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Novel Pincer Complex-Catalyzed Transformations

Including Asymmetric Catalysis

Juhanes Aydin

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To my parents and wife

Abstract

This thesis is focused on the development of new pincer complex-catalyzed transformations. Optimization of the catalytic properties (fine-tuning) was directed to increase the catalytic activity as well as the chemo-, stereo- and enantioselectivity of the complexes. This was achieved by varying the heteroatoms in the terdentate pincer ligand, by changing the electronic properties of the coordinated aryl moiety and by implementing chiral functionalities in the pincer complexes.

In the cross-coupling reaction of vinyl epoxides and aziridines with organoboronic acids the chemoselectivity of the reaction could be increased by employment of pincer complexes instead of commonly used Pd(0) catalysts. Furthermore, the introduction of a methoxy substituent in the aromatic subunit of the complex considerably increased the activity of the pincer complex catalyst.

Fine-tuning of the enantioselectivity in electrophilic allylation reactions was achieved by using a wide variety of new BINOL and biphenanthrol-based pincer complexes. The highest enantioselectivity (85% ee) was obtained by applying biphenanthrol-based pincer complexes.

Stereoselective pincer complex-catalyzed condensation of sulfonylimines with isocyanoacetate could be achieved under mild reaction conditions. By application of chiral PCP catalysts, 2-imidazolines could be obtained with up to 86% ee.

A new pincer complex-catalyzed C-H bond functionalization based reaction between organonitriles and sulfonylimines affords homoallylic amines and β-aminonitriles in high yields. The asymmetric version of this process affords β-aminonitriles with up to 71% ee.

In the last chapter, a pincer complex-catalyzed redox coupling reaction is described. In this highly regio- and stereoselective process the integrity of the pincer catalysts is fully retained. This catalytic reaction proceeds with a high level of functional group tolerance, as allylic acetate and aryl halide functionalities are retained.

List of publications

This thesis is based on the following papers, which will be referred to by Roman numerals:

I. **Palladium Pincer Complex Catalyzed Cross-Coupling of Vinyl Epoxides and Aziridines with Organoboronic Acids**
J. Kjellgren, J. Aydin, O. A. Wallner, I. Saltanova and K. J. Szabó
Chem. Eur. J. **2005**, *11*, 5260 – 5268

II. **Strategies for Fine-tuning the Catalytic Activity of Pincer-complexes**
J. Aydin, N. Selander and K. J. Szabó
Tetrahedron Lett. **2006**, *47*, 8999 – 9001

III. **Synthesis and Catalytic Application of Chiral 1,1´-Bi-2-naphthol- and Biphenanthrol-Based Pincer Complexes: Selective Allylation of Sulfonimines with Allyl Stannane and Allyl Trifluoroborate**
J. Aydin, K. S. Kumar, M. J. Sayah, O. A. Wallner and K. J. Szabó
J. Org .Chem. **2007**, *72*, 4689 – 4697

IV. **Palladium-Pincer Complex Catalyzed Condensation of Sulfonimines and Isocyanoacetate to Imidazoline Derivatives. Dependence of the Stereoselectivity on the Ligand Effects**
J. Aydin, K. S. Kumar, L. Eriksson and K. J: Szabó
Adv. Synth. Catal. **2007**, *349*, 2585 – 2594

V. **Chiral Palladium-Pincer Complex Catalyzed Asymmetric Condensation of Sulfonimines and Isocyanoacetate**
J. Aydin, A. Rydén and K. J. Szabó
Tetrahedron: Asymmetry **2008**, *19*, 1867 – 1870

VI. **Palladium-Pincer Complex Catalyzed C-C Coupling of Allyl Nitriles with Tosyl Imines *via* Regioselective Allylic C-H Bond Functionalization**
J. Aydin and K. J. Szabó
Org. Lett. **2008**, *10*, 2881 – 2884

VII. **Stereoselective Pincer-Complex Catalyzed C-H Functionalization of Benzyl Nitriles under Mild Conditions. An Efficient Route to β-Aminonitriles**
J. Aydin, C. S. Conrad and K. J. Szabó
Org. Lett. **2008**, *10*, 5175 – 5178

VIII. **Pincer Complex-Catalyzed Coupling Reactions *via* Palladium (IV) Intermediates**
J. Aydin, J. M. Larsson and K. J. Szabó.
Submitted

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Contents

Abbreviations

The abbreviations are used in agreement with standards of the subject.[1] Only non-standard and unconventional ones that appear in the thesis are listed here.

BINOL	1,1´-Bi-2-naphthol
Bs	Benzenesulfonyl
Cond	Conditions
D	Donor atom
dba	Dibenzylidene acetone
ee	Enantiomeric excess
eqv	Equivalents
lb	Line broadening
L_n	Unspecified number of ligands
M	Metal
R	Substituent
Q	Oxygen atom or toluenesulfonyl amide
X	Halogen

[1] *Org. Lett.* **2009**, *11*, 24A-22A.

1 Introduction

Development of new catalytic transformations for selective carbon-carbon bond formation reactions is an important field in modern organic synthesis.[1-5] Palladium catalysis offers a versatile method for creating new carbon-carbon bonds with high regio-, stereo- and chemoselectivity under mild conditions.[4,6-10]

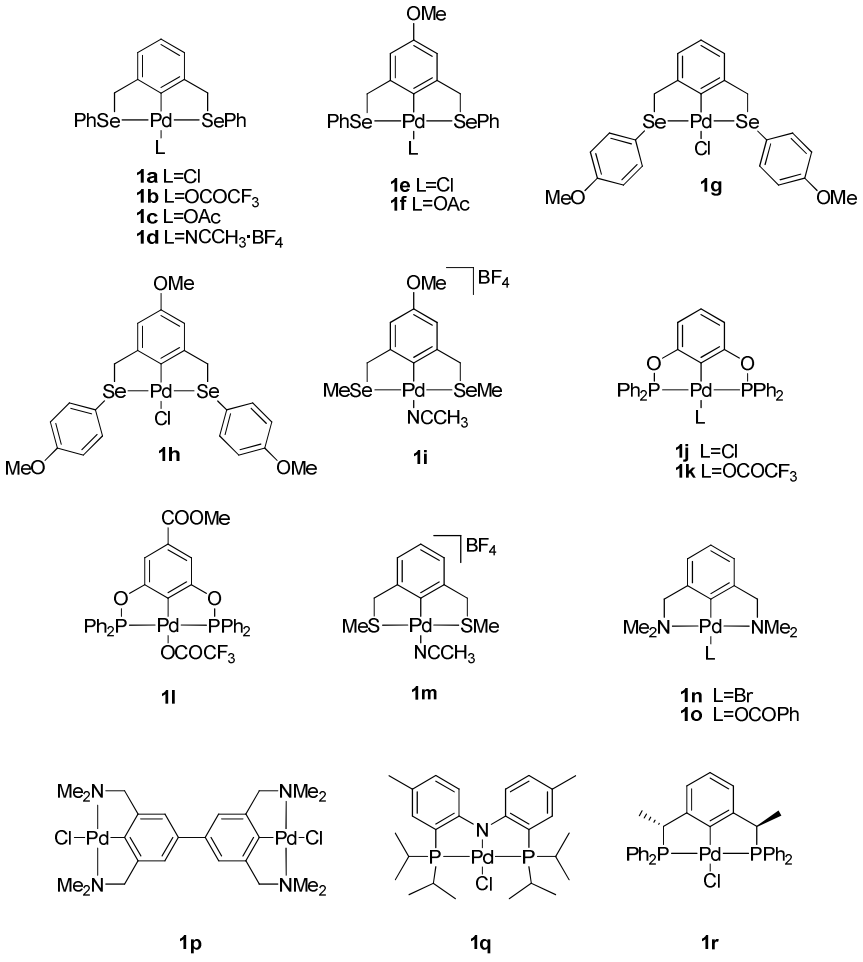


Figure 1. Selected pincer complexes.

The use of the so-called palladium pincer complexes is a rapidly expanding field in palladium-catalyzed organic synthesis.[11-18] Compared to traditional palladium catalysts, pincer complexes often offer higher efficiency, selectivity and functional group tolerance. This thesis is focused on the synthesis of electronically and sterically fine-tuned palladium pincer complexes, and their use in new organic transformations.

1.1 Nomenclature, properties and synthesis of pincer complexes

The nomenclature of the pincer complexes is based on the heteroatoms of the side arms and the *ipso* atom bound to palladium. For example, the abbreviated name of complex **1a** is SeCSe palladium pincer complex (Figure 1).

As a consequence of the terdentate pincer ligand structure and the strong ligand-metal interaction, ligand exchange processes are prevented, leading to air-, moisture- and thermostable pincer based catalysts.[12-16] Since the pincer ligand occupies three of the four coordination sites, only a single site is available for external ligands when the palladium atom is in oxidation state +II. Limiting the number of free sites on the catalyst leads to an increase in the regio- and stereoselectivity of organic transformations.[14,16] In addition, the high stability and catalytic selectivity make pincer complex catalysts suitable for immobilization on solid support.[12,14] Because of the well-defined structure, the high catalytic activity and selectivity, pincer complexes can be efficiently fine-tuned by varying the heteroatom in the side arms, or by substitution of the aryl subunit of the complex (Figure 2).

Two oxidation states, +II and +IV, are accessible for the palladium in pincer complexes. However, when the palladium atom is reduced to its lowest oxidation state (Pd(0)) the complex decomposes.[19] In the majority of the direct pincer complex-catalyzed transformations the palladium atom is in +II oxidation state. Although, catalytic transformations *via* Pd(IV) pincer intermediates have never been reported, Canty[20] and van Koten[21] have shown that NCN complexes **1o**-**p** react with hypervalent iodonium(III) salts affording Pd(IV) pincer complexes (see chapter 7).

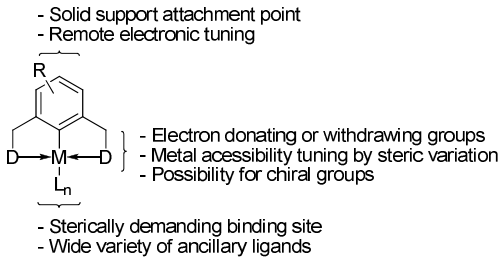
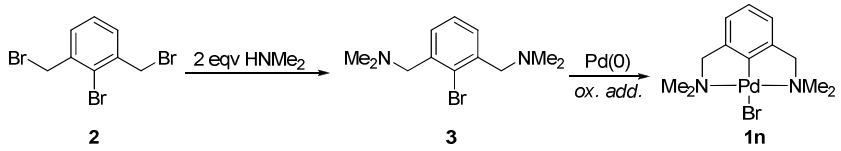


Figure 2. General features of pincer complexes.

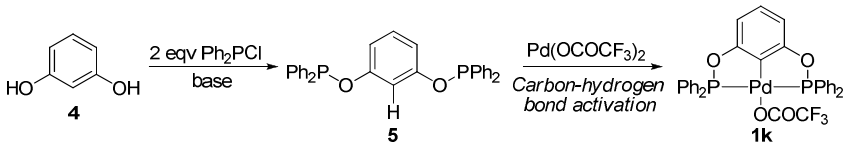
There are several strategies to introduce the metal atom into the pincer ligand. One of the approaches is based on oxidative addition of Pd(0) to the aryl-halogen bond of the pincer pro-ligand (Scheme 1).



Scheme 1. Synthesis of NCN palladium pincer complex **1n** *via* oxidative addition.

For example, the synthesis of NCN palladium pincer complex **1n** is initiated by amination of tribromide **2** with secondary amines such as dimethyl amine yielding NCN ligand **3**. Subsequently, palladium is inserted to the aryl-bromide bond *via* a facile oxidative addition to obtain complex **1n** (Scheme 1).[22,23]

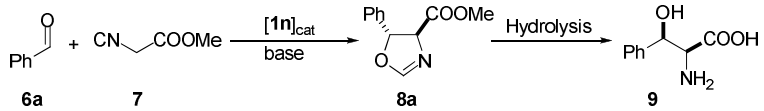
Another strategy for introduction of palladium to a pincer ligand is aromatic carbon-hydrogen bond activation, such as in preparation of complex **1k** (Scheme 2). In this process resorcinol (**4**) was first reacted with Ph_2PCl affording **5**. When $Pd(OCOCF_3)_2$ is added to **5**, the phosphorus side arms coordinate to the palladium atom, and this ligation process triggers *ortho*-metalation of the aromatic ring providing complex **1k**.[12,14,15,24]



Scheme 2. Synthetic route to PCP Pd pincer complex **1k** *via* C-H bond activation.

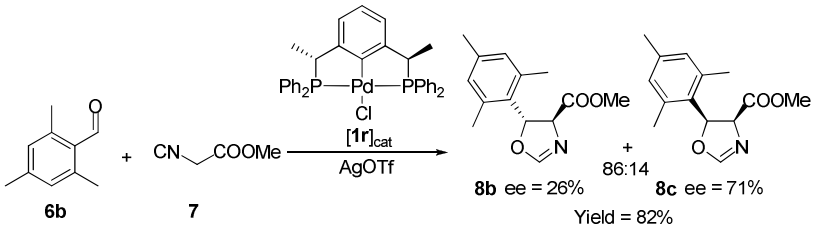
1.2 Application of pincer complexes in organic transformations

Aldol reactions. One of the main application areas of palladium pincer complex catalysis is the aldol reaction of aldehydes **6** with isocyanoacetates **7** affording oxazoline derivatives **8**,[25-31] which can be hydrolyzed to β-hydroxy amino acids **9** (Scheme 3).



Scheme 3. Catalytic aldol reaction of aldehyde **6a** and isocyanoacetate.

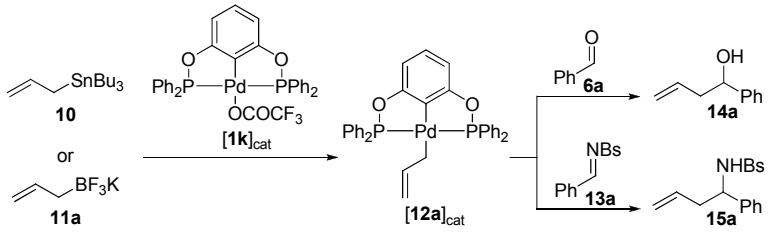
Using the appropriate chiral catalyst this reaction has a potential for synthesis of optically active β-hydroxy amino acids.



Scheme 4. Asymmetric version of the aldol reaction.

Indeed, Zhang and co-workers developed an asymmetric version of this condensation reaction using chiral pincer catalyst **1r** (Scheme 4).[26]

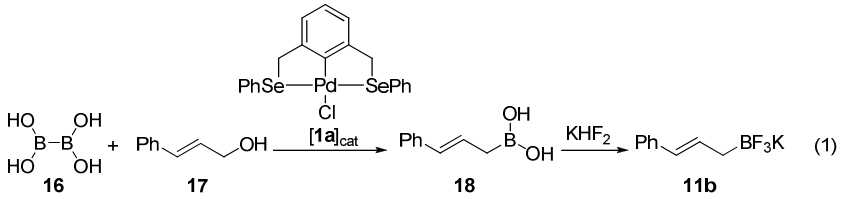
Allylation of aldehydes and imines. Although the palladium-catalyzed nucleophilic allylic substitution is an important area in palladium catalysis,[4,6,7,32-36] recently, electrophilic allylation reactions have attracted considerable attention.[35,37-47] It was shown by Szabó and co-workers[48-50] that palladium pincer complexes efficiently catalyze the electrophilic allylation of imines and aldehydes. In these reactions allyl stannanes (such as **10**) and potassium trifluoro(allyl)borates (such as **11a**) were employed as allylating reagents (Scheme 5). The reaction afforded homoallylic alcohols (such as **14a**) and amines (such as **15a**) in high yields and selectivity.[51,52] Mechanistic studies have shown[48-50] that complex **1k** undergoes transmetalation with **10** (or **11a)** affording η^1-allyl palladium complex **12a**. Subsequently complex **12a** reacts with an electrophile (e.g. **6a** or **13a**) providing the functionalized homoallylic product (e.g. **14a** or **15a**).



Scheme 5. Pincer complex catalyzed allylation of aldehydes and sulfonylimines.

Synthesis of allylic boronates. The Szabó group has also shown[53-55] that allylic substrates can be converted to allylic boronates using hypodiboric acid **16** and catalytic amounts of palladium pincer complex **1a**.[56] For example, using this methodology, cinnamyl alcohol (**17**) can directly be transformed into the corresponding cinnamyl boronic acid **18** (eq 1). Subse-

quently, the synthesized allyl boronic acid derivatives (**18**) were converted to more stable allyl trifluoroborates, such as **11b**, which can be employed as substrate[50] in stereoselective allylation of sulfonylimines (c.f. Scheme 5).



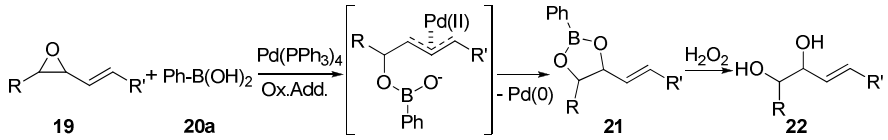
(1)

1.3 Aim of this thesis

This thesis is focused on the development of new pincer complex-catalyzed reactions and the fine-tuning of the catalytic activity of palladium pincer complex catalysts. The development of new transformations is focused on the broadening of the synthetic scope of palladium pincer complex catalysis on several new areas, such as: cross-coupling reaction of vinyl epoxides and aziridines (papers I and II); catalytic C-C coupling of organonitriles with sulfonylimines (papers VI and VII) and oxidative Heck-reaction (paper VIII). Another important aim is to develop asymmetric catalysis based on the use of chiral pincer complex catalysts (papers III, V and VI). The synthetic work is also combined with mechanistic studies to allow a systematic design of selective pincer complex catalysts.

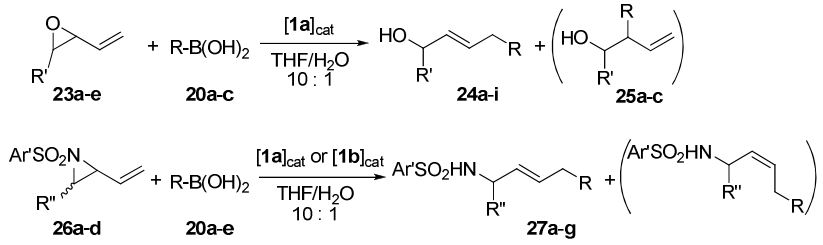
2. Pincer complex-catalyzed cross-coupling of vinyl epoxides and aziridines with organoboronic acids (Paper I)

Although palladium-catalyzed coupling of organoboronic acids with various unsaturated substrates (Suzuki-Miyaura cross-coupling[57-62]) has become one of the most important processes in synthetic organic chemistry, the literature of Pd-catalyzed cross-coupling reactions of organoboron compounds with vinyl epoxides and aziridines is surprisingly scarce. One of the few literature procedures is reported by Suzuki and Miyaura on a Pd(0)-catalyzed C-C coupling reaction of vinyl epoxides with alkenylboronates.[63]



Scheme 6. Pd(0) catalyzed C-O coupling with arylboronic acids and vinyl epoxides.

Interestingly, using $Pd(PPh_3)_4$ as the catalyst source, vinyl epoxides **19** undergo C-O coupling with arylboronic acids **20** *via* (η^3-allyl)palladium intermediates.[64] In this reaction the boronic acid derivatives **20** react as oxygen nucleophiles instead of carbon nucleophiles (Scheme 6).[64,65]

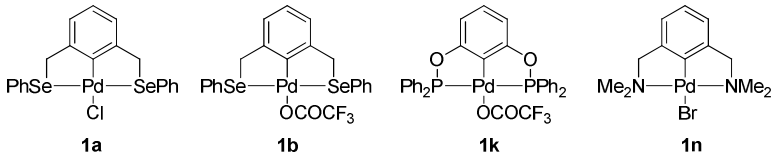


Scheme 7. Pincer complex-catalyzed arylation of vinyl epoxides and aziridines.

However, Pd-catalyzed C-C coupling of vinyl epoxides with aryl- and alkenylboronic acids has not been reported in the literature. There is also a

remarkable lack of reports in the literature concerning Pd-catalyzed ring opening reactions of vinyl aziridines with organoboronic acids (Scheme 7).

Our studies demonstrate that palladium pincer complexes **1a**,[56] **1b** and **1n**[66] (Scheme 8) are efficient catalysts in the cross-coupling of vinyl epoxides and aziridines with organoboronic acids (Scheme 7).



Scheme 8. Pincer complexes employed in this study.

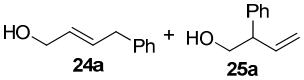
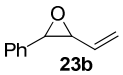
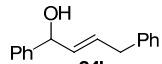
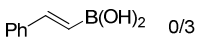
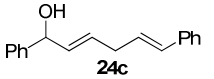
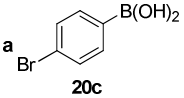
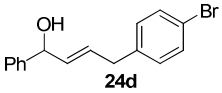
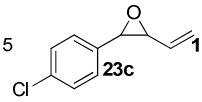
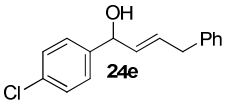
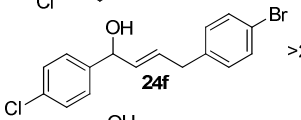
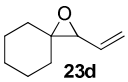
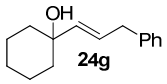
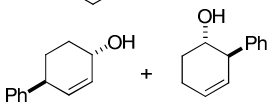
2.1 Synthesis of functionalized allylic alcohols and amines *via* pincer complex-catalyzed cross-coupling of vinyl epoxides and aziridines with organoboronic acids

In our studies we have coupled vinyl epoxides **23a**-**e** and aziridines **26a-d** with arylboronic acids **20a**-**e** using catalytic amounts of complex **1a** or **1b** (Scheme 7) under typical Suzuki-Miyaura conditions[57-62] including the use of base and water as additives. The reactions are operationally simple and proceed in high yield. In a typical procedure, the appropriate epoxide (**23a**-**e**) or aziridine (**26a-d**), the organoboronic acid derivative **20a**-**e** (1.2 eqv), Cs_2CO_3 or CsF (2 eqv) and catalyst **1a** (0.5-2.5 mol%) in THF/water 10:1 were stirred at 20 °C for 8 hours. Subsequently, the product was purified by chromatography. Neither inert atmosphere nor carefully dried solvent were required in these reactions. As a consequence of the mild reaction conditions and the redox stability of the catalyst, halide (I, Cl and Br) substituents are tolerated (Table 1, entries 4, 5 and 6; Table 2, entry 5; Table 4, entry 1). It was found that the reactivity of the acyclic epoxides **23a**-**d** is lower than that of cyclic epoxide **23e** (Table 1, entries 1-7 compared to entry 8), and that the parent epoxide **23a** reacted faster than its substituted analogues **23b**-**d** (Table 1, entry 1 compared to entries 2-8).

We have briefly studied the substituent effects on the reactivity of the vinyl epoxide and aziridine components. In the presence of an electron-withdrawing chloro substituent on the vinyl epoxide substrate (**23c**), the reactivity is increased leading to about 50% faster cross-coupling reactions (Table 1, entries 2 and 5). Surprisingly, the presence of aromatic substituents did not influence significantly the reactivity of the aziridine substrates (**26a-d**). The reactivity also depends on the substituents of the organoboronic acid component. In the cross-coupling reaction with vinyl epoxides, alkenylboronic acid **20b** reacts much faster than arylboronic acids **20a** and **20c** (Table

1, entries 2-4). The same trend was observed for the cross-coupling reaction of vinyl aziridines, where boronic acid **20b** reacted faster than boronic acids **20a** and **20e** (Table 2, entries 1-2 and Table 4, entry 1).

Table 1. Pincer complex-catalyzed arylations of vinyl epoxides.[a]

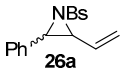
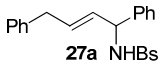
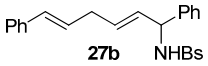
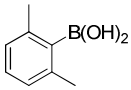
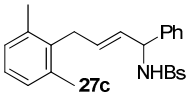
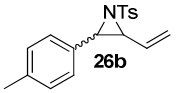
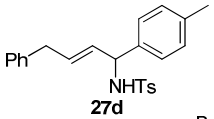
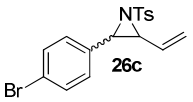
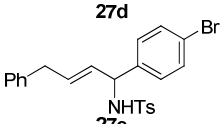
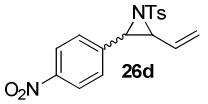
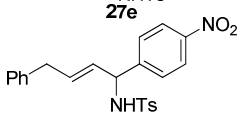
Entry	Substrate	Cat.[b]	R-B(OH)$_2$	Cond.[c]	Product	Ratio[d]	Yield[e]
1	 **23a**	**1a**	PhB(OH)$_2$ **20a**	0/16	 **24a** + **25a**	11:1	94
2	 **23b**	**1a**	**20a**	20/9 (20/17)	 **24b**	>20:1 (>20:1)	86 (85)[f]
3	**23b**	**1a**	 **20b**	0/3	 **24c**	>20:1	95
4	**23b**	**1a**	 **20c**	20/6	 **24d**	>20:1	88
5	 **23c**	**1a**	**20a**	20/5 (20/17)	 **24e**	>20:1 (>20:1)	95 (81)[f]
6	**23c**	**1a**	**20c**	20/4	 **24f**	>20:1	76
7	 **23d**	**1a**	**20a**	20/9 (20/17)	 **24g**	>20:1 (>20:1)	95 (91)[f]
8	 **23e**	**1a**	**20a**	-20/2	 **24h** + **25b**	2:1	95

[a] The reactions were carried out using 2.5 mol% catalyst in the presence of Cs_2CO_3 in THF/H_2O 10:1. [b] 2.5 mol% catalyst was used. [c] Reaction temperature / reaction time [°C] / [h]. [d] Isomer ratio of **24/25**. The > 20:1 ratio indicates that isomer **25** was not detected in the crude or in the isolated product by ^{1}H NMR spectroscopy. [e] Isolated yield [%]. [f] The results indicated in parentheses were run with 0.5 mol% catalyst.

Bromo substitution of the arylboronic acid component (**20c**) clearly accelerates the cross-coupling process with vinyl epoxides (Table 1, entries 2 and 4). Sterically hindered boronic acids (such as **20d**) represent challenging substrates. Indeed the cross-coupling reaction of **20d** with aziridine **26a** could not be performed efficiently using catalyst **1a**. It was found that exchange of the chloride counter ion of **1a** to trifluoroacetate (**1b**) leads to an increase of the catalytic activity of the complex. Accordingly, complex **1b** catalyzed the opening of vinyl aziridine **26a** with excellent selectivity and yield (Table 2, entry 3). The pincer complex-catalyzed reactions also tolerate *ortho* substituents in the aromatic substrates (**20d**). In these processes, trifluoroacetate complex **1b** was employed as catalyst to provide high yields

(entry 3 in Table 2). The cross-coupling reaction of **26a** and **20d** was also attempted with $Pd_2(dba)_3$ as catalyst. ^1H NMR analysis of the crude reaction mixture indicated formation of **27c** together with several unidentified by-products.

Table 2. Selected entries for catalytic arylation of vinyl aziridines.[a]

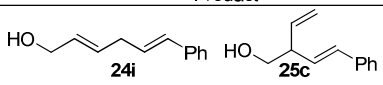
Entry	Substrate[b]	Cat.	R-B(OH)$_2$	Cond.[c]	Product	trans/cis[d]	Yield[e]
1	 **26a**	**1a**	**20a**	20/18	 **27a**	19:1	95
2	**26a**	**1a**	**20b**	20/3	 **27b**	19:1	95
3	**26a**	**1b**	 **20d**	20/18	 **27c**	25:1	95
4	 **26b**	**1a**	**20a**	20/17	 **27d**	17:1	82
5	 **26c**	**1a**	**20a**	20/16	 **27e**	10:1	86
6	 **26d**	**1a**	**20a**	20/16	 **27f**	19:1	95

[a] The reactions were carried out using 2.5 mol% catalyst in the presence of CsF in THF/H_2O 10:1. [b] *Trans/cis* (approximately 2:1) mixture was used as substrate. Bs = benzenesulfonyl; Ts = toluenesulfonyl. [c] Reaction temperature / reaction time [°C] / [h]. [d] *Trans/cis* ratio of the double bond geometry in the products. [e] Isolated yield [%]. [f] 5 mol% catalyst was employed.

We also attempted to use other pincer complex catalysts in the cross-coupling reactions. It was found that catalyst **1n** (Scheme 8) displayed lower reactivity and regioselectivity than **1a** (compare entries 1 and 2 in Table 3). Catalyst **1k** has been employed by Bedford and co-workers[67] for the Suzuki coupling of aryl boronic acids with aryl halides at elevated temperatures (130 °C). Nevertheless, under our mild reaction conditions, catalyst **1k** showed no catalytic activity (Table 3, entry 3).[51,67] $Pd_2(dba)_3$ showed high catalytic reactivity, however the regioselectivity of the coupling reaction was lower than with pincer catalyst **1a** (Table 3, entry 4).

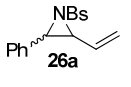
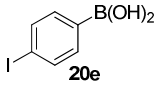
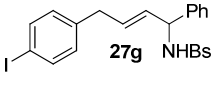
Iodo functionalities are usually incompatible with Pd(0) catalysts due to the rapid oxidative addition of the carbon-iodine bond. Indeed, the reaction of **26a** and **20e** with $Pd_2(dba)_3$ as catalyst (entry 2, Table 4) proceeds with a considerably lower yield than the corresponding reaction catalyzed by pincer complex **1b** (entry 1, Table 4).

Table 3. Comparison of different catalysts in the opening of vinyl epoxides.[a]

Entry	Substrate	Cat.[b]	R-B(OH)$_2$	Cond.[c]	Product	Ratio[d]	Yield[e]
1	 **23a**	**1a** **20b**		0/3	 **24i** **25c**	9:1	95
2	**23a**	**1n**	**20b**	20/4	**24i + 25c**	7:3	95
3	**23a**	**1k**	**20b**	20/4	-	-	-
4	**23a**	$Pd_2(dba)_3$	**20b**	0/3	**24i + 25c**	3:2	94

[a] The reactions were carried out using 2.5 mol% catalyst in the presence of Cs_2CO_3 in THF/H_2O 10:1. [b] 2.5 mol% catalyst was employed [c] Reaction temperature / reaction time [°C] / [h]. [d] Isomer ratio of **24/25**. [e] Isolated yield [%].

Table 4. Comparison between pincer catalyst **1b** and $Pd_2(dba)_3$.[a]

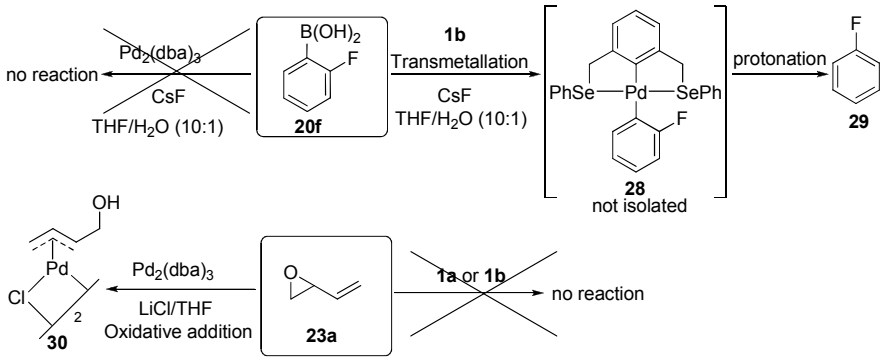
Entry	Substrate[b]	Cat.	R-B(OH)$_2$	Cond.[c]	Product	trans/cis[d]	Yield[e]
1	 **26a**	**1b**	 **20e**	20/16	 **27g**	8:1	93
2	**26a**	$Pd_2(dba)_3$	**20e**	20/18	**27g**	8:1	50

[a] The reactions were carried out using 5 mol% catalyst in the presence of CsF in THF/H_2O 10:1. [b] *Trans*/*cis* (about 2:1) mixture was used as substrate. [c] Reaction temperature / reaction time [°C] / [h]. [d] *Trans*/*cis* ratio of the double bond geometry in the products. [e] Isolated yield [%].

2.2 Elucidation of the mechanistic details in the cross-coupling reactions

Since both Pd(0) (such as $Pd_2(dba)_3$) and Pd(II) pincer complexes (such as **1b**) are able to catalyze the cross-coupling reaction of arylboronic acids and vinyl epoxides, we compared the mechanistic features of these two types of catalysts. Accordingly, stoichiometric reactions (monitored by ^{19}F and ^{1}H NMR spectroscopy) were carried out with two different palladium complexes ($Pd_2(dba)_3$ and **1b**), arylboronic acid **20f** and epoxide substrate **23a** (Scheme 9). It was found that complex **1b** reacted readily with **20f** in the presence of CsF and water in THF even in the absence of the vinyl epoxide component (Scheme 9). According to ^{19}F NMR spectroscopy, fluorobenzene **29** was formed after 20 minutes. Under the same reaction conditions using $Pd_2(dba)_3$ in place of **1b** the fluoroboronic acid **20f** remained unchanged and formation of **29** was not observed even after several hours of reaction time. The same result was obtained in the absence of any palladium source. Another series of stoichiometric reactions were performed using $Pd_2(dba)_3$ or complexes **1a** or **1b** and vinyl epoxide **23a**. When $Pd_2(dba)_3$ was mixed with vinyl epoxide **23a** in THF-d_8 in the presence of LiCl the color of the solution rapidly turned from purple to yellow, and the ^{1}H NMR spectrum showed formation of (η^3-allyl)palladium complex **30**, which could be isolated. Pin-

cer complexes with chloride and trifluoroacetate counter ions (**1a** and **1b**) did not react with epoxide **23a** at all. These reaction mixtures remained unchanged after several days.

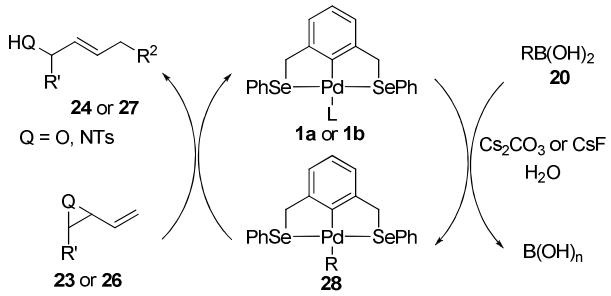


Scheme 9. Stoichiometric reactions with epoxide **23a** and fluoroboronic acid **20f**.

These stoichiometric studies clearly show that the mechanism of the catalytic cross-coupling reactions with $Pd_2(dba)_3$ and pincer complexes (**1a** or **1b)** are substantially different. The applied $Pd_2(dba)_3$ initiates the catalytic cycle by an oxidative addition to the vinyl epoxide **23a.**[63-65] The relatively rapid appearance of fluorobenzene **29** in the reaction between pincer catalyst **1b** and boronic acid **20f** (Scheme 9) can be explained by the transmetalation of **20f** with pincer complex **1b** to give **28**, which then undergoes hydrolysis providing **29** (Scheme 9). Unfortunately, in the presence of water, direct observation or isolation of complex **28** was prevented by this hydrolysis process.

Considering the above, we assume that the initial step of the catalytic cycle (Scheme 10) is transmetalation of **1a** or **1b** with the corresponding organoboronic acid derivative (**20**). Prior to this step the $B(OH)_2$ group is converted to a better leaving group by the action of Cs_2CO_3/CsF and water.[57,60] Transmetalation of **20** with **1a**, **1b** or **1n** results in complex **28**, from which the aryl or vinyl functionality (R) is subsequently transferred to the vinyl epoxide or aziridine substrate in an S_N2' (or S_N2) type reaction. A fast S_N2' process requires a high electron-density on the organic functionality (R) ensured by the electron-donating SeCSe and NCN ligands, when **1a**, **1b** or **1n** is employed as catalyst. Consequently, the low catalytic activity of **1k** can be explained by the presence of π-acceptor phosphorus ligands, which decrease the electron-density on the organic group. The reaction rate also depends on the electronic properties of the epoxide and aziridine substrates **23** or **26**. An electron-withdrawing group on the epoxide or aziridine substrate, such as the chloro or nitro functionality in **23c** or **26d**, increases the

electrophilicity of this substrate leading to a fast transfer of the organic group.



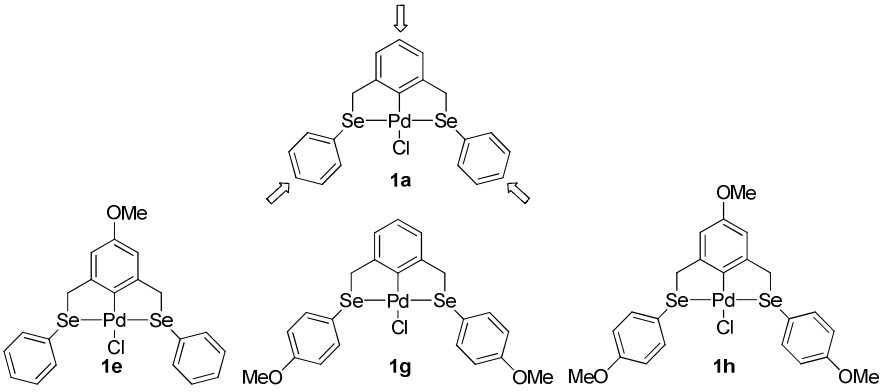
Scheme 10. Catalytic cycle for the pincer complex (**1a**-**b**) catalyzed reaction.

2.3 Concluding remarks

Palladium pincer complexes **1a** and **1b** are highly efficient catalysts for the carbon-carbon cross-coupling reaction of vinyl epoxides **23** and aziridines **26** with organoboronic acids **20**. These catalytic transformations proceed with high regioselectivity affording allylic alcohols and amines in good to excellent yields. Because of the high redox stability of the Pd(II) pincer complex catalyst, aromatic chloro-, bromo- and iodo-substituents are tolerated. The catalysts **1a** and **1b** are readily available, and the catalytic reaction does not require the use of inert gas atmosphere or dry solvents. The pincer complex-catalyzed reactions are more selective than the corresponding $Pd_2(dba)_3$ catalyzed processes. Our mechanistic studies indicate that the pincer complex catalyst does not undergo redox reactions; and that the oxidation state of the palladium atom is +II under the catalytic process. It was concluded that the initial step of the reaction is transmetalation of the organoboronic acid to the pincer complex followed by an S_N2' type transfer process. The presented pincer complex-catalyzed process allows cross-coupling reactions of easily accessible organoboronic acids with vinyl epoxides and aziridines, broadening the synthetic scope of selective palladium catalysis.

3. Enhancing the catalytic activity of pincer complexes by altering the electronic properties of the pincer backbone through substitution (Paper II)

As mentioned in the introduction (section 1.1) one of the most important features of the pincer complexes is the strong terdentate coordination between the palladium and the pincer ligand. Thus, during a catalytic reaction the ligand remains tightly bound to the metal center for the entire reaction. Accordingly, the activity and selectivity of pincer complex catalysts are expected to be efficiently fine-tuned by substitution of the pincer ligand.



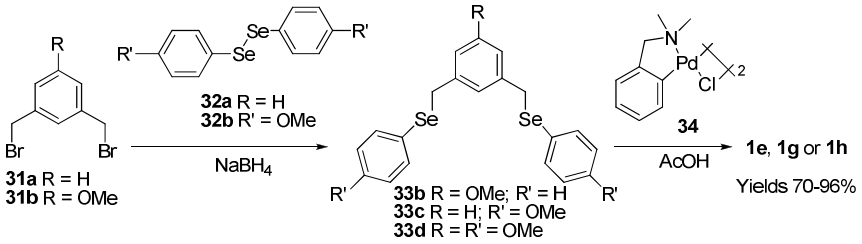
Scheme 11. Pincer complexes applied in this study

3.1 Synthesis of methoxy substituted SeCSe complexes

Our mechanistic studies (section 2.2) suggested that the catalytic activity of **1a** could be increased for several catalytic transformations by increasing the electron density on palladium. Therefore, we prepared several analogs of **1a** (Scheme 11) to investigate the electronic effects of the electron-donating methoxy substituents on the catalytic activity of the complex. In complex **1e**, the methoxy substituent is located *para* to the metal, while in **1g** the side arms are substituted. Expecting a synergistic effect on the methoxy substitu-

tion, we also prepared complex **1h**, which is substituted both at the *para* position and in the side arms.

Pincer complexes **1e**, **1g**, and **1h** were synthesized by a slightly modified version of the procedure reported by Yao and co-workers.[56] Dibromoxylene derivatives **31a-b** were reacted with the appropriate diselenide (**32a** or **32b**) to obtain pro-ligands **33b-d**, which underwent a transcyclometalation reaction[13,28] with **34** to give complexes **1e**, **1g**, and **1h** in good to excellent yields (Scheme 12). Characterization of the complexes by ^{77}Se NMR spectroscopy revealed an interesting trend. The ^{77}Se NMR shift values obtained for **1a**[68] (427.1 and 424.9 ppm) and **1e** (427.1 and 425.7 ppm) were almost identical, while methoxy substitution of the side arms led to an increase of the shielding of the selenium nuclei (**1g**, 420.5 and 419.3 ppm; **1h**, 420.7 and 419.1 ppm). This indicates that only methoxy substitution of the side arms affects the electron-density at the selenium atoms.



Scheme 12. Synthesis of pincer complexes **1e**, **1g** and **1h**.

3.2 Comparison of the catalytic activity of substituted pincer complexes in the arylation of vinyl epoxide and in the borylation of cinnamyl alcohol

In the ring opening reaction of vinyl epoxides and aziridines with organoboronic acids described in chapter 2, complex **1a** was successfully applied as catalyst. Since our stoichiometric studies suggested that the initial step in the catalytic cycle was a rapid transmetalation (Scheme 9), we reasoned that the subsequent step where the organic moiety is transferred from the catalyst to the vinyl epoxide substrate was the rate determining step. Therefore, the second step was expected to be faster if the electron density on palladium could be increased, thereby increasing the nucleophilicity of the organic moiety.

Consequently, we investigated the effects of the methoxy substituted pincer ligands on the catalytic ring opening (eq 2) of vinyl epoxide **23b** with phenyl boronic acid **20a**. The progress of the reaction was monitored by ^{1}H NMR spectroscopy (Figure 3). Under the reaction conditions applied, the complete conversion of **23b** to **24b** required about 10 hours using the parent

catalyst **1a**. Application of monomethoxy complex **1e** instead of complex **1a** led to about a four-fold acceleration of the process (eq 2), thus the reaction was completed in only two hours. Surprisingly, methoxy substitution of the catalyst in the side-arms led to a weak deactivating effect. Complex **1g** proved to be slightly less reactive than the parent complex **1a**, and the trimethoxy substituted catalyst **1h** was less efficient than the monomethoxy complex **1e**.

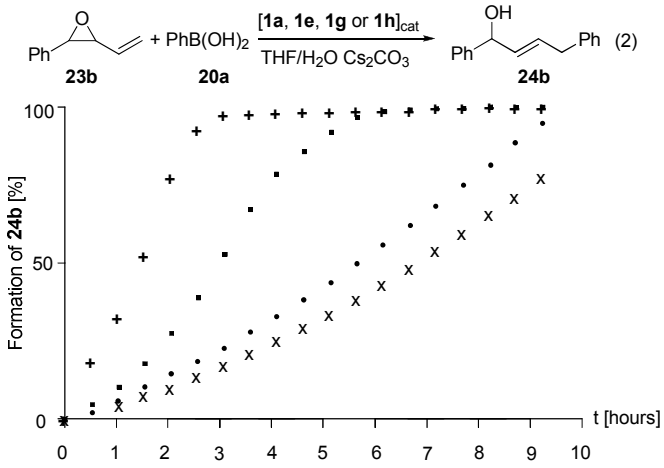


Figure 3. Catalytic opening of **23b** giving **24b**. Cat. (2.5 mol%): **1a** (•), **1e** (+), **1g** (x) and **1h** (■).

Subsequently, we studied the borylation[53,55] of cinnamyl alcohol **17** with hypodiboric acid **16** (see section 1.2), in the presence of catalytic amounts of **1a**, **1e** and **1h** (Figure 4, eq 3).

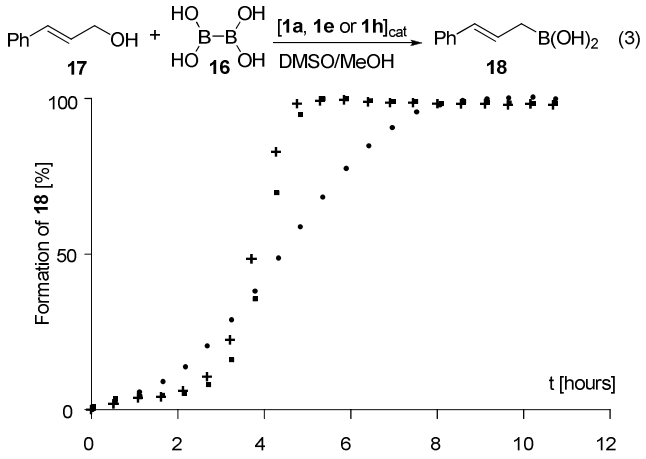


Figure 4. Catalytic borylation of **17** to obtain cinnamyl boronic acid **18** at 55°C. Cat. (5 mol%): **1a** (•), **1e** (+), and **1h** (■).

The reaction[55] was complete in about 8 hours using the parent catalyst **1a**. Similarly to the cross-coupling reaction, the borylation reaction was also accelerated when the parent complex **1a** was replaced with *para*-methoxy-substituted complex **1e**. On the other hand, the catalytic activity was unaffected by the methoxy substituents on the side-arms, as the reaction was completed about as quickly with **1h** as with **1e**.

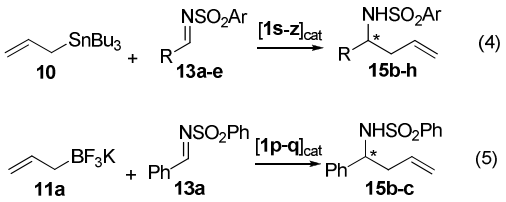
The above results clearly indicate that the most efficient fine-tuning of the catalytic activity of pincer complexes can be achieved by *para* substitution of the aromatic ring, while substitution of the side arms has much weaker effects on the catalytic activity.[28]

3.3 Summary for the fine-tuning of the reactivity of pincer complexes

In summary, we have shown that in arylation and borylation reactions, the catalytic activity of pincer complex **1a** can be effectively increased by *para*-methoxy substitution of the catalyst (**1e**). On the other hand, methoxy substitution in the side arms does not increase the catalytic activity of the complexes, and even has a slight deactivating effect. These substituent effects probably apply to other pincer complex-catalyzed substitution reactions in which charge accumulation on the metal atom is required for an increase in the catalytic activity of the complex.

4. Synthesis of chiral BINOL and biphenanthrol-based pincer complexes, and their application to the allylation of sulfonylimines with allyl stannane and potassium trifluoro(allyl)borate (Paper III)

Asymmetric allylation of imines leads to the formation of chiral homoallylic amines, which are important structural motifs in bioactive natural products and pharmaceuticals.[69-71] Therefore, considerable effort has been devoted to devising new synthetically useful versions of these reactions.[45,72-80] Our studies are focused on using BINOL-based chiral pincer complexes for allylation of sulfonylimines (eqs. 4-5).



These reactions afford homoallylic sulfonylamides, which can easily be deprotected to give homoallylic amines. Exploration of palladium-catalyzed asymmetric allylation of sulfonylimines is particularly important, as these species cannot be selectively allylated *via* chiral bis-allylpalladium complexes.[72]

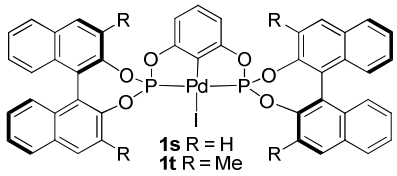


Figure 5. BINOL-based chiral pincer complexes published by the Szabó group.[73]

Preliminary studies have shown that the synthetically easily accessible BINOL-based pincer complex **1s** (Figure 5) gave poor enantioselectivity (20%

ee) in the asymmetric allylation of sulfonylimines, while the synthesis of the more selective catalyst **1t** (up to 59% ee) could only be achieved in poor yield (18%).[73]

Our recent studies employing an extensive array of chiral pincer complexes clearly show that the enantioselectivity of the allylation can be considerably enhanced by application of thioalkyl/aryl substituents (**1u-x**) in the γ-position of the BINOL ligands, or employment of biphenanthrol-based complexes (**1y-z**) (Figure 6). We have also prepared both enantiomers of the thiomethyl (**1u-v**) and biphenanthrol-based complexes (**1y-z**) to study the possibilities of having a full control over the enantioselectivity of the allylation processes. Furthermore, we employed allyl trifluoroborate **11a** as an alternative allyl source to allyl stannanes **10** in the substitution reactions.

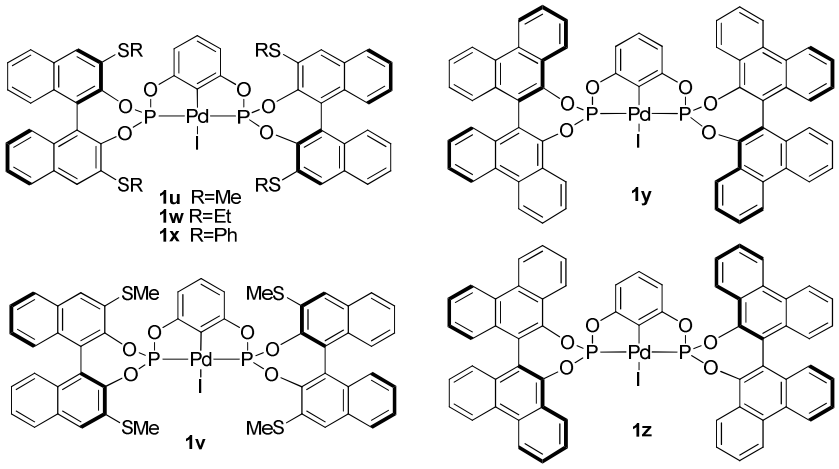
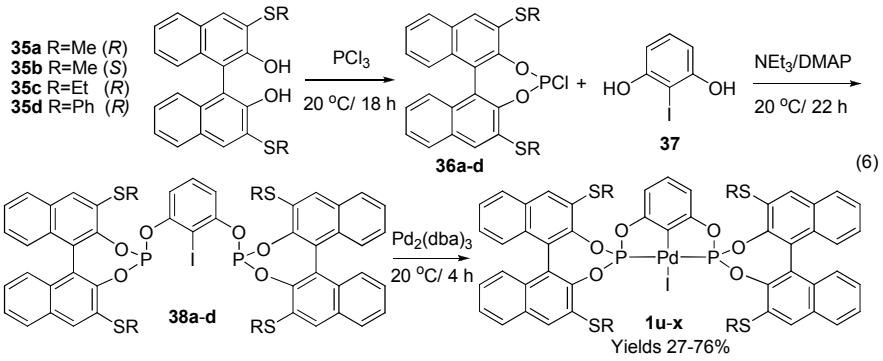


Figure 6. Novel chiral pincer complexes developed for allylation of sulfonylimines.

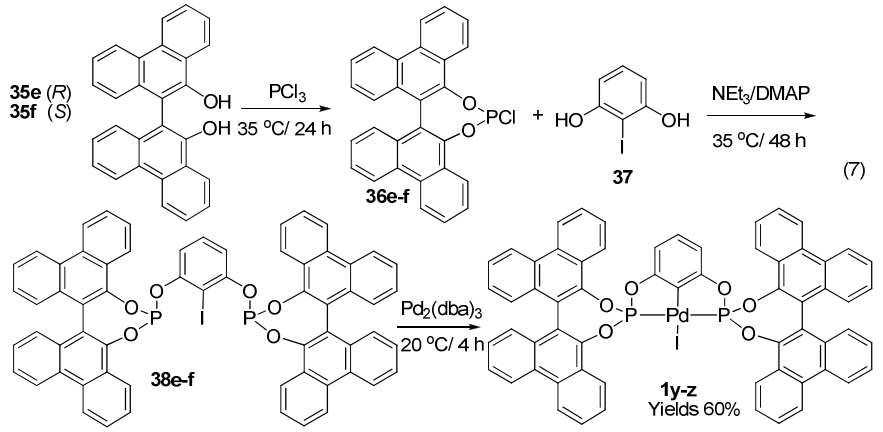
4.1 A modular approach for preparation of chiral pincer complexes

Complexes **1u**-**z** could be obtained by a flexible modular approach (eqs. 6-7) starting from optically pure BINOL (**35a**-**d**) or biphenanthrol derivatives (**35e**-**f**). In the first step, **35a**-**f** are converted into the corresponding phosphochloridates **36a-f**, which were coupled with iodoresorcinol **37** to obtain pro-ligands **38a-f**. These pro-ligands are usually very sensitive to hydrolysis, and therefore their purification is difficult. However, it was found that the crude product of **38** could be metalated under mild conditions (20 °C, 4 h) with $Pd_2(dba)_3$ *via* facile oxidative addition of Pd(0) to the carbon-iodine bond. The yields obtained were usually high (60-76%), with the exception of the synthesis of ethyl-sulfide **1w** (27%). The mild reaction conditions (20 °C

- 35 °C/ 4 h) ensure that the BINOL moieties do not undergo racemization.[81] In our experience, raising the reaction temperature above 60 °C in any of the reaction steps leads to some degree of racemization, decreasing the optical purity of pincer complexes **1u-z**.

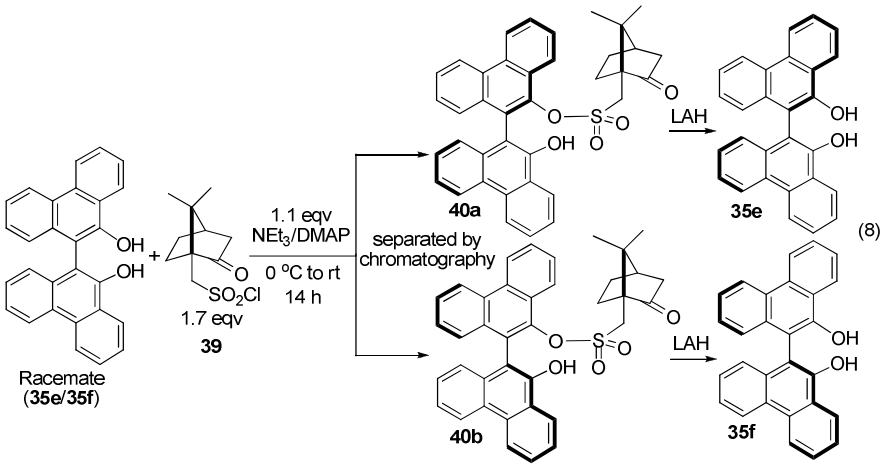


As it appears from eqs. 6-7, synthesis of the chiral pincer complexes using the above sequence is a flexible and highly modular synthetic route. Thus, starting from (*R*)-BINOL derivative[82,83] **36a** (eq 6) chiral pincer complex **1u** was obtained, while its enantiomer **1v** can be prepared from (*S*)-BINOL derivative[82] **35b** (eq 6). Similarly, both enantiomers **1y** and **1z** can be prepared from optically pure biphenanthrol derivatives **35e** (*R*)-form and **35f** (*S*)-form respectively (eq 7) by slight modification of the reaction conditions applied for the preparation of **1u**-**x**. Accordingly, using the above procedure, a great variety of chiral pincer complexes can be prepared by applying the appropriate BINOL or biphenanthrol derivatives.



Optically pure BINOL derivatives **35a**-**d** were synthesized according to literature procedures.[82,83] Although there are literature procedures available for resolution of bisphenanthrole,[84] in our hands, these procedures did not pro-

vide **35e** and **35f** in sufficiently high optical purities and quantities required for the syntheses of **1y** and **1z**. Therefore, a new method for the resolution of biphenanthrol was devised. A racemic mixture of **35e** and **35f**[85] was reacted with 1.7 eqv of (1*S*)-(+)-10 camphorsulfonyl chloride (**39**) in the presence of 1.1 eqv of NEt_3 to give diastereomeric monosulfonates **40a** and **40b** (eq 8). These species could be easily separated by column chromatography in high yields, and then reduced to optically pure **35e** and **35f** using LAH.



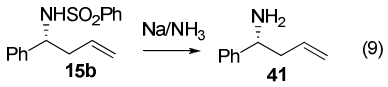
4.2 Catalytic allylation of sulfonylimines with chiral pincer complexes

The allylation reactions using allyl stannane **10** and benzenesulfonyl imine **13a** could be carried out under mild conditions (6 °C to 20 °C) in dry DMF or DMSO without additives (eq 4, Table 5). Application of (*R*)-BINOL-based thiomethyl catalyst (5 mol%) **1u** in DMF provided encouraging levels of enantioselectivity, affording homoallylic amine **18b** with 73% ee (Table 5, entry 1). The yield of this reaction (49%) could be improved using DMSO as solvent (57%); however, the enantioselectivity in this reaction (Table 5, entry 2) is slightly decreased (71% ee).

The reaction product (**15b**) was deprotected using sodium in liquid NH_3 providing homoallylic amine[86,87] **41** in 67% yield (without racemization) showing that the major enantiomer, **15b**, has (*R*) configuration (eq 9).

The allylation reaction was also carried out using the (*S*)-BINOL analogue of **1u** (**1v**). The major product (74% ee) of this reaction was the (*S*)-enantiomer **15c** (Table 5, entry 3). As the availability of (*R*)- and (*S*)-BINOL precursors for preparation of **1u** and **1v** are similar, the enantioselectivity of the presented reaction can be fully controlled by the choice of the appropriate pincer complex catalyst.

The allyl stannane reagent (**10**) could be successfully replaced with potassium trifluoro(allyl)borate (**11a**),[88] which reacted readily[50,52] with **13a** providing homoallylic amine derivative **15b** or **15c** in good yield (eq 5), albeit with somewhat lower enantioselectivity than **10** (Table 5, entries 6 and 7). Similarly to allyl stannane (**10**), the reaction of **11a** catalyzed by (*R*)-BINOL derivative **1u** gave predominantly (*R*)-product **15a**, while using (*S*)-BINOL derivative **1v** the main product had (*S*)-configuration (**15c**).



(9)

We have also studied the effects of the steric bulk of the R substituent in **1u-x** on the selectivity of the allylation process. It was found that as one goes from methyl substituent (**1u**) to ethyl substituent (**1w**), the enantioselectivity is slightly decreased (Table 5, entries 1 and 4), while thiophenyl derivative **1x** proved to be a relatively unselective (48% ee) catalyst (Table 5, entry 5). This trend suggests that simple replacement of the thiomethyl functionality with more bulky substituents was not enough to increase the enantioselectivity of the reaction.

Attempts to allylate sterically bulky sulfonylimine **13b** (Table 5, entry 8) resulted in a slower reaction and lower selectivity (48% ee) compared to the corresponding process with **13a**. Cinnamyl derivative **13c** displayed high reactivity in the allylation reaction, providing the corresponding allyl amine derivative with 59% ee (Table 5, entry 9).

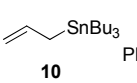
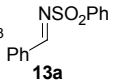
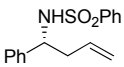
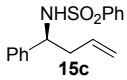
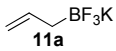
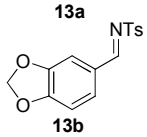
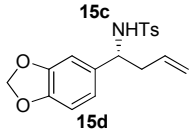
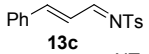
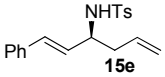
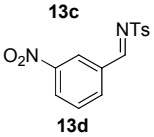
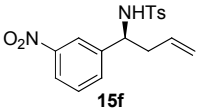
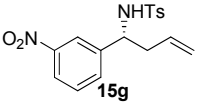
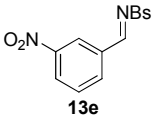
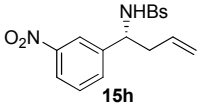
By nitro-substitution of the aromatic ring of the imine derivative **13d,** the reactivity of the imine component could be increased. Accordingly, **13d** could be allylated with high yield (85%) and only slightly lower selectivity (66% ee) than **13a**.

From the results presented above, it was concluded that the enantioselectivity (71%-74% ee) obtained by **1u** and **1v** cannot be improved by simply increasing the steric bulk of the thioalkyl substituent on the γ-position.

Based on our DFT modeling studies[52] for pincer complex-catalyzed allylation of sulfonylimines, we reasoned that substitution of the δ-position, or simultaneous substitution of both the γ and δ-positions of the BINOL system would further increase the selectivity of the allylation reaction. Therefore we envisaged replacement of the BINOL units with biphenanthrols (such as in **1y-z**), which involves substitution of both the γ and δ-positions of the BINOL moieties with an annulated aryl group.

Indeed, enantioselectivities of up to 85% for the allylation reaction could be achieved using biphenanthrol complexes **1y-z**. Thus, nitro-substituted imine **13d** reacted (Table 5, entry 11) with **10** in the presence of 5 mol% **1y** in high yield (71%) and enantioselectivity (85% ee).

Table 5. Allylation of imines in the presence of chiral pincer complexes **1u**-**z**.[a]

Entry	Allyl	Imine	Cat.	Temp./time[b]	Solvent	Product	ee[%]	Yield[c]
1	 **10**	 **13a**	**1u**	6/66	DMF	 **15b**	73	49
2	**10**	**13a**	**1u**	20/94	DMSO	**15b**	71	57
3	**10**	**13a**	**1v**	20/94	DMSO	 **15c**	74	53
4	**10**	**13a**	**1w**	20/94	DMSO	**15b**	67	44
5	**10**	**13a**	**1x**	20/94	DMF	**15b**	48	70
6	 **11a**	**13a**	**1u**	20/96	DMSO	**15b**	60	66
7	**11a**	**13a**	**1v**	20/96	DMSO	**15c**	54	68
8	**10**	 **13b**	**1u**	20/116	DMF/THF[d]	 **15d**	48	55
9	**10**	 **13c**	**1v**	6/66	DMF	 **15e**	59	53
10	**10**	 **13d**	**1v**	20/68	DMF	 **15f**	66	85
11	**10**	**13d**	**1y**	20/94	DMF	 **15g**	85	71
12	**10**	 **13e**	**1y**	20/68	DMF	 **15h**	82	78
13	**10**	**13a**	**1z**	20/91	DMF	**15c**	83	28
14	**10**	**13a**	**1z**[e]	20/91	DMF	**15c**	80	50

[a] In a typical reaction 5 mol% of catalyst **1u**-**z** was employed. [b] Reaction temperature [°C] and time [h]. [c] Isolated yield [%]. [d] A 1:1 mixture of DMF/THF was employed. [e] 10 mol% catalyst was employed.

The yield could be increased by using benzenesulfonamide derivative **13e**, affording **15h** (78%) at the cost of a slight decrease in selectivity (82% ee). The parent sulfonylimine **13a** also reacted with comparable selectivity to **13d**. Thus, the allylation reaction with **10** in the presence of **1z** provided **15c** with 83% ee (Table 5, entry 13). Similarly to the thiomethyl complexes, the (*R*)-biphenanthrol based complex **1y** provides the homoallylic amine products (**15g-h**) with (*R*)-selectivity, while complex **1z** comprising (*S*)-biphenanthrol moieties induce (*S*)-configuration at the stereogenic carbon of the product **15c**. It was found that the higher selectivity of biphenanthrol complexes **1y**-**z** was accompanied by lower catalytic activity than BINOL derivatives **1u**-**v**. This is reflected (Table 5, entries 3 and 13) by the rela-

tively low yield (28%) obtained for allylation of **13a** with **1z** compared to **1v** (53%). The yield with **1y**-**z** could be improved either by increasing the catalyst loading to 10 mol% (Table 5, entry 14), or by using activated sulfonylimines, such as **13d** and **13e** (Table 5, entries 11 and 12).

4.3 Suggested mechanism for the enantioselection in the pincer complex-catalyzed asymmetric allylation of sulfonylimines

Even though the exact mechanism of the enantioselection is not yet fully understood, a qualitative model could be constructed based on previous DFT studies on the (achiral) pincer complex-catalyzed allylation of sulfonylimines.[52]

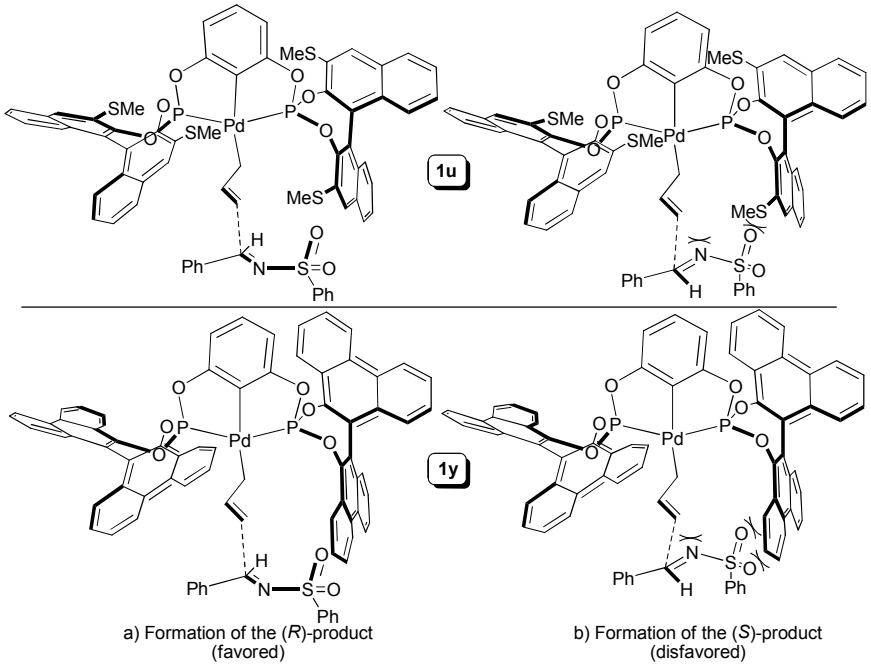
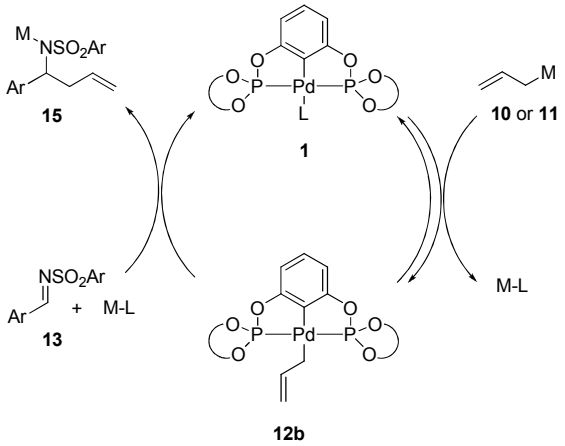


Figure 7. Model for the enantioselection in the allylation of sulfonylimine **13a** using (*R*)-BINOL based catalyst **1u** and biphenanthrol derivative **1y**. a) Formation of **15b**; and b) formation of **15c**.

According to this model (Figure 7); the electrophilic carbon of sulfonylimine **13a** interacts with the γ-position of the η^1-allyl moiety. Formation of the (*R*)-enantiomer of homoallylic amine **15b** is supposed to proceed *via* TS a), in

which the sulfonylimine functionality points away from the (*R*)-BINOL-based moiety. On the other hand, in the TS structure for formation of the (*S*)-enantiomer **15c**, the sulfonylimine group points in the opposite direction, experiencing repulsive steric interactions with the thiomethyl group of the binaphthyl ligands. This interaction is destabilizing, and therefore formation of the (*S*)-form **15c** is disfavored. Replacement of the BINOL moieties with biphenanthrol units is expected to increase the selectivity of the catalyst by increasing the destabilizing interactions with the sulfonylimine functionality in the b) type TS structures.



Scheme 13. Proposed catalytic cycle for the allylation of sulfonylimines.

The present study further confirms the mechanistic description previously given for the pincer complex-catalyzed allylation reactions (Scheme 13).[48-50,52,89] According to this mechanism, the applied pincer complex (**1**) undergoes transmetalation with the allyl metal reagent (**10** or **11**) to give η^1-allyl palladium complex **12b.** Complex **12b** is then able to efficiently allylate electrophiles (such as **13**) under catalytic conditions. In the presented mechanistic picture, the palladium atom does not undergo redox reactions during the catalytic transformation, and the enantioselectivity of the process is determined by the reaction of the η^1-allyl moiety of **12b** with the electrophilic substrate. It has recently been shown,[19,90] that catalytically active Pd(0) species can be generated from pincer complexes; however, this process involves decomposition of the pincer complex, which for the presented transformations (eqs. 4-5) would involve a complete loss of the enantioselectivity of the catalyst. Considering the enantioselectivity (up to 85% ee) achieved in the above study, a possible Pd(0) catalyzed process can be ruled out. On the contrary, complexes **1u**-**z** displayed excellent stability during the allylation reactions, and could be detected in the final reaction mixture of the process.

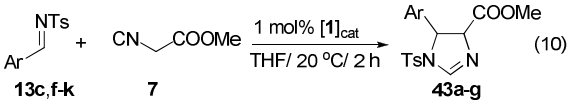
This high stability suggests that highly durable easily recyclable catalysts may be obtained by immobilization of **1u**-**z**.

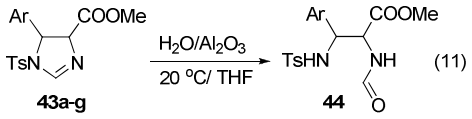
4.4 Concluding remarks for the synthesis and application of BINOL and biphenanthrol-based pincer complexes in the allylation of sulfonylimines

Easily accessible chiral BINOL and biphenanthrol-based pincer complexes **1u-z** readily catalyze the allylation of sulfonylimines **13** with up to 85% ee. So far, this is the highest enantioselectivity achieved in pincer complex-catalyzed allylation reactions,[91-93] and also in palladium catalyzed[72] allylation of sulfonylimines **13**. Both allyl stannanes **10** and allyl trifluoroborates **11a** can be employed as allyl sources in these processes. The enantioselectivity of the transformation can be reversed by changing the configuration of the BINOL or biphenanthrol ligands, and thus a full control of the enantioselectivity can be achieved. The enantioselection is assumed to be determined in the TS of the electrophilic attack of the η^1-allyl moiety coordinated to the chiral complex.

5. Palladium pincer complex-catalyzed condensation of sulfonylimines with isocyanoacetate to 2-imidazoline derivatives (Paper IV and V)

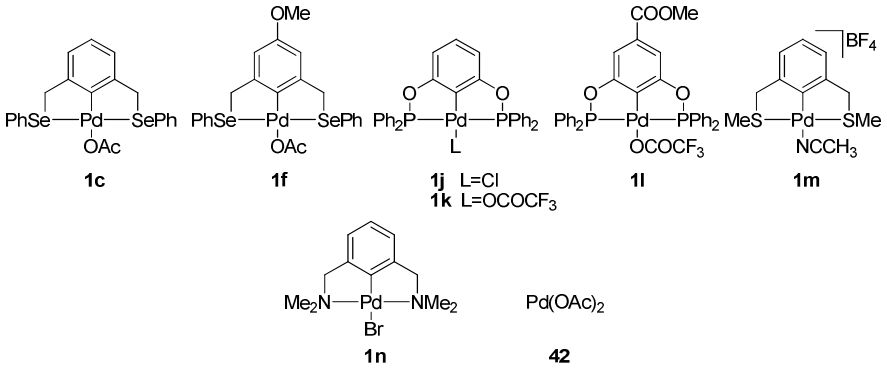
As mentioned in section 1.2, the aldol condensation is one of the main areas of application of palladium pincer complex catalysis affording oxazoline derivatives.[25-31] The analogous process using imine substrates (**13**) instead of aldehydes (**6**) is expected to give 2-imidazolines (**43**) (eq 10), which can easily be converted to α,β-diamino acids[94] (eq 11).





Although this important condensation reaction can be performed in the presence of gold,[95-97] ruthenium[98] and copper[99] catalysts, reports on palladium-catalyzed reactions are very scarce.[97,98] This can be explained by the fact that the palladium-catalyzed coupling of sulfonylimines **13** with isocyanoacetate **7** has been reported to be a slow and non-selective process.[97,98]

According to our studies palladium pincer complexes show a very high catalytic activity in the coupling of sulfonylimines **13** with isocyanoacetate **7**; and the stereoselectivity of the process is highly dependent on the electronic properties of the applied pincer complex catalysts (Scheme 14). Therefore, we investigated the synthetic scope and selectivity of this reaction employing various sulfonylimines (**13c**, **13f**-**k**) and isocyanoacetate **7** in the presence of catalytic amounts of pincer complexes **1c**, **1f**, **1j**-**n** affording 2-imidazoline products **43a**-**g** (eq 10). In addition to the synthetic studies, we have also investigated the mechanistic aspects of the condensation reaction. Furthermore, an asymmetric version of this condensation reaction could be developed using chiral BINOL and biphenanthrol-based palladium pincer complexes such as **1y**-**z**.



Scheme 14. Palladium catalysts investigated in this study.

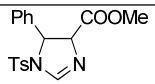
5.1 Scope and selectivity of the condensation reactions

The condensation reaction of sulfonylimines (**13c,** and **13f-k**) and isocyanoacetate **7** was carried out at rt for 2 h in the presence of 1 mol% of pincer complex (**1c, 1f**, **1j-n**) (Scheme 14) affording 2-imidazoline products **43a-g** with excellent yields. In contrast to the corresponding condensation reaction employing aldehydes (Scheme 3), the condensation with imines could be carried out without the addition of base (eq 10). The 2-imidazoline products **43a-g** showed some tendency for decomposition during chromatography on silica gel or neutral alumina. In fact, the corresponding diamino acid derivatives **44** could be easily obtained by stirring 2-imidazoline derivatives **43** in the presence of water and neutral aluminum oxide (eq 11). We could not observe any reaction between sulfonylimines **13** and isocyanoacetate **7** in the absence of a palladium catalyst.

The most interesting feature of the condensation reaction (eq 10) is that the stereochemistry of the formation of 2-imidazoline products (Table 6 and Table 7) depends on the applied pincer complex catalyst. When electron-poor catalysts with the PCP pincer backbone (**1j-l**) were used, high *syn* selectivity was obtained. For example, with complex **1k** a high *syn* selectivity (*syn*/*anti* ratio 10:1) was observed in the product (Table 6, entry 1). Changing the counter ion to chloride (**1j**) gave a slight decrease in *syn* stereoselectivity (Table 6, entry 2, *syn*/*anti* ratio 7:1). Catalyst **1l** was then used to study the electron-withdrawing effects of the COOMe group on the stereoselectivity. However, using **1l** did not change the *syn* stereoselectivity significantly (Table 6, entry 3, *syn*/*anti* ratio 8:1). Surprisingly, the SeCSe complex **1c**[100] led to a reversal of stereoselectivity, giving the *anti* stereoisomer of **43a** (*syn*/*anti* ratio 1:3) as the major product (Table 6, entry 4). A further increase in the electron density of the complex was achieved by introduction of a *para*-methoxy substituent[101] in catalyst **1f**. Complex **1f** further increased

(*syn*/*anti* ratio 1:4) the amount of the *anti* product in the condensation reaction (Table 6, entry 5). The *anti* selectivity could also be obtained when using SCS (**1m**) and NCN (**1n**) complexes, although with lower ratio (Table 6, entries 7-8, *syn*/*anti* ratio 2:3). Finally, we tested $Pd(OAc)_2$ (**42**) as catalyst (Table 6, entry 8), which afforded the 2-imidazoline product **43a** in a somewhat lower yield than the pincer complex-catalyzed reactions (Table 6, entries 1-7). The $Pd(OAc)_2$ catalyzed process also provides the *anti* form as the major diastereomer, however, the selectivity is relatively low (*syn*/*anti* ratio 1:2). Similar reactivity and selectivity has been reported for Pd(II) and Pd(0) salts used as catalysts in analogous condensation reactions.[97,98]

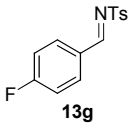
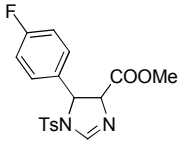
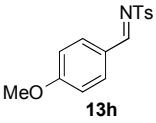
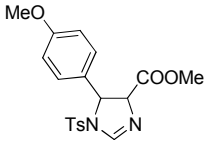
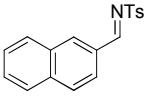
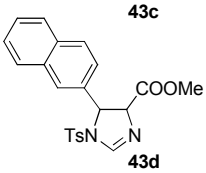
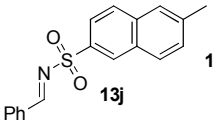
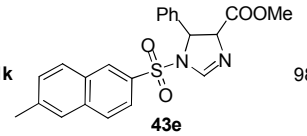
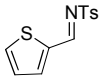
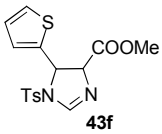
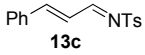
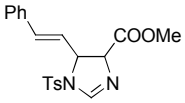
Table 6. Condensation of sulfonylimines **13f** with isocyanoacetate **7** in the presence of various palladium pincer complex catalysts.[a]

Entry	Imine	Cat.	Product	Yield[b]	dr[c] (*syn*/*anti*)
1	 **13f**	**1k**	 **43a**	98	10:1
2	**13f**	**1j**	**43a**	99	7:1
3	**13f**	**1l**	**43a**	99	8:1
4	**13f**	**1c**	**43a**	98	1:3
5	**13f**	**1f**	**43a**	99	1:4
6	**13f**	**1m**	**43a**	98	2:3
7	**13f**	**1n**	**43a**	99	2:3
8	**13f**	**42**	**43a**	82	1:2

[a] All reactions were performed using 1 mol% catalyst at 20 °C in THF. [b] Isolated yield [%]. [c] Ratio of the *syn* and *anti* products determined by ^{1}H NMR spectroscopy.

Subsequently, we have studied the electronic effects of the aromatic substituents in the sulfonylimine component. The fluoro substituted **13g** was reacted with **7** in the presence of **1k** (Table 7, entry 1) with the same reactivity and about the same selectivity (*syn*/*anti* ratio 9:1), as the parent sulfonylimine **13f** (Table 6, entry 1). Similarly to the above condensation of **13f** and **7**, the stereoselectivity of the reaction was reversed (Table 7, entry 2) when SeCSe complex **1f** was employed instead of PCP complex **1k** (*syn*/*anti* ratio 1:3). Application of **13h** with the electron donating *para*-methoxy group (Table 7, entry 3) gave somewhat higher selectivity (*syn*/*anti* ratio 11:1) than **13f**. The highly *syn* selective process is also insensitive to the increase in bulkiness of the sulfonyl group of imine **13j** (Table 7, entry 5). The high *syn* selectivity (*syn*/*anti* ratio 7:1) of the condensation reaction was maintained even in the presence of the bulky naphthyl substituted imine **13i** (Table 7, entry 4). Moreover, the selectivity and reactivity of the reaction is unchanged in the presence of sulfur-containing heterocycles, such as **13k** (Table 7, entry 6), or even with non-aromatic sulfonylimines, such as **13c** (Table 7, entry 7).

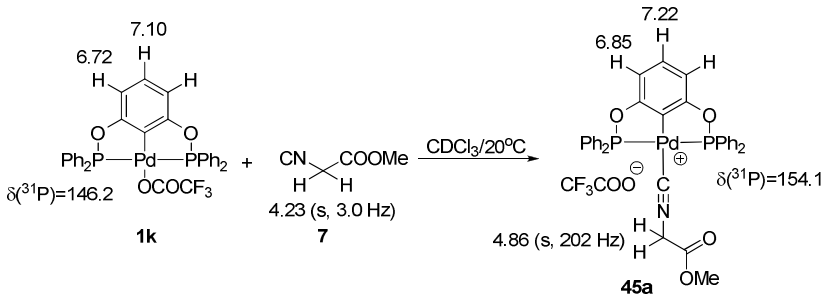
Table 7. Reaction of imines **13** and isocyanoacetate **7** in the presence of **1k** or **1f**.[a]

Entry	Imine	Cat.	Product	Yield[b]	dr[c] (*syn*/*anti*)
1	 **13g**	**1k**	 **43b**	98	9:1
2	**13g**	**1f**	**43b**	93	1:3
3	 **13h**	**1k**	 **43c**	98	11:1
4	 **13i**	**1k**	 **43d**	99	7:1
5	 **13j**	**1k**	 **43e**	98	8:1
6	 **13k**	**1k**	 **43f**	99	10:1
7	 **13c**	**1k**	 **43g**	99	8:1

[a] All reactions were performed using 1 mol% catalyst at 20 °C in THF. [b] Isolated yield [%]. [c] Ratio of the *syn* and *anti* products determined by ^{1}H NMR spectroscopy.

5.2 Mechanistic insights into the condensation reaction of imines and isocyanoacetate

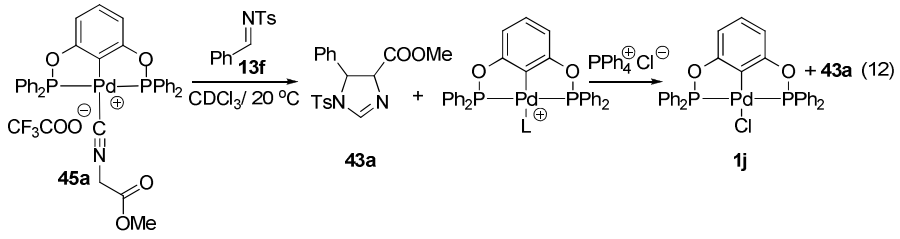
In order to elucidate the mechanism of the condensation reaction (eq 10), we studied the stoichiometric reactions of PCP complex **1k** with isocyanoacetate **7** using NMR spectroscopy. When **1k** and **7** were mixed, the proton signal of **7** (4.23 ppm, singlet, lb = 3.0 Hz) was shifted downfield and considerably broadened (4.91 ppm broad singlet, lb = 202 Hz). At the same time, the doublet (6.72 ppm) and triplet shifts (7.10 ppm) of the aromatic ring of complex **1k** moved downfield to 6.85 ppm and 7.22 ppm, respectively (Scheme 15).



Scheme 15. Change of NMR shifts (ppm) in the stoichiometric reaction of **1k** and **7**.

The ^{31}P NMR signal of the phosphorus atom in the side arms in **1k** appears as a single peak at 146.2 ppm. This signal shifted downfield by eight ppm (154.1 ppm) upon addition of **7** without any splitting of the peak, indicating that the symmetrical tridentate pincer architecture remained intact in the resulting complex **45a**. Considering the above systematic changes, we reasoned that **7** was coordinated to the palladium atom of the pincer complex affording complex **45a**. The formation of similar metal pincer complexes were postulated in condensation reactions of **7** with aldehydes (**6**) (section 1.2) in pincer complex-catalyzed processes.[102,103]

After **1k** was completely converted to **45a**, the solvent and the excess of isocyanoacetate **7** were evaporated. Subsequently, **45a** was redissolved in $CDCl_3$ and sulfonylimine **13f** was added. It was found that the reaction of **13f** and **45a** leads to rapid formation of the condensation product **43a**. Subsequent addition of organic chloride salt PPh_4Cl led to the appearance of two ^{31}P NMR shift. The first was assigned to chloro-pincer complex **1j**, which could be isolated upon chromatography (eq 12), while the second was assigned to PPh_4Cl.



5.3 X-ray structure of the key intermediate in the studied condensation reaction

We were also able to isolate and crystallize catalytic intermediate **45a**. The X-ray diffraction structure of **45a** clearly shows a pincer complex architec-

ture (Figure 8). The Pd-P and Pd-C1 bond lengths (2.27 and 2.00 Å) in **45a** are very close to the corresponding bond lengths in the parent **1k** reported by Bedford and co-workers.[67]

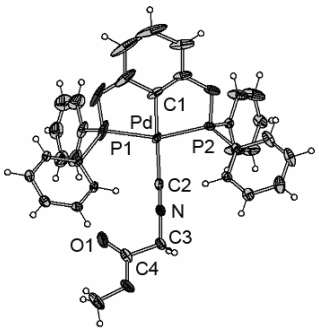


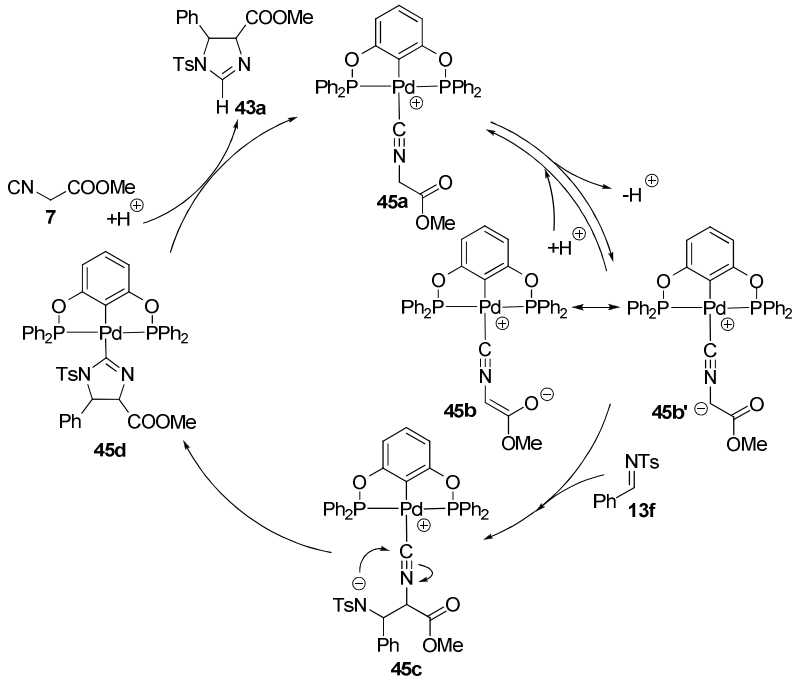
Figure 8. X-ray structure of **45a**. Selected bond lengths (Å) and angles: Pd-P1, 2.278; Pd-P2, 2.269; Pd-C1, 2.004; Pd-C2, 2.025; C2-N, 1.123, N-C3, 1.424; C3-C4, 1.532; C4=O1, 1.198; P1-Pd-P2, 159.0; Pd-C2-N, 173.3; N-C3-C4, 108.8. For the sake of clarity, the triflouroacetate counter-ion and the included $CHCl_3$ molecule are not shown in the Figure.

As a typical feature of PCP pincer complexes, the PCP angle (159°) deviates from the linear alignment (180°), which would have been required for an ideal MO overlap in square planar complexes. Most interestingly, the palladium-carbon bond to the coordinated isocyanoacetate molecule (Pd-C2) is relatively short, 2.025 Å. This indicates that the palladium-carbon bonding to the aryl ring and to the carbon atom of the coordinated isocyanoacetate are about equally strong. Thus, the interaction between the isocyanoacetate carbon and palladium can be classified as a strong covalent bond, instead of a donor-acceptor interaction between a Lewis-acid (the pincer complex) and a Lewis base (**7**). This is probably an important structural feature, as in the aldol reaction of isocyanoacetates with aldehydes, the pincer complexes are often referred to as Lewis acid catalysts.[25] Another interesting structural features of the coordinated isocyanoacetate moiety are the bond lengths of the C3-C4 bond (1.532 Å) and the carbonyl carbon-oxygen (C4=O1, 1.198 Å) bonds. The observed bond lengths clearly indicate the presence of a typical carbon-carbon single bond and a carbon-oxygen double bond, while in most mechanistic schemes formation of an enolate has been invoked, which would increase the nucleophilicity of the coordinated isocyanoacetate.[15,102] Although there are some indications for enolization of the carbonyl group in solution, such as broadening of the ^{1}H NMR signals at 4.86 ppm (Scheme 15), the X-ray structure clearly shows a non-enolized isocyanoacetate species. Thus, the catalytic activity of the palladium pincer complex catalyst in

the aldol reaction is not necessarily exerted *via* enolization of isocyanoacetate reagent.

5.4 Proposed catalytic cycle for the pincer complex-catalyzed synthesis of 2-imidazolines

Considering the above studies, a plausible catalytic cycle was constructed (Scheme 16).



Scheme 16. Plausible catalytic cycle based on the mechanistic studies.

The catalytic reaction starts with deprotonation of **45a** providing **45b**. It should be stressed that external addition of base is not necessary under the applied catalytic conditions. The next step is nucleophilic attack by the isocyanoacetate moiety of **45b** on the sulfonylimine substrate to give **45c**. The condensation reaction is accomplished by a nucleophilic attack on the carbon atom of the isocyanide group, which is probably still coordinated to palladium, affording complex **45d**. Protonation of the C2 carbon of the 2-imidazoline ring leads to decomplexation of the product (**43a**), and regeneration of the catalyst. The stereoselectivity of the process is determined in the addition step of **13f**, in the **45b** → **45c** process. Employing PCP complex **1k** as catalyst, the *syn* selectivity is very high. Our studies indicate that using

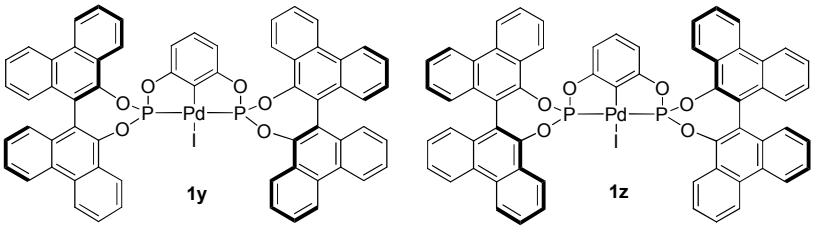
electron-donating substituents, such as sulfur, nitrogen and selenium instead of phosphorus leads to an increase in the amount of the *anti* product (Table 6). Previous studies indicate that PCP complexes and pincer complexes[103-105] with sulfur or nitrogen atoms in the side arms (such as **1m** and **1n**) probably react by different mechanisms in aldol reactions. It appears from the presented studies that the use of PCP complexes **1k** and **1j** leads to formation of the *syn* isomer of **43a-g** according to the above mechanism (Scheme 16), while changing the heteroatoms in the side arms to selenium (**1c**, **1f),** sulfur (**1m**) or nitrogen (**1n**) may change the reaction mechanism,[105] shifting the stereoselectivity towards formation of the *anti* diastereomer. The different stereoselectivities obtained with palladium acetate (**42**) and PCP complex **1k** also suggest a different mechanism for condensation of sulfonylimines with isocyanoacetate **7**.

5.5 Chiral palladium pincer complex-catalyzed asymmetric condensation of sulfonylimines and isocyanoacetate

We have decided to investigate the asymmetric condensation of isocyanoacetate **7** and sulfonylimines **13** using chiral biphenanthrol based palladium pincer complexes (**1y-z**, Scheme 17, Table 8). Asymmetric condensation reactions of **13f** and **7** affording 2-imidazoline derivatives **43a** have previously been performed, for example, by using gold catalysis.[95,96] Enantioselective synthesis of the *anti*-product (**43a**-*anti* and **44a**-*anti*) is particularly interesting, as these species are not accessible by the gold-ferrocenyl complex-catalyzed asymmetric condensation of **13** and **7** reported by Lin and co-workers.[95,96] Pincer complexes **1y-z** proved to be efficient catalysts affording 2-imidazoline derivatives in near quantitative yield (Table 8). The best enantioselectivity (*syn* 86% ee (2*S*,3*S*), *anti* 28% ee (2*R*,3*S*)) was obtained using (*R*)-biphenanthrol-based pincer complex catalyst **1y**. Unfortunately, the reaction proceeded without any diastereoselection (1:1 *syn*:*anti*, Table 8, entry 1). When (*S*)-biphenanthrol-based pincer complex catalyst **1z** was employed under identical reaction conditions the major *syn*-enantiomer was **43a**-*syn* (2*R*,3*R*) (Table 8, entry 4) with slightly lower ee (72%).

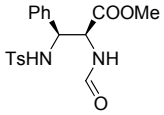
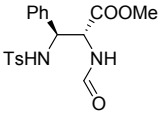
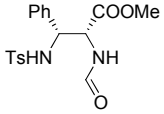
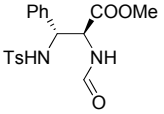
The diastereo- and enantioselectivity showed an interesting solvent dependence as well. It was found that application of **1z** in diglyme as solvent instead of THF, leads to a preferential formation of the *anti* diastereomer (1:4 *syn*:*anti*). Interestingly, the ee of the *anti* diastereomer (**43a**-*anti* (2*S*,3*R*) 75% ee) was also considerably increased (Table 8, entry 2 and 4). When the solvent is changed from THF to dioxane, the ee of the *anti* diastereomer was increased to 68% (c.f. entries 3 and 4, Table 8). Considering the above results, application of **1z** as catalyst in diglyme (entry 2, Table 8) affording

selectively the *anti* product (**43a**-*anti* (2*S*,3*R*)) can be considered a complement to the gold-ferrocenyl complex-catalyzed reaction, which is *syn* selective.[95]



Scheme 17. Asymmetric condensation of sulfonylimine **13f** and isocyanoacetate **7**.

Table 8. Pincer catalyzed (**1y**-**z**) formation of 2-imidazoline **43a** (Scheme 17).[a]

Entry	Cat.	Imine	Yield **43a**[b]	Syn/anti[c]	ee[%] syn[d]	ee[%] anti[d]
1	**1y**	 **13f**	98	1:1	 **44a**-*syn* (2*S*,3*S*) 86% ee	 **44a**-*anti* (2*R*,3*S*) 28% ee
2[e]	**1z**	**13f**	98	1:4	 **44a**-*syn* (2*R*,3*R*) 25% ee	 **44a**-*anti* (2*S*,3*R*) 75% ee
3[f]	**1z**	**13f**	98	1:1	**44a**-*syn* (2*R*,3*R*) 73% ee	**44a**-*anti* (2*S*,3*R*) 68% ee
4	**1z**	**13f**	98	1:1	**44a**-*syn* (2*R*,3*R*) 72% ee	**44a**-*anti* (2*S*,3*R*) 18% ee

[a] **13f** (0.2 mmol), **7** (0.2 mmol) and the corresponding catalyst **1y-z** (1 mol%) were reacted in THF at 20 °C for 18 h. [b] Isolated yield [%]. [c] Diastereomeric ratio determined by ^{1}H NMR. [d] Enatiomeric excess [%]. [e] Diglyme used as solvent. [f] Dioxane used as solvent.

5.6 Conclusions concerning the condensation reaction

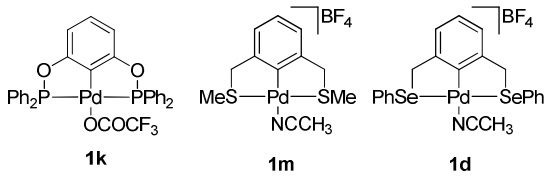
We have shown that condensation of sulfonylimines **13** with isocyanoacetate **7** can be accomplished using palladium pincer complexes in low (1 mol%)

catalyst loadings. The synthetic scope of the condensation reaction using **1k** is broad and the diastereomeric outcome of the reaction could be controlled by the choice of pincer catalyst. Using the electron-deficient and relatively bulky PCP complex **1k**, the major product is the *syn* form, however, the diastereoselectivity is reversed when SeCSe-based catalyst **1f** is used. It was found that the reaction proceeds *via* complex **45a**. An X-ray structure of the key intermediate **45a** was presented, where isocyanoacetate **7** is coordinated to the pincer complex. The pincer complex catalyst is stable throughout the entire process, and can be recovered unchanged after the condensation reaction.

Chiral palladium pincer complexes based on biphenanthrol ligands (**1y**-**z**) are also efficient catalyst for the condensation of isocyanoacetate **7** and sulfonylimines **13**, furnishing the products with up to 86% ee. The catalytic condensation in diglyme shows a tendency for selective formation of the *anti* diastereomer of the product, and thus it may complement the *syn*-selective gold-ferrocenyl catalyzed method published by Lin and co-workers.[95,96]

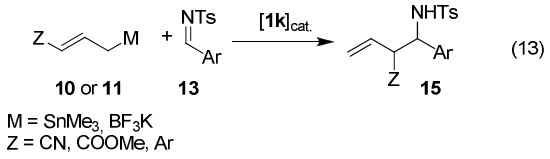
6. Palladium pincer complexes as highly efficient catalysts for C-H functionalization of organonitriles (Paper VI and VII)

Palladium-catalyzed substitution reactions based on allylic C-H bond activation are valuable tools in organic transformations.[2,106-116] Several catalytic methods using nucleophiles to perform allylic C-H bond functionalizations have been reported in the literature.[110-116] However, literature procedures for the application of carbon electrophiles in these types of transformations are relatively scarce.[25,117-125] Nevertheless, electrophilic allylation or benzylation of imines may offer new routes for the synthesis of functionalized amines and amino acid[48-52,69-73,94,126] derivatives, which are important natural products and drug intermediates.[94,127,128]



Scheme 18. Pincer complexes employed in the presented study.

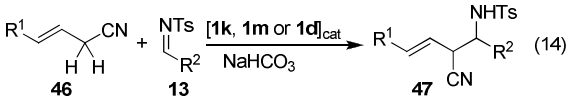
The previous studies by the Szabó group[48-52,73,126] have shown that palladium pincer complexes[11-18,56,67,89,93,100,129-133] (such as **1k**, Scheme 18) efficiently and selectively catalyze the allylation of imines. However, in these applications organometallic substrates [48-52,73,126] such as stannanes and borates were employed as allylating reagents (Scheme 18 and eq 13).

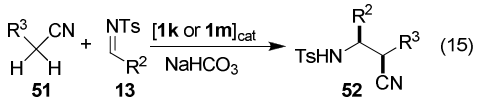


(13)

Our studies show that allyl cyanides or benzyl cyanides can be used directly for regioselective allylation or benzylation of sulfonylimines using pincer

complex catalysts (**1k**, **m** and **d**) under mild conditions (typically at rt), in the presence of $NaHCO_3$ and molecular sieves (eqs. 14-15).





In these processes, the cooperative interaction[119-122] between the catalyst and the employed weak base was employed for C-H bond functionalization. The principle of the cooperative interaction is to enhance the acidity of the transition-metal-coordinated organonitrile substrate, which then readily undergoes deprotonation generating a metal-bound carbon nucleophile.[119-122] The nucleophile generated in this process is usually coupled with aldehyde or imine reagents under very mild reaction conditions. Indeed, many excellent applications have appeared in the literature using the cooperative catalytic concept for the coupling of organonitriles with imines and aldehydes employing Ru,[119,120,122,123] Pd,[134] Rh,[124] Cu[121] and Ni[125] catalysts. Of course, α–cyano carbanions can also be generated without assistance of transition metal catalysts.[135-137] However, the deprotonation of allyl- (pK_a 21.1)[138] alkyl (pK_a = 31.3)[119] and benzyl cyanides (pK_a = 21.9)[119] requires very strong bases, such as LDA[137] and proazaphosphatranes,[135,136] which may trigger undesired side reactions, such as dehydration[135,136] or epimerization of the product.[137]

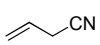
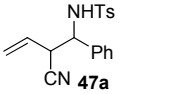
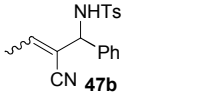
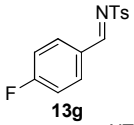
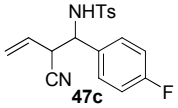
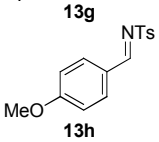
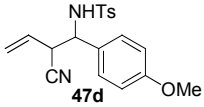
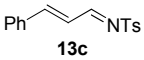
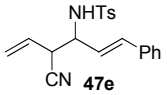
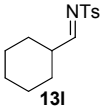
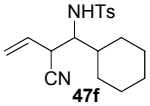
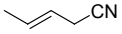
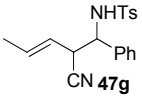
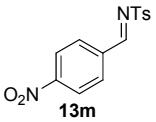
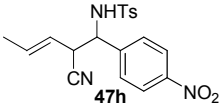
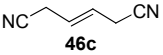
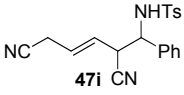
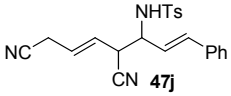
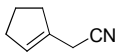
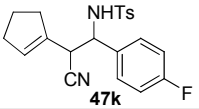
6.1 Carbon-Carbon coupling of allylic nitriles with tosyl imines *via* regioselective allylic C-H bond functionalization

Pincer complexes with weakly coordinating counterions (Table 9, entries 1-3) displayed high catalytic activity for direct coupling of allylic nitriles with sulfonimines. Since we have developed the synthesis of a large variety of chiral PCP-complex derivatives (chapter 4),[73,93,126] we directed our investigation to explore the synthetic scope of PCP complex **1k**.[67]

Allyl cyanide (**46a**) reacted rapidly with various aromatic (**13f-h** and **13m**), vinyl (**13c**), and alkyl sulfonylimines (**13l**) (Table 9, entries 1-8). The electronic effects strongly influenced the reactivity of the sulfonylimine substrates. For example, imine **13g** bearing an electron withdrawing group reacted five times faster than the parent imine **13f** (c.f., entries 1 and 5, Table 9), while methoxy substituted imine **13h** (Table 9, entry 6) was comparable

in rate to **13f** (c.f., entries 1 and 6, Table 9). Vinyl (**13c**), and alkyl sulfonylimines (**13l**) reacted considerably slower (Table 9, entries 7 and 8) than the aromatic ones.

Table 9. Pincer complex-catalyzed coupling of allyl cyanides and sulfonylimines.[a]

Entry	Substrates		T[°C]/ t[h]	Cat.	Products	dr[b]	Yield[c]
1	 **46a**	 **13f**	20/5	**1k**	 **47a**	3:2	90
2	**46a**	**13f**	20/4	**1d**	**47a**	1:1	81
3	**46a**	**13f**	20/5	**1m**	**47a**	3:2	83
4[d]	**46a**	**13f**	20/12	**1k**	 **47b**	2:1[e]	88
5	**46a**	 **13g**	20/1	**1k**	 **47c**	3:2	91
6	**46a**	 **13h**	20/5	**1k**	 **47d**	3:2	91
7	**46a**	 **13c**	20/14	**1k**	 **47e**	2:1	93
8	**46a**	 **13l**	20/12	**1k**	 **47f**	1:1	90
9	 **46b**	**13f**	40/14	**1k**	 **47g**	1:1	98
10	**46b**	 **13m**	20/18	**1k**	 **47h**	1:1	57
11	 **46c**	**13f**	20/4	**1k**	 **47i**	1:1	97
12	**46c**	**13c**	20/3	**1k**	 **47j**	2:1	83
13	 **46d**	**13g**	20/20	**1k**	 **47k**	3:2	94

[a] Catalyst **1** (5 mol %), $NaHCO_3$ (0.2 mmol), **46** (0.3 mmol) and **13** (0.2 mmol) in THF (0.3 ml) were reacted at the given temperatures and reaction times. [b] Diastereomeric ratio. [c] Isolated yield [%]. [d] Cs_2CO_3 (0.2 mmol) was employed as base. [e] *E*/*Z* ratio.

The regioselectivity of the reaction is excellent, as the branched allylic product is formed exclusively. The only exception is when Cs_2CO_3 (or other strong bases, Table 9, entry 4) was used as the base instead of $NaHCO_3$. In these cases the primary homoallylic amine product **47a** isomerizes to allylic amine **47b**. The allylation reactions could be extended to substituted allyl cyanides (Table 9, entries 9-13) incorporating internal double bonds. The catalytic process with substituted allyl cyanides **46b** and **46d** proceeded slower than **46a** (Table 9, entries 9-10 and 13). For symmetrical allyl cyanide **46c**, the catalytic reaction could be stopped after substituting one of the allylic carbons, thereby the desymmetrization of **46c** successfully provided products **47i-j** in excellent yields (Table 9, entry 11-12).

The mild reaction conditions applied in the described process allows the presence of a wide array of functional groups such as CN, NTs, F and OMe, and even NO_2 is tolerated[139] (Table 9, entry 10). Under the applied mild reaction conditions the formation of the product could not be detected at all when pincer complex catalyst **1k** was replaced by traditional palladium catalysts, such as $Pd(OCOCF_3)_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$, or $Pd(PPh_3)_4$. The absence of reaction with $Pd(OCOCF_3)_2$ indicates that the activation effects of trifluoroacetate complex **1k** cannot be explained simply by its Lewis acid activity.

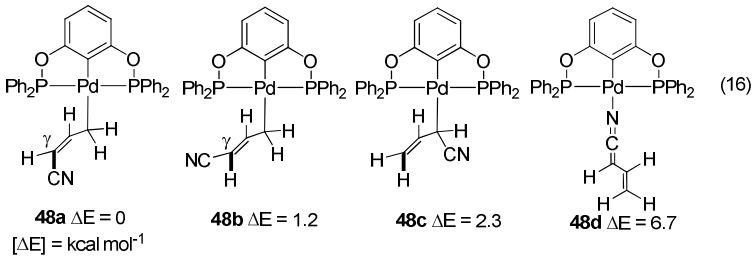
Although the presented reaction proceeds with an excellent regioselectivity (Table 9, entries 1-13) and *trans* stereoselectivity for the double bond (Table 9, entries 9-13), the diastereoselectivity of the transformation is poor. This finding is in line with the low diastereoselectivity obtained for the related allyl stannane-based process (eq 13).[51]

The reactions proved to be rather sensitive to moisture, and therefore we employed molecular sieves, which efficiently dried the reaction medium. It is important to note that the catalytic transformations proceed even in the absence of molecular sieves or with substoichiometric amounts of $NaHCO_3$; however these reactions were slow and poorly reproducible.

6.1.1 Mechanistic proposal for the catalytic allylation of sulfonylimines

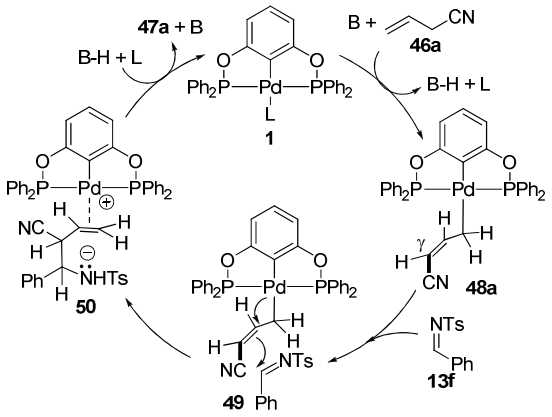
The coupling reaction probably involves coordination of the allyl cyanide anion to the pincer complex catalyst affording complex **48**. The relatively facile deprotonation of allyl nitrile is probably a cooperative action of the employed weak base ($NaHCO_3$) and the palladium atom.[138] We have considered **48a**-**d** as possible structures for the allyl cyanide anion coordinated pincer complex intermediates (eq 16). DFT modeling studies (B3PW91/6-31G(d) level) indicate that the η^1-allylpalladium structures (**48a**-**c**) are much more stable (up to 6.7 kcal·mol^{-1}) than the N-coordinated form **48d**. Consid-

ering that in the most stable forms (**48a**-**b**), the nitrile group is in the terminal position, the new C-C bond is created[52] between the substituted γ-carbon of the allyl moiety and **13** (Scheme 19, structure **49**), which explains the observed regiochemistry of the process. Our previous DFT modeling studies[52] on the C-C bond formation between the allyl moiety of palladium pincer complexes (such as **48a**-**c**) and sulfonylimines revealed that the stereoselectivity of the reaction is dependent on the geometry of the double bond in the functionalized (e.g., CN) allyl moiety. Based on these results, the relatively small energy difference between **48a** and **48b** may account for the poor diastereoselectivity of the allylation process. In addition, formation of (η^1-allyl)palladium complexes **48a**-**b** (required for reaction with electrophiles[49,52]) is favored by the terdentate pincer ligand architecture, which explains the fact that traditional palladium (i.e., non-pincer, $Pd(OCOCF_3)_2$) catalysts are inefficient in the presented transformations.



(16)

Based on the above synthetic and modeling results, we propose that the catalytic cycle (Scheme 19) is initiated by coordination of the allyl cyanide anion to the pincer complex catalyst affording complex **48**. Thereafter, in the stereodiscriminating step,[49,50,52,89] intermediate **48** reacts with sulfonylimine **13f** (**49**) affording intermediate **50**, which upon protonation and decomplexation affords product **47a** and regenerates the catalyst.



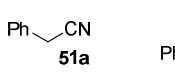
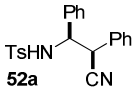
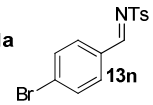
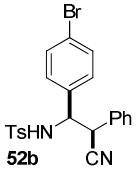
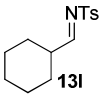
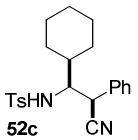
Scheme 19. Mechanistic proposal for the catalyzed allylation of sulfonylimines.

6.2 Stereoselective pincer complex-catalyzed C-H functionalization of phenyl acetonitrile derivatives

The above described coupling reaction of allyl nitriles (**46**) with imines (**13**) could also be extended to phenyl acetonitrile derivatives (**51**). It was found that **1k** and **1m** are very powerful catalysts for coupling of phenyl acetonitrile derivatives (**51**) and various sulfonylimines (**13f**, **13n** or **13l**) under mild conditions in the presence or even absence of $NaHCO_3$ (eq 15).

The reactions are usually conducted at 20 °C, however in the presence of electron donating substituents (such as methyl (**51f**) group) on the aromatic ring of the phenyl acetonitrile substrate a higher temperature (up to 40 °C) had to be applied (Table 11, entry 6). Unfortunately, using the parent phenyl acetonitrile **51a** and sulfonylimines **13f**, **13l** and **13n** the reaction proceeds with poor stereoselectivity (Table 10, entries 1-3).

Table 10. C-H functionalization of phenyl acetonitrile.[a]

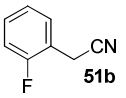
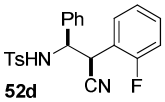
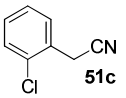
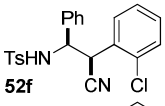
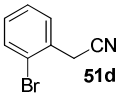
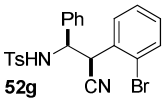
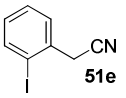
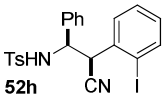
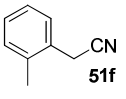
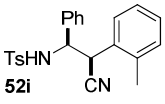
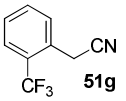
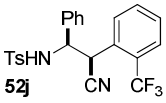
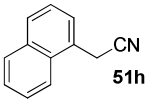
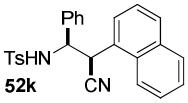
Entry	Substrates	T[°C]/ t[h]	Cat.	Product[b]	d.r.[c]	Yield[d]
1	 **51a** **13f**	20/15	**1k**	 **52a**	2:1	99
2	**51a**  **13n**	20/3	**1k**	 **52b**	1.5:1	99
3	**51a**  **13l**	20/18	**1k**	 **52c**	1.4:1	91

[a] Nitrile **51** (0.3 mmol), **13** (0.2 mmol), $NaHCO_3$ (0.2 mmol) and catalyst **1** (5 mol %) in THF (0.3 ml) were stirred for the times and temperatures given.[b] Major diastereomer. [c] Diastereomeric ratio (*syn*/*anti*). [d] Isolated yield [%].

In the presence of aromatic *ortho* substitutents in the phenyl acetonitrile substrate the stereoselectivity of the reaction is considerably increased (**51b-j**, Table 11 and Table 12). As it appears by entries 1-4 in Table 11, the diastereoselectivity increases as one goes from electronegative *ortho* halides to electropositive ones (**51b** → **51e**) in the order of F < Cl < Br ≈ I. As the carbon-halogen bond lengths increases in the same order, this trend would suggest that the selectivity is increased with the steric bulkiness of the *ortho* substituent. However, phenyl acetonitrile derivatives with methyl (**51f**) and trifluoromethyl (**51g**) groups (which are bulkier than the bromo (**51d**) and iodo (**51e**) groups) are substituted with lower selectivity (c.f. entries 3, 4 with 6, 7, Table 11). Thus the level of stereoselectivity cannot be explained

solely by the steric effects of the *ortho* substituents of the phenyl acetonitrile substrate, but certainly electronic interactions are also important. The exact nature of the steric and electronic effects on the diastereoselectivity of the coupling reaction will be assessed by DFT modelling studies.

Table 11. C-H functionalization of substituted phenyl acetonitrile derivatives.[a]

Entry	Substrates	T[°C]/ t[h]	Cat.	Product[b]	d.r.[c]	Yield[d]
1	 **51b**	**13f** 6/68	**1k**	 **52d**	4.6:1	95
2	 **51c**	**13f** 20/16	**1k**	 **52f**	8.4:1	99
3	 **51d**	**13f** 20/16	**1k**	 **52g**	10:1	83
4	 **51e**	**13f** 20/15	**1k**	 **52h**	10:1	99
5	**51e**	**13f** 20/16	**1m**	**52h**	10:1	70
6	 **51f**	**13f** 40/16	**1k**	 **52i**	4:1	92
7	 **51g**	**13f** 6/68	**1k**	 **52j**	8:1	88
8	 **51h**	**13f** 20/24	**1k**	 **52k**	10:1	83

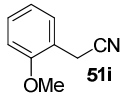
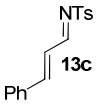
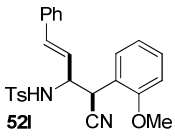
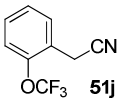
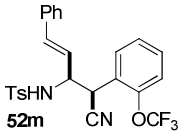
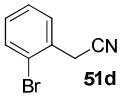
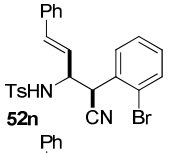
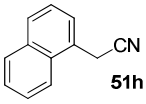
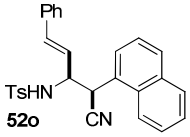
[a] Nitrile **51** (0.3 mmol), **13** (0.2 mmol)**,** $NaHCO_3$ (0.2 mmol) and catalyst **1** (5 mol %) in THF (0.3 ml) were stirred for the times and temperatures given.[b] Major diastereomer. [c] Diastereomeric ratio (*syn*/*anti*). [d] Isolated yield [%].

Vinyl imine **13c** and *ortho*-substituted phenyl acetonitrile derivatives (**51h**-**j**, **d**) were also reacted with good to excellent stereoselectivity (Table 12). Interestingly, deactivated nitrile **51i** could be reacted (Table 12, entry 2) without addition of $NaHCO_3$; however, in this case the reaction time had to be extended (c.f. entries 1 and 2, Table 12).

We have also tested commonly used Pd(II) sources, such as $Pd(OAc)_2$ and $Pd(OCOCF_3)_2$, which proved to be inactive in most of the presented processes. Formation of traces of product (along with large amounts of byproducts) could be observed in the coupling reaction of **51e** and **13f** catalyzed by

$Pd(OCOCF_3)_2$. Pd(0) sources, such as $Pd_2(dba)_3$ proved to be completely inefficient as catalysts in the coupling reactions.

Table 12. Coupling of imine **13c** with *ortho* substituted phenyl acetonitriles.[a]

Entry	Substrates	T[°C]/ t[h]	Cat.	Product[b]	d.r.[c]	Yield[d]
1	 **51i** +  **13c**	20/16	**1k**	 **52l**	8.4:1	93
2[e]	**51i** + **13c**	20/66	**1k**	**52l**	6:1	92
3	 **51j** + **13c**	20/16	**1k**	 **52m**	3.4:1	74
4	 **51d** + **13c**	6/72	**1k**	 **52n**	6.7:1	65
5	 **51h** + **13c**	20/16	**1k**	 **52o**	17:1	95

[a] Nitrile **51** (0.3 mmol), **13** (0.2 mmol), $NaHCO_3$ (0.2 mmol) and catalyst **1** (5 mol %) in THF (0.3 ml) were stirred for the times and temperatures given.[b] Major diastereomer. [c] Diastereomeric ratio (*syn*/*anti*). [d] Isolated yield [%]. [e] Performed without $NaHCO_3$.

The above results clearly indicate that a high diastereoselectivity can be achieved in the coupling reaction of sulfonylimines (**13**) with *ortho*-substituted phenyl acetonitrile derivatives (**51**); however the selectivity is influenced by both the steric and electronic substituent effects. The presented process provides functionalized (for example I and Br) β-aminonitrile products (**52**) in high yield without elimination reactions. These products can in turn serve as useful substrates in Pd(0) catalyzed Suzuki-Miyaura or Heck coupling reactions.

We have also developed an asymmetric version for the coupling of phenyl acetonitriles (**51**) with sulfonylimines (**13**) using chiral analogs of PCP complex **1k**.[73,93,126,140] Our results (Figure 9) indicate that chiral pincer complex catalysts have a high potential to create chiral carbon-carbon bonds between benzyl cyanides (such as **51a**) and sulfonylimines (such as **13n**). Under base free conditions complex **1aa** delivered β-aminonitrile product **52b** with up to 71% ee (*syn*-**52b** 71% ee and *anti*-**52b** 33% ee; *syn*:*anti* 1.3:1) in 99% yield. A particular advantage of using pincer complex catalysis is that the reaction can be conducted under base-free conditions. This is particularly important

in order to avoid the possible base-catalyzed epimerization of the reaction products.

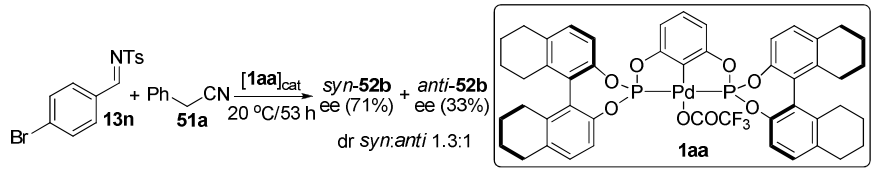
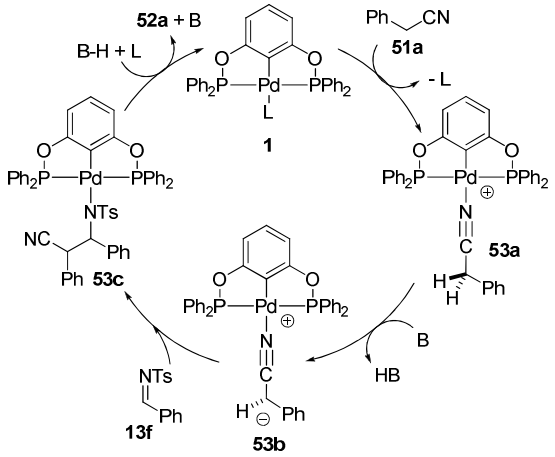


Figure 9. Preliminary studies for coupling phenyl acetonitrile **51a** and sulfonylimine **13n** using chiral catalyst **1aa** (3 mol%) (yield 99%).

6.2.1 Plausible mechanism of the coupling between benzyl cyanides and sulfonylimines

Based on the mechanistic proposal given for the allylation of imines (Scheme 19) and other transition metal-assisted deprotonation reactions that have appeared in the literature,[119-122,125,134] a plausible catalytic cycle (Scheme 20) was constructed.



Scheme 20. Mechanism for the coupling of phenyl acetonitriles and sulfonylimines.

Accordingly, the first step of the transformation is coordination of phenyl acetonitrile **51a** to the palladium atom of **1**, affording complex **53a**. The next step is α-deprotonation of **53a** to give complex **53b**. The deprotonation is facilitated by the coordinated palladium pincer complex. An alternative mode of coordination can also be considered for intermediate **53b**. Instead of the zwitterionic structure (**53b**) a direct carbon metal bond may also be formed between the benzyl anion and the palladium atom[125] (c.f. **48a-c**). The

next step is coupling of the palladium coordinated α-cyano carbanion with sulfonylimine **13f** to give **53c**, which subsequently undergoes protonation and decomplexation to provide the final product **52a** and regenerate the catalyst **1**.

6.3 Summary of the pincer complex-catalyzed C-H bond functionalization reactions

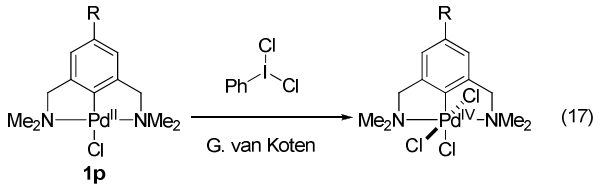
In this chapter the palladium pincer complex-catalyzed coupling of allyl- or benzyl cyanides with sulfonylimines was described. The coupling reaction of allyl cyanides with imines represents a mechanistically new catalytic process which opens new synthetic routes to palladium pincer complex-catalyzed C-H bond activation reactions. The regioselectivity of the presented C-H functionalization process is excellent, as only the branched allylic isomer was formed. The coupling of *ortho* substituted benzyl cyanides with sulfonylimines proceeds with high diastereoselectivity (up to 17:1 *syn*:*anti*). Furthermore, our preliminary studies indicate that chiral pincer complex catalysts (such as **1aa**) have a high potential for creating chiral carbon-carbon bonds between benzyl cyanides (such as **51a**) and sulfonylimines (up to 71% ee).

7. Pincer complex-catalyzed coupling reactions *via* palladium(IV) intermediates (Paper VIII)

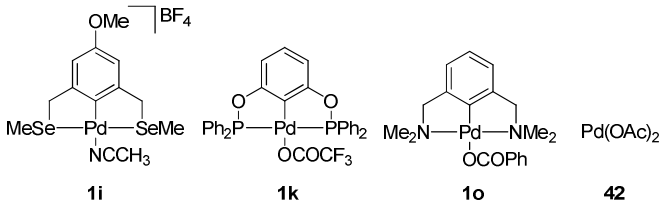
Catalytic transformations involving Pd(IV) complexes as key intermediates represent important recent innovations in transition metal catalysis.[141-158] In these transformations the traditional Pd(0)/Pd(II) redox cycle is replaced by a Pd(II)/Pd(IV) cycle. Employment of a Pd(II)/Pd(IV) catalytic cycle offers some beneficial features over the conventional Pd(0)/Pd(II) redox process.[141-158] Three features are particularly important: a) increased reactivity for reductive elimination *via* Pd(IV) intermediates; b) increased chemoselectivity for the oxidative addition to Pd(II) catalytic precursors; c) avoidance of Pd(0) intermediates, which often precipitate as Pd-black, deactivating the catalyst.

These attributes enable the harnessing of unconventional reactivity for new bond-forming processes, and provide unusual avenues for the synthesis of new target molecules inaccessible by Pd(0)/Pd(II)-based catalytic systems.

Recent studies[19,90,159] have concluded that simple aryl halides are not able to oxidize Pd(II) in pincer complexes. However, van Koten[21] and Canty[20] have shown that NCN pincer complexes (**1p** and **1o**) undergo stoichiometric oxidative addition to iodonium(III) salts,[160-163] affording Pd(IV) pincer complexes (eqs. 17-18).

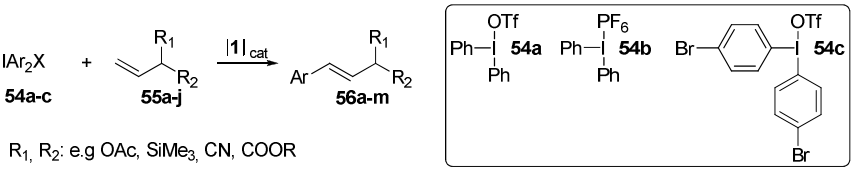


These results inspired us to design novel Pd(II)/Pd(IV) based catalytic systems by employment of palladium pincer complexes with iodionium(III) salts as reagents.



Scheme 21. Palladium catalysts used in the presented study.

Indeed, it was found that palladium pincer complexes **1i**, **1k** and **1o** (Scheme 21) can be employed as highly active catalysts in Heck-type coupling[164-169] reactions of aryl-iodonium salts (**54a-c**) with functionalized alkenes (**55a-j**) under mild conditions (Scheme 22 and Table 13).



Scheme 22. Pincer complex-catalyzed Heck reaction.

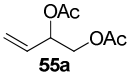
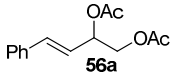
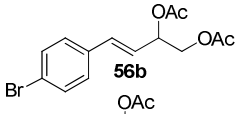
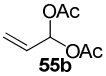
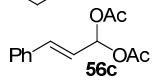
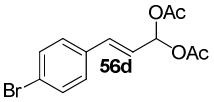
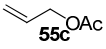
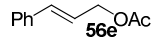
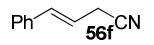
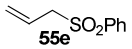
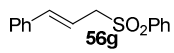
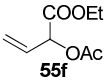
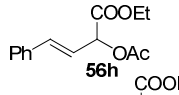
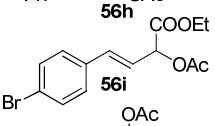
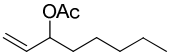
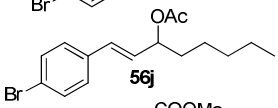
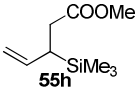
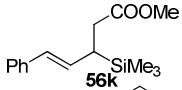
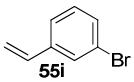
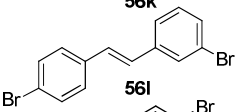
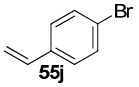
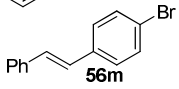
In these transformations we wished to demonstrate the increased chemoselectivity of the oxidative addition in the Pd(II)/Pd(IV) manifold, by concentrating on the preparation of functionalized allylic acetates (**56a-e** and **56h-j**) and aryl bromides (**56b, 56d, 56i-j, 56l-m**). Unless application of special reaction conditions[169] these functional groups (allylic acetate and/or aryl bromide) would easily undergo oxidative addition in a Pd(0) catalyzed transformation, but remains unchanged in the presented Pd(II)/Pd(IV) redox cycle based process.

7.1 Pincer complex-catalyzed Heck reaction

In a typical reaction, we used 5 mol% of complex **1i**, **1k** or **1o** in the presence of 1 eqv $NaHCO_3$ in THF or CH_3CN. The mild reaction conditions (typically 50 °C) and the high chemoselectivity of the catalysts allowed many allylic functionalities, including OAc (Table 13, entries 1-8), CN (Table 13, entry 9-10), SO_2Ph (Table 13, entry 11), COOEt (Table 13, entries 12-13), $SiMe_3$ (Table 13, entry 15), and some of their combinations

(Table 13, entries 12, 13 and 15), as well as aryl bromides (Table 13, entries 4, 7 and 16-18). Iodonium salts **54a**-**c** proved to be equally efficient aryl sources.

Table 13. Pd-catalyzed coupling of alkenes with iodonium salts.[a]

Entry	Substrate	Cat.	Ar_2IX	Solvent	t[h]	Product	Yield[%][b]
1	 **55a**	**1k**	**54a**	THF	14	 **56a**	94
2	**55a**	**1i**	**54a**	THF	16	**56a**	98
3	**55a**	**42**	**54b**	CH_3CN	20	**56a**	98
4	**55a**	**1k**	**54c**	CH_3CN	21	 **56b**	91
5	 **55b**	**1k**	**54a**	CH_3CN	20	 **56c**	91
6	**55b**	**42**	**54a**	CH_3CN	22	**56c**	99
7	**55b**	**1k**	**54c**	CH_3CN	14	 **56d**	89
8	 **55c**	**1k**	**54a**	THF	18	 **56e**	71
9	 **55d**	**1k**	**54a**	THF	14	 **56f**	77
10	**55d**	**1o**	**54a**	THF	17	**56f**	83
11[c]	 **55e**	**1k**	**54b**	CH_3CN	22	 **56g**	77
12	 **55f**	**1k**	**54b**	CH_3CN	19	 **56h**	92
13	**55f**	**1k**	**54c**	CH_3CN	21	 **56i**	83
14	 **55g**	**1k**	**54c**	CH_3CN	21	 **56j**	90
15[d]	 **55h**	**1k**	**54b**	THF	19	 **56k**	82
16	 **55i**	**1k**	**54c**	CH_3CN	21	 **56l**	89
17	 **55j**	**1i**	**54a**	THF	16	 **56m**	91
18	**55j**	**1o**	**54a**	THF	17	**56m**	95

[a] Unless otherwise stated alkene **55** (0.3 mmol), iodonium salt **54** (0.2 mmol), $NaHCO_3$ (0.2 mmol) and the corresponding catalyst **1** (5 mol%) were dissolved in THF or CH_3CN (0.3 ml), and stirred for the indicated period of time at 50 °C. [b] Isolated yield [%]. [c] The reaction was conducted at 65 °C. [d] 0.4 mmol of **55h** was used.

Under the applied mild reaction conditions the architecture of pincer complexes **1i**, **1k** and **1o** was fully preserved (shown, for example, by the ^{31}P NMR spectrum of the crude reaction mixture) and precipitation of Pd-black was not observed.

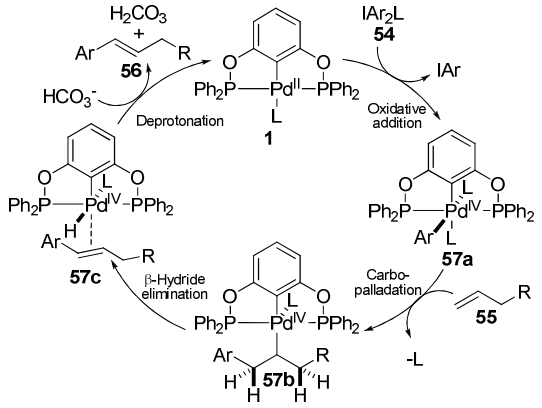
Furthermore, the reactions proceeded with a high regio- and stereoselectivity, as only a single regio- and stereoisomer is formed. PCP catalyst **1k** and SeCSe catalyst **1i** showed an equally high catalytic activity (c.f. entries 1-2, and 16-17, Table 13). Pincer complex **1o** (used in the stoichiometric generation of a Pd(IV) pincer complex using an organo-iodonium salt (eqs. 17-18)) also proved to be an efficient catalyst (Table 13, entries 10 and 18) under our standard catalytic conditions. It was found that, commonly used palladium catalyst $Pd(OAc)_2$ **42** also catalyzed the presented coupling reactions (Table 13, entries 3 and 6). However, unlike the reactions catalyzed by pincer complexes **1i**, **1k** or **1o**, when **42** was employed as catalyst formation of Pd-black was observed.

7.2 Mechanistic proposal

Our results and the published literature data is in line with the assumption that the above reaction proceeds *via* Pd(IV) pincer complex intermediate. The main arguments can be summarized as follows: a) The presented coupling reaction is obviously a redox process. Pincer complexes are known[11,19,90,130,159] to decompose, when the metal atom is reduced to Pd(0). The fact that we have not observed decomposition of the pincer complex catalysts indicates that Pd(0) species are unlikely to occur as catalytic intermediates. (ii) The presented transformation fully tolerates allylic acetates (**55a**, **55c** and **55g**), even activated ones (**55b** and **55f**), which are known to undergo facile oxidative addition with Pd(0) species.[2] (iii) The NCN complex **1o**, which is known to form a Pd(IV) complex with organo-iodonium salts[20,21] (eqs. 17-18), is an active catalyst in the presented process (Table 13, entries 10, 18).

In fact, according to our literature survey the reported complexes obtained by stoichiometric reactions of palladacycles and iodonium(III) salts are all Pd(IV) species,[141,143] while the direct formation of Pd(II) species using hypervalent iodonium salts has not been reported.

Accordingly, the catalytic cycle (Scheme 23) is initiated by an oxidative addition of **54** to catalyst **1** affording Pd(IV) complex **57a** (see also eqs. 17-18). In the next step (**57a** $\rightarrow$ **57b**) a carbo-palladation takes place followed by β-hydride elimination affording complex **57c**, which subsequently undergoes deprotonation by $NaHCO_3$, and regeneration of the catalyst (**1**).



Scheme 23. Proposed Pd(II)/Pd(IV) catalytic cycle.

7.3 Conclusions for chapter 7

We have presented the first palladium pincer complex-catalyzed redox coupling reaction, in which the integrity of the pincer complex is fully retained. The presented process is highly regio- and stereoselective, as only a single regio- and stereoisomer is obtained. Due to the mild reaction conditions, sensitive functionalities such as allylic acetates and aryl halides are fully tolerated. The presented method allows the application of pincer complexes as efficient catalysts in redox transformations.

8. General conclusions and outlook

This thesis demonstrates that new catalytic processes can be efficiently developed by fine-tuning the steric and electronic effects of the side arms in palladium pincer complexes. This principle was exploited for design of several new carbon-carbon bond forming reactions, such as cross-coupling of organoboronic acids with vinyl epoxides and aziridines; coupling of organonitriles with sulfonylimines and chemoselective Heck-type coupling of functionalized alkenes with hypervalent iodonium salts. Chiral BINOL and biphenanthrol-based pincer complexes proved to be efficient catalysts for asymmetric transformation of sulfonylimines, such as allylation, benzylation and condensation with isocyanoacetates.

The enantioselectivity of the pincer complex-catalyzed processes can be further improved by application of new type of BINOL, biphenanthrol or related moieties in the side arms of PCP complexes. Another interesting area is the development of new redox reactions via Pd(IV) pincer complex intermediates, which could substantially broaden the synthetic scope of the pincer complex-catalyzed reactions.

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References

(1) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; Oxford University Press: Mill Valley, California, 1987.
(2) Tsuji, J. Palladium Reagents and Catalysts. New Perspectives for the 21st Century; Wiley: Chichester, 2004.
(3) Tsuji, J. Perspectives in Organopalladium Chemistry for the 21st Century; Elsevier, 1999.
(4) Tsuji, J. Palladium Reagents and Catalysis: Innovations in Organic Synthesis; Wiley: Chichester, 1995.
(5) Negishi, E.; Meijre, A. d. *Organopalladium Chemistry for Organic Synthesis*; Wiley: New York, 2002.
(6) Bäckvall, J.-E. *Metal-catalyzed Cross Coupling Reactions*; VCH: Weinheim, 1998.
(7) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.
(8) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, California, 1999.
(9) Tsuji, J. Transition Metal Reagents and Catalysts. Innovation in Organic Synthesis; Wiley: Chichester, 2000.
(10) Crabtree, R. H. The Organometallic Chemistry of the Transition Metals; Wiley: Hoboken, 2005.
(11) *The Chemistry of Pincer Compounds*; Elsevier: Amsterdam, 2007.
(12) Albrecht, M.; Koten, G. v. *Angew. Chem. Int. Ed.* **2001**, 3750.
(13) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527.
(14) Singleton, J. T. *Tetrahedron* **2003**, *59*, 1837.
(15) Boom, M. E. v. d.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759.
(16) Szabó, K. J. *Synlett* **2006**, 811.
(17) Benito-Garagorri, D.; Kirchner, K. *Acc. Chem. Res.* **2008**, *41*, 201.
(18) Bedford, R. B. *Chem. Commun.* **2003**, 1787.
(19) Sommer, W. J.; Yu, K.; Sears, J. S.; Ji, Y.; Zheng, X.; Davis, R. J.; Sherrill, C. D.; Jones, C. W.; Weck, M. *Organometallics* **2005**, *24*, 4351.
(20) Canty, A. J.; Rodemann, T.; Skelton, B. W.; White, A. H. *Organometallics* **2006**, *25*, 3996.
(21) Lagunas, M. C.; Gossage, R. A.; Spek, A. L.; Koten, G. v. *Organometallics* **1998**, *17*, 731.
(22) Beek, J. A. M. v.; Koten, G. v.; Dekker, G. P. C. M.; Wissing, E.; Zoutberg, M. C.; Stam, C. H. *J. Organomet. Chem.* **1990**, *394*, 659.

(23) Kuil, L. A. v. d.; Luitjes, H.; Grove, D. M.; Zwikker, J. W.; Linden, J. G. M. v. d.; Roelofsen, A. M.; Jenneskens, L. W.; Drenth, W.; Koten, G. v. *Organometallics* **1994**, *13*, 468.
(24) Rimml, H.; Venanzi, L. M. *J. Organomet. Chem.* **1983**, *259*, C6.
(25) Stark, M. A.; Richards, C. J. *Tetrahedron Lett.* **1997**, *38*, 5881.
(26) Longmire, J. M.; Zhang, X.; Shang, M. *Organometallics* **1998**, *17*, 4374.
(27) Slagt, M. Q.; Jastrzebski, J. T. B. H.; Klein-Gebbink, R. J. M.; Ramesdonk, H. J. v.; Verhoeven, J. W.; Ellis, D. D.; Spek, A. L.; Koten, G. v. *Eur. J. Chem.* **2003**, 1962.
(28) Slagt, M. Q.; Rodríguez, G.; Grutters, M. M. P.; Gebbink, R. J. M. K.; Klopper, W.; Jenneskens, L. W.; Lutz, M.; Spek, A. L.; Koten, G. v. *Chem. Eur. J.* **2004**, *10*, 1331.
(29) Giménez, R.; Swager, T. M. *J. Mol. Cat. A* **2001**, *166*, 265.
(30) Gosiewska, S.; Veld, M. H. i.; Pater, J. J. M. d.; Bruijnincx, P. C. A.; Lutz, M.; Spek, A. L.; Koten, G. v.; Klein-Gebbink, R. J. M. *Tetrahedron: Asymmetry* **2006**, *17*, 674.
(31) Donkervoort, J. G.; Vicario, J. L.; Rijnberg, E.; Jastrzebski, J. T. B. H.; Kooijman, H.; Spek, A. L.; Koten, G. v. *J. Organomet. Chem.* **1998**, *463*, 463.
(32) Maitlis, P. M.; Espinet, P.; Russel, M. J. H. *Compunds with Palladium-Carbon σ-Bonds*; Pergamon Press: Oxford, 1982; Vol. 6.
(33) Harrington, P. J. In *Transition Metal Allyl Complexes: Pd, W, Mo-assisted Nucleophilic Attack*; Abel, E. W., Gordon, F., Stone, A., Wilkinson, G., Puddephatt, R. J., Eds.; Elsevier: New York, 1995; Vol. 12, p 797.
(34) Gatti, R. G. P.; Larsson, A. L. E.; Bäckvall, J.-E. *J. Chem. Soc. Perkin 1* **1997**, 577.
(35) Jolly, P. W. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 283.
(36) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067.
(37) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641.
(38) Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1985**, *41*, 5779.
(39) Wallner, O. A.; Szabó, K. J. *Chem. Eur. J.* **2003**, *9*, 4025.
(40) Wallner, O. A.; Szabó, K. J. *J. Org. Chem.* **2003**, *68*, 2934.
(41) Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2002**, *4*, 1563.
(42) Solin, N.; Narayan, S.; Szabó, K. J. *Org. Lett.* **2001**, *3*, 909.
(43) Solin, N.; Narayan, S.; Szabó, K. J. *J. Org. Chem.* **2001**, *66*, 1686.
(44) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614.
(45) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242.
(46) Nakamura, H.; Bao, M.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 3208.

(47) Szabó, K. J. *Chem. Eur. J.* **2000**, *6*, 4413.
(48) Solin, N.; Kjellgren, J.; Szabó, K. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 3656.
(49) Solin, N.; Kjellgren, J.; Szabó, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 7026.
(50) Solin, N.; Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2005**, *7*, 689.
(51) Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2004**, *6*, 1829.
(52) Wallner, O. A.; Szabó, K. J. *Chem. Eur. J.* **2006**, *12*, 6976.
(53) Sebelius, S.; Olsson, V. J.; Szabó, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 10478.
(54) Sebelius, S.; Olsson, V. J.; Wallner, O. A.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 8150.
(55) Olsson, V. J.; Sebelius, S.; Selander, N.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 4588.
(56) Yao, Q.; Kinney, E. P.; Zheng, C. *Org. Lett.* **2004**, *6*, 2997.
(57) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(58) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.
(59) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.
(60) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11.
(61) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.
(62) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419.
(63) Miyaura, N.; Tanabe, Y.; Suginome, H.; Suzuki, A. *J. Organomet. Chem.* **1982**, *233*, C13.
(64) Hirai, A.; Yu, X.-Q.; Tonooka, T.; Miyashita, M. *Chem. Commun.* **2003**, 2482.
(65) Yu, X.-Q.; Hirai, A.; Miyashita, M. *Chem. Lett.* **2004**, *33*, 764.
(66) Alsters, P. L.; Baesjou, P. J.; Janssen, M. D.; Kooijman, H.; Sicherer-Roetman, A.; Spek, A. L.; Koten, G. v. *Organometallics* **1992**, *11*, 4124.
(67) Bedford, R. B.; Draper, S. M.; Scully, P. N.; Welch, S. L. *New J. Chem.* **2000**, *24*, 745.
(68) Wallner, O. A.; Szabó, K. J. *J. Org. Chem.* **2005**, *70*, 9215.
(69) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815.
(70) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10.
(71) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651.
(72) Fernandes, R. A.; Stimac, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14133.
(73) Wallner, O. A.; Olsson, V. J.; Eriksson, L.; Szabó, K. J. *Inorg. Chim. Acta* **2006**, *359*, 1767.
(74) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.
(75) Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2001**, *40*, 1896.
(76) Ferraris, D.; Dudding, T.; Young, B.; Drudy, W. J.; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168.

(77) Cook, G. R.; Kargbo, R.; Maity, B. *Org. Lett.* **2005**, *7*, 2767.
(78) Hamada, T.; Manabe, K.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 3927.
(79) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. C.; Jorgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844.
(80) Tan, K. L.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2007**, *46*, 1315.
(81) Kyba, E. P.; Gokel, G. W.; Jong, F. d.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Sogah, G. D. Y.; Cram, D. J. *J. Org. Chem.* **1977**, *42*, 4173.
(82) Börner, C.; Dennis, M. R.; Sinn, E.; Woodward, S. *Eur. J. Org. Chem.* **2001**, 2435.
(83) Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253.
(84) Lin, Y.; Chien, L.-C. *Tetrahedron: Asymmetry* **1998**, *9*, 63.
(85) Nakajima, M.; Miyoshi, I.; Hashimoto, S.-i. *J. Org. Chem.* **1999**, *64*, 2264.
(86) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766.
(87) Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11038.
(88) Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, 990.
(89) Johansson, R.; Wendt, O. F. *Dalton Trans.* **2007**, 488.
(90) Eberhard, M. R. *Org. Lett.* **2004**, *6*, 2125.
(91) Motoyama, Y.; Okano, M.; Narusawa, H.; Makihara, N.; Aoki, K.; Nishiyama, H. *Organometallics* **2001**, *20*, 1580.
(92) Motoyama, Y.; Narusawa, H.; Nishiyama, N. *Chem. Commun.* **1999**, 131.
(93) Baber, R. A.; Bedford, R. B.; Betham, M.; Blake, M. E.; Coles, S. J.; Haddow, M. F.; Hurthouse, M. B.; Orpen, A. G.; Pilarski, L. T.; Pringle, P. G.; Wingad, R. L. *Chem. Commun.* **2006**, 3880.
(94) Viso, A.; Pradilla, R. F. d. l.; Garcia, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167.
(95) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X.; Sun, J.; Xia, L.-J.; Tang, M.-H. *J. Org. Chem.* **1999**, *64*, 1331.
(96) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X. *Tetrahedron: Asymmetry* **1999**, *10*, 855.
(97) Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969.
(98) Lin, Y.-R.; Zhou, X.-T.; Dai, L.-X.; Sun, J. *J. Org. Chem.* **1997**, *62*, 1799.
(99) Benito-Garagorri, D.; Bocokic, V.; Kirchner, K. *Tetrahedron Lett.* **2006**, *47*, 8641.
(100) Yao, Q.; Sheets, M. *J. Org. Chem.* **2006**, *71*, 5384.
(101) Aydin, J.; Selander, N.; Szabó, K. J. *Tetrahedron Lett.* **2006**, *47*, 8999.

(102) Gorla, F.; Togni, A.; Venanzi, L. M. *Organometallics* **1994**, *13*, 1607.
(103) Mehendale, N. C., Utrecht University, 2007.
(104) Zografidis, A.; Polborn, K.; Beck, W.; Markies, B. A.; Koten, G. v. *Naturforsch., B* **1994**, *49*, 1494.
(105) Gagliardo, M.; Selander, N.; Mehendale, N. C.; Koten, G. v.; Klein-Gebbink, R. J. M.; Szabó, K. J. *Chem. Eur. J.* **2008**, *14*, 4800.
(106) Dyker, G. Handbook of C-H Transformations: Applications in Organic Synthesis; Wiley-VCH: Weinheim, 2005.
(107) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2440.
(108) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.
(109) Hosokawa, T.; Murahashi, S.-I. *Acc. Chem. Res.* **1990**, *23*, 49.
(110) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970.
(111) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076.
(112) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274.
(113) Franzén, J.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2003**, *125*, 6056.
(114) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 164.
(115) Byström, S. E.; Larsson, E. M.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 5674.
(116) Zanoni, G.; Porta, A.; Meriggi, A.; Franzini, M.; Vidari, G. *J. Org. Chem.* **2002**, *67*, 6064.
(117) Naota, T.; Taki, H.; Mizuno, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1989**, *111*, 5954.
(118) Paganelli, S.; Schionato, A.; Botteghi, C. *Tetrahedron Lett.* **1991**, *32*, 2807.
(119) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 13632.
(120) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Chem. Commun.* **2005**, 3600.
(121) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757.
(122) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 8598.
(123) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436.
(124) Goto, A.; Endo, K.; Ukai, Y.; Irle, S.; Saito, S. *Chem. Commun.* **2008**, 2212.
(125) Fan, L.; Ozerov, O. V. *Chem. Commun.* **2005**, 4450.
(126) Aydin, J.; Kumar, K. S.; Sayah, M. J.; Wallner, O. A.; Szabó, K. J. *J. Org. Chem.* **2007**, *72*, 4689.
(127) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991.
(128) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1.
(129) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917.

(130) Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055.
(131) Morales-Morales, D.; Grause, C.; Kasaoka, K.; Redón, R.; Cramer, R. E.; Jensen, C. M. *Inorg. Chem. Acta* **2000**, *300*, 958.
(132) Dupont, J.; Beydoun, N.; Pfeffer, M. *J. Chem. Soc. Dalton Trans.* **1989**, 1715.
(133) Aydin, J.; Kumar, K. S.; Eriksson, L.; Szabó, K. J. *Adv. Synth. Catal.* **2007**, *349*, 2585.
(134) Aydin, J.; Szabó, K. J. *Org. Lett.* **2008**, *10*, 2881.
(135) D'sa, B. A.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3961.
(136) Kisanga, P.; McLeod, D.; D'sa, B.; Verkade, J. *J. Org. Chem.* **1999**, *64*, 3090.
(137) Viteva, L.; Gospodova, T.; Stefanovsky, Y.; Simova, S. *Tetrahedron* **2005**, *61*, 5855.
(138) Yazaki, R.; Nitabaru, T.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 14477.
(139) Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 426.
(140) Aydin, J.; Rydén, A.; Szabó, K. J. *Tetrahedron: Asymmetry* **2008**, *19*, 1867.
(141) Canty, A. J.; Rodemann, T.; Ryan, J. H. *Advances in Organometallic Chemistry*; Elsevier: New York, 2008; Vol. 55.
(142) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83.
(143) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924.
(144) Catellani, M. *Synlett* **2003**, 298.
(145) Daugulis, O.; Zaitsev, V. D.; Shabashov, D.; Pham, Q. N.; Lazareva, A. *Synlett* **2006**, 3382.
(146) Whitfield, R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142.
(147) Dick, R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *27*, 12790.
(148) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330.
(149) Daugulis, O.; Zaitsev, V. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4046.
(150) Tong, X.; Beller, M.; Tse, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 4906.
(151) Muniz, K.; Hvelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763.
(152) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179.
(153) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148.
(154) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690.
(155) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759.
(156) Chaudhuri, P. D.; Guo, R.; Malinakova, H. C. *J. Organomet. Chem* **2008**, *693*, 567.
(157) Yoneyama, T.; Crabtree, R. C. *J. Mol. Catal., A: Chem.* **1996**, *108*, 35.

(158) Spencer, J.; Chowdhry, B. Z.; Mallet, A. I.; Rathnam, R. P.; Adatia, T.; Bashall, A.; Rominger, F. *Tetrahedron* **2008**, *64*, 6082.
(159) Phan, N. T. S.; Sluys, M. v. d.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609.
(160) Zhadankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.
(161) Ochiai, M.; Sumi, K.; Takaoka, Y.; Nagao, Y.; Shiro, M.; Fujita, E. *Tetrahedron* **1988**, *44*, 4095.
(162) Hossain, M. D.; Ikegami, Y.; Kitamura, T. *J. Org. Chem.* **2006**, *71*, 9903.
(163) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610.
(164) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
(165) Moriarty, R. M.; Epa, W. R.; Awasthi, A. K. *J. Am. Chem. Soc.* **1991**, *113*, 6315.
(166) Zhu, M.; Song, Y.; Cao, Y. *Synlett* **2007**, 853.
(167) Kang, S.-K.; Yamaguchi, T.; Pyun, S.-J.; Lee, Y.-T.; Baik, T.-G. *Tetrahedron Lett.* **1998**, 2127.
(168) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Kim, T.-H.; Pyun, S.-J. *J. Org. Chem.* **1996**, *61*, 2604.
(169) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4729.