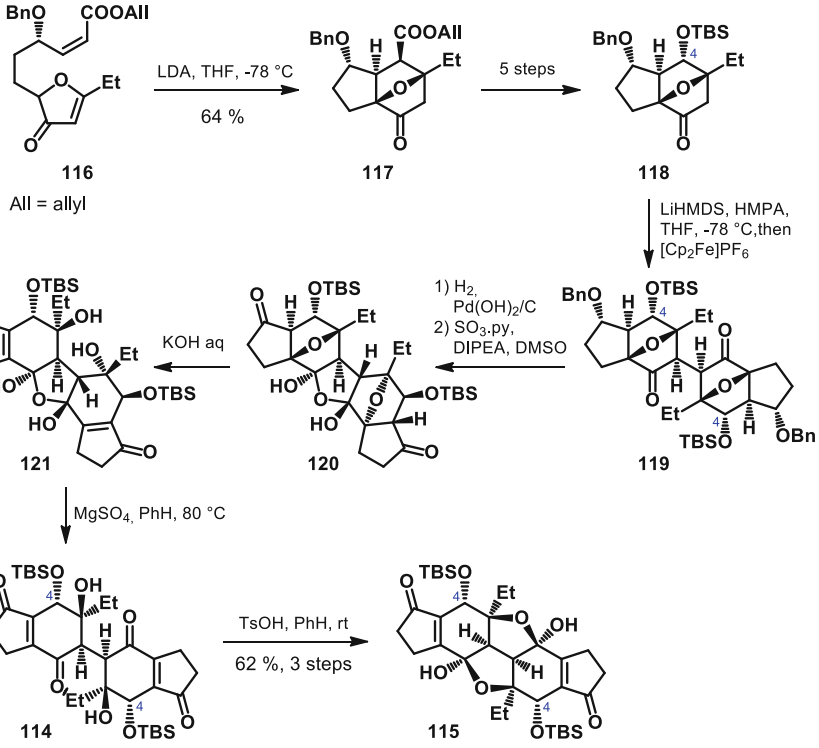
Synthesis of the bis(cyclohexenone) core of lomaiviticin A **122**, carrying also the oleandrose derived carbohydrate residue, was reported [39] by Herzon et al. Scheme 27 indicates that the target molecule could be secured from 1,3-diene **123**, itself accessible by dimerization of vinyl iodide **124**, which could be traced back to starting ketone **125** and oleandrose donor **126**.

Thus, alcohol **127** (dr 4:1), obtained by an addition of EtMgBr to ketone **125** at −78°C, was reacted with fluoride **126** activated with boron trifluoride etherate at −25°C, and afforded α–anomer **124** as the only product (45%), Scheme 28. Iodide **124** then underwent the Stille cross-coupling with the derived stannane **128** in the presence of tetrakis(triphenylphosphine)palladium(0) (25 mol%), copper(I) thiophene-2-carboxylate (CuTc), and tetra-*n*-butylammonium diphenyl phosphite and yielded 1,3-diene **123** in 64% yield on a gram scale. The latter compound was converted in 3 steps into 1,5-diene **129**, and then by *cis*-dihydroxylation into tetraol **130**.

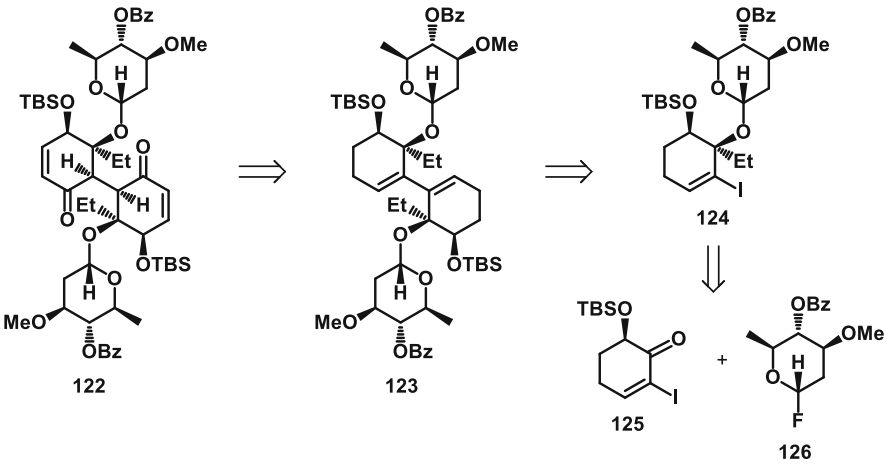
Both **129** and the derived diol **130** were independently transformed into the target **122**. A more efficient route from **130** is described in Scheme 29. Bis-diol **130** was selectively oxidized with dimethyldioxirane (DMDO) to ketone **131**, then converted with the excess of hydrazine to the unstable bis-hydrazone **132** which underwent oxidations with iodine, and afforded bis(iodoketone) **133** in 50% yield from **131** by a process that probably involved an interrupted Barton vinyl iodide synthesis. Oxidation with DMDO completed synthesis of the target bis(cyclohexenone) **122** (80%).



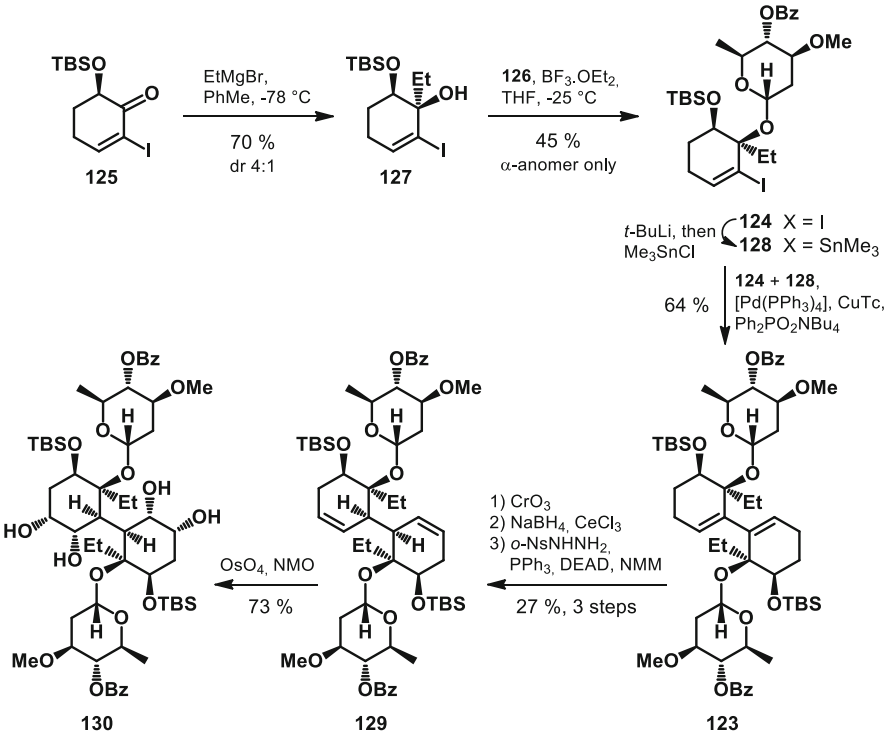
Scheme 25 Synthesis of the *ent*-bicycle **109** by Feldman



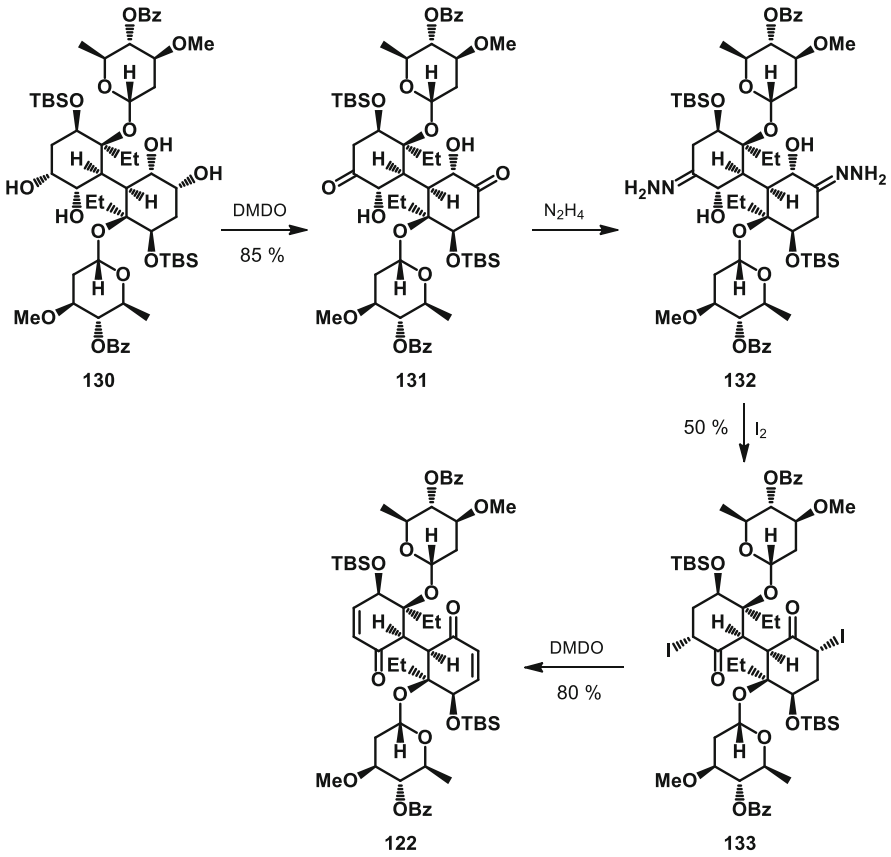
Scheme 26 Synthesis of the lomaiviticin cores **114** and **115** by Shair



Scheme 27 Retrosynthetic analysis of the lomaiviticin A core **122** by Herzon



Scheme 28 Synthesis of the intermediates **129** and **130** by Herzon



Scheme 29 Completion of the synthesis of **122** by Herzon

4 Summary

The articles on the chemistry of natural diazofluorenes reads like a chemical thriller. Corrections of originally ascribed structures on the basis of discrepancies of properties prompted synthetic endeavors. Several groups embarked on a journey to synthesize kinamycins and lomaiviticins. The review illustrates the ideas and the creativity brought by chemists in order to synthesize, in part, entities that were not real. With lomaiviticins, metabolites with interesting pharmacological properties, the correction of structures just very recently will no doubt induce further interest in their total synthesis. We can expect brilliant pieces of synthesis published in not too distant future.

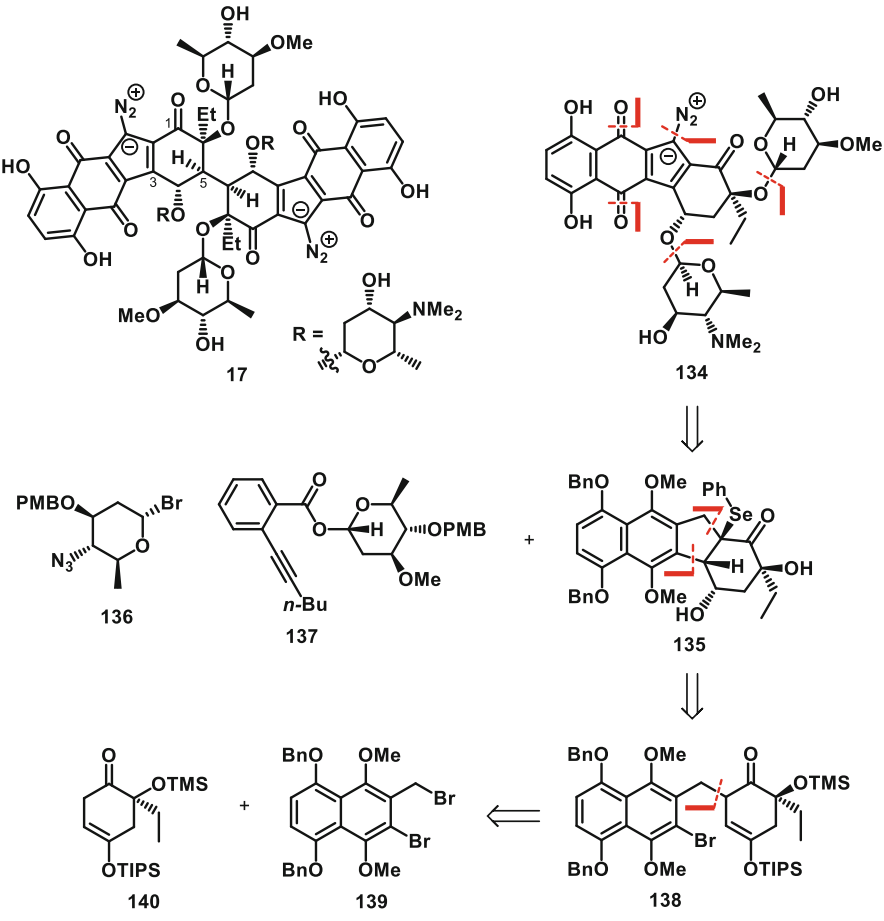
4.1 Synthesis Added in Proof (March 2, 2023)

Recently, Herzon and coworkers have reported [40] on total synthesis of the monomer with "correct" structure decorated with sugar moieties, see **134** in

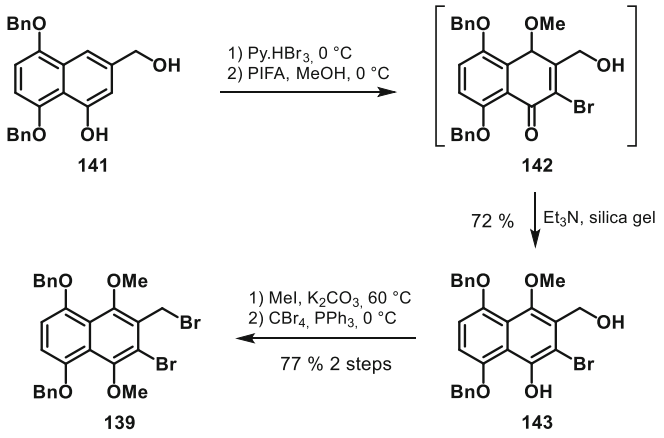
Scheme 30. After some experimentation it became clear that previous methodology would be hardly adaptable [41] for efficient approach to **134**, and the pursued strategy is shown retrosynthetically in Scheme 30.

It was believed that that monomeric unit **134** could be made accessible from tetracyclic ketone **135** by sequential glycosylation with bromide **136** and benzoate ester **137**, introduction of diazo group and oxidations, Scheme 30. Advanced intermediate could have been secured from aryl bromide **138** by cyclization and selenylation. The latter compound would be preparable from ketone **140** by alkylation with benzyl bromide **139**.

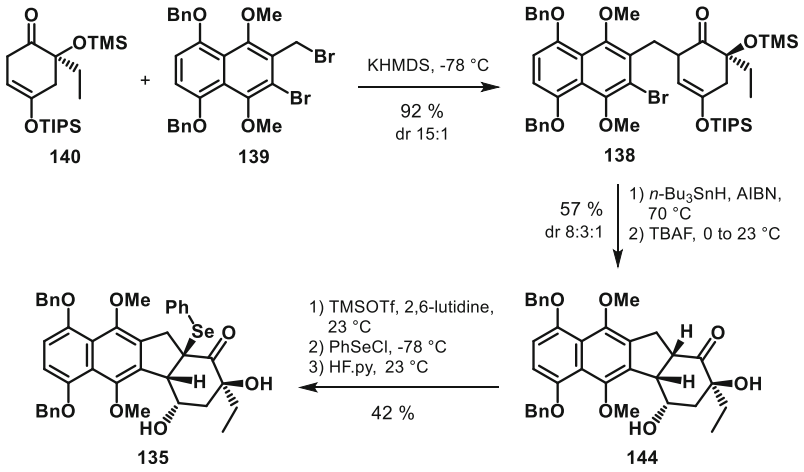
Alcohol **141**, prepared by $LiAlH_4$ reduction of the corresponding ethyl naphthoate (85%), was subjected to site selective bromination with pyridinium tribromide followed by oxidation with bis(trifluoroacetoxy)iodobenzene (PIFA) to give cyclohexanone **142**, Scheme 31. Purification on triethylamine-impregnated silica gel promoted enolization and afforded bromonaphthalene **143** in 72% yield



Scheme 30 Retrosynthetic analysis of monomer **134** by Herzon



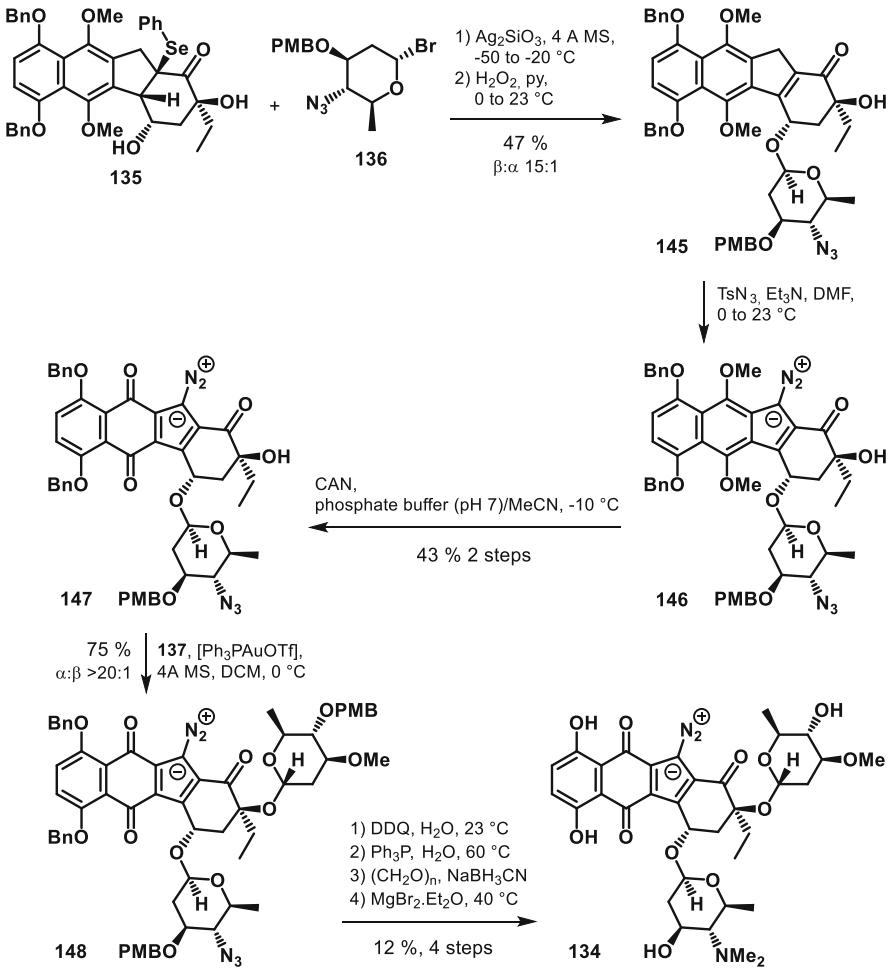
Scheme 31 Synthesis of bromide **139** by Herzon



Scheme 32 Synthesis of tetracyclic ketone **135** by Herzon

from **141**. Phenol alcohol **143** then underwent *O*-methylation followed by final conversion to target bromide **39**; 77% over 2 last steps.

The ketone **140**, obtained from the alcohol **72** (91% ee, see Scheme 14) by IBX oxidation and silylation in 65% yield, was alkylated with the bromide **139** using KHMDS (potassium bis(trimethylsilyl)amide) as a base at −78°C and afforded ketone **138** (92%) with dr 15:1, Scheme 32. The following radical 5-*exo*-trig cyclization of bromide **138** (n-Bu_3SnH, AIBN) yielded, after desilylation, the tetracycle **144** with dr 8:3:1 (57% from **138**). The major diastereoisomer could be separated by PTLC (preparative thin layer chromatography), but advantageously, the mixture was subjected to α-phenylselenylation (TMSOTf (trimethylsilyl trifluoromethanesulfonate), then PhSeCl), and afforded after deprotection and purification the ketone **135** as a single stereoisomer (42%).



Scheme 33 Synthesis of the monomer **134** by Herzon

Diol **135** then underwent β-glycosidation with excessive bromoazide **136** using Koenigs–Knorr protocol with silver silicate at −50 to −20°C. The β-glycoside **145** was obtained, after oxidation with hydrogen peroxide, in 47% yield from **135** with dr 15:1. The direct diazo group transfer was achieved by reaction of **145** with *p*-toluenesulfonyl azide and Et_3N, and the unstable derivative **146** was immediately oxidized to naphthoquinone **147** with ceric ammonium nitrate (CAN, 43%, 2 steps). Then, the attachment of *L*-oleandrose moiety was efficiently achieved by using the alkynyl benzoate ester **137** (β:α 4:1) under (triphenylphosphine)gold triflate catalysis in 75% yield and with excellent α-selectivity >20:1 (see Scheme 23 for previous application). Final steps involved deprotection as well as a conversion of azide to dimethylamino group; the target monomer **134** was isolated in 12% from **148** (Scheme 33).

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