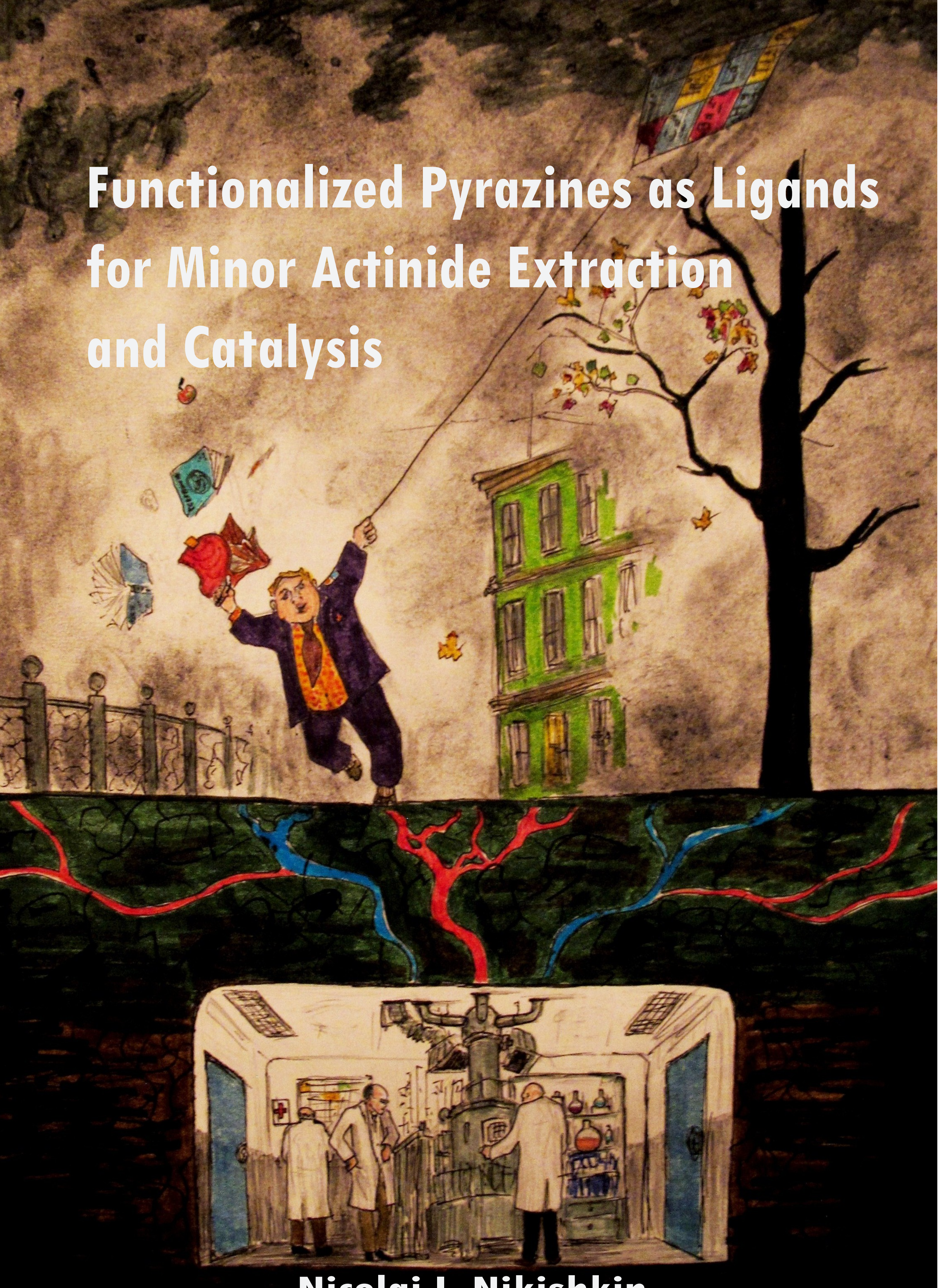
Functionalized Pyrazines as Ligands for Minor Actinide Extraction and Catalysis



Nicolai I. Nikishkin

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FUNCTIONALIZED PYRAZINES AS LIGANDS FOR MINOR ACTINIDE EXTRACTION AND CATALYSIS

DISSERTATION

to obtain
the degree of doctor at the University of Twente,
on the authority of the rector magnificus,
prof.dr. H. Brinksma,
on account of the decision of the graduation committee,
to be publicly defended
on Thursday January 24, 2013 at 14.45

by

Nicolai Igorevich Nikishkin

born on May 31, 1980
in Minsk, Belarus

This dissertation has been approved by:

Promotor: Prof. dr. ir. J. Huskens

Assistant-Promotor: Dr. W. Verboom

Dedicated to my Father,
Who passed away in 2010.

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Chapter 1

General Introduction

One of the most interesting and challenging topics of modern synthetic chemistry is the design of ligands with fine-tuned structural and electronic properties.[1,2,3] The successful application of polydentate ligands in selective metal ion extraction,[4] sensing,[5] and catalysis[6] has motivated further developments in this area. Nowadays the design and synthesis of ligands is mainly oriented towards polydentate multifunctional molecules, which combine the desired electronic and steric properties of the selected donor groups together with auxiliary functional groups. Functional groups (such as a pendant acid[7] or base,[8] solubilizing substituents,[9] fluorophores,[10] *etc*) can be varied depending on the application of the ligand.

Within the vast family of polydentate ligands, N-donor heterocyclic ligands are of particular interest. Pyridyl-based ligands have been utilized as frameworks for various organometallic materials and active complex catalysts.[11] Pyrazole-containing ligands have been used for the synthesis of inorganic models of metallo-enzymes and as synthons in supramolecular chemistry and catalysis.[12] Pincer complexes of tridentate *N,N,N*-donor ligands, such as 2,6-bis(oxazolinyl)pyridines,[13] 2,6-bis(imino)pyridines,[14] terpyridines,[15] and other,[16] have also become attractive scaffolds due to their easily tunable properties and broad applications.[17]

In contrast, pyrazine derivatives as a ligand motif only recently attracted the attention of chemists, mainly due to difficulties in functionalization due to the unique nature of the pyrazine aromatic system. Nevertheless, functionalized pyrazines have already found widespread applications as 2,3,5,6-mono and disubstituted, symmetrical and non-symmetrical derivatives bearing various substituents. In recent years, pyrazine-based compounds have been used as ligands or building blocks for the construction of multinuclear transition metal complexes,[18] coordination polymers,[19] metal-organic frameworks,[20] highly luminescent complexes,[21] and catalysts.[22]

This thesis is centered around the development of methods for the functionalization of pyrazines, the synthesis of novel ligands based on the developed approaches, and the application of the new ligands for selective actinide extraction and rhodium catalysis. Chapter 2 summarizes the recent advances in the field of transition metal-catalyzed functionalization of pyrazines. Chapter 3 contains a study on the reactivity of malonate-type compounds in Pd/C-catalyzed reactions. Chapter 4 deals with the development of a novel methodology for Pd-catalyzed C-P cross-coupling of various phosphorus pronucleophiles with chloropyrazines. The synthesis and the extraction behaviour of novel water-soluble actinide-selective ligands is described. Chapter 5 is devoted to the application of this methodology for the preparation of supramolecular multivalent calix[4]arene-based extractants. The extraction behavior of these novel extractants towards model nuclear waste solutions is also described. Another application involves the synthesis of polydentate hydrophilic phosphinopyrazines. They are successfully used for the aqueous asymmetric hydrogenation of acetophenone (Chapter 6) and the aqueous/alcohol polymerization of terminal arylacetylenes (Chapter 7).

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Chapter 2

Transition Metal-Catalyzed Functionalization of Pyrazines

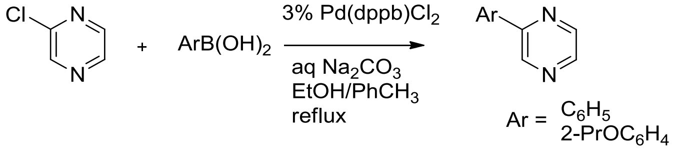
This overview deals with the recent progress in the field of transition-metal-catalyzed cross-coupling reactions on pyrazine systems. The most important C–C and C–X-bond formation methodologies (Heck, Negishi, Stille, Sonogashira, Suzuki–Miyaura, C–H activation) are reviewed.

2.1. Introduction

Transition-metal-catalyzed cross-coupling reactions are a well-established tool for carbon–carbon and carbon–heteroatom bond formation.[1,2,3] However, most of the publications focus on the development of novel, more efficient catalysts relative to existing methods. Heterocyclic examples remain rare in these studies and are typically restricted to readily available pyridine derivatives.[4,5] Pyrazines represent an important class of heterocyclic compounds, since the pyrazine scaffold is found in many vital pharmaceuticals[6] and biologically active compounds.[7] Functionalized pyrazines are being applied as selective extractants for f-block metals,[8] photovoltaic devices,[9] and effective catalysts,[10] as well as ligands for catalysis.[11] However, the chemistry of pyrazines is still relatively unexplored. Examples of cross-coupling reactions on pyrazine derivatives are mainly limited to reactions leading to prominent target compounds for pharmaceutical applications, however, there are only few methodological studies. On the other hand, the highly electron-deficient nature of the pyrazine system allows the successful use of the aromatic nucleophilic substitution reaction for the functionalization of halogenated pyrazines,[12,13] so that the cross-coupling chemistry of pyrazines was given naturally much less attention. Although these factors led to a limited number of cross-coupling examples in this heterocyclic series, interesting reactions and applications were introduced in recent years and may give rise to further improvement and broadening of the scope of this methodology within the area of pyrazine chemistry. This chapter summarizes existing methods for transition metal-catalyzed functionalization of pyrazines.

2.2. Suzuki Coupling

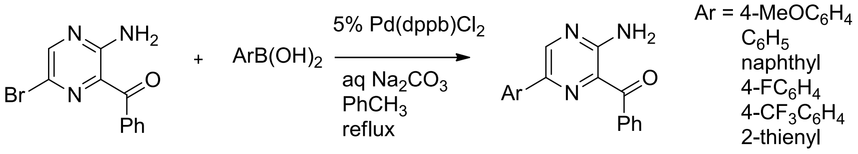
The popularity of the Suzuki reaction[14] as a powerful and straightforward tool for carbon-carbon bond formation, is undisputable among synthetic and industrial chemists. As many other palladium-catalyzed couplings, the Suzuki reaction utilizes aryl halides and pseudohalides, such as triflates, as substrates. Amongst these, special attention was paid to "activated" electron-deficient hetaryl halides. The reactivity of hetaryl chlorides and their commercial availability (wide abundance) predefined their eligibility for palladium-catalyzed coupling reactions. At the same time the presence of the pyrazine scaffold in a variety of natural biologically active compounds has made halogenated pyrazines popular hetaryl substrates for natural and pharmaceutical products synthesis. One of the very first examples of a Suzuki coupling performed on halogenated pyrazines was published by McKillop *c.s.*,[15] who successfully attempted the coupling of chloropyrazine with aryl boronic acids (Scheme 2.1) using conventional palladium-phosphine catalysts in good to excellent yields.



Scheme 2.1. Suzuki coupling of chloropyrazine. dppb = 1,4-bis(diphenylphosphino)butane.

It is interesting to note that $Pd(PPh_3)_4$, used as the catalyst in the original Suzuki reaction,[16] failed to give any coupled product in the reaction of chloropyrazine with a variety of aryl boronic acids. However, when $Pd(dppb)Cl_2$ was used as a catalyst, chloropyrazine was smoothly converted into coupled products with good to excellent yields and the presence of an electron-withdrawing or -donating group on the boronic acid did not adversely affect the reaction. These results indicate the greater effectiveness of Pd(dppb)Cl_2 in this type of cross-coupling.

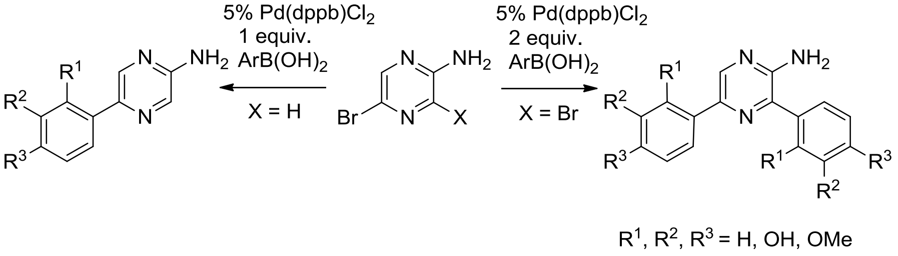
Using the McKillop catalyst (Pd(dppb)Cl_2), Jones *et al.*[17] extended the scope of hetaryl coupling to highly functionalized bromopyrazines (Scheme 2.2).



Scheme 2.2. Suzuki coupling of bromopyrazines.

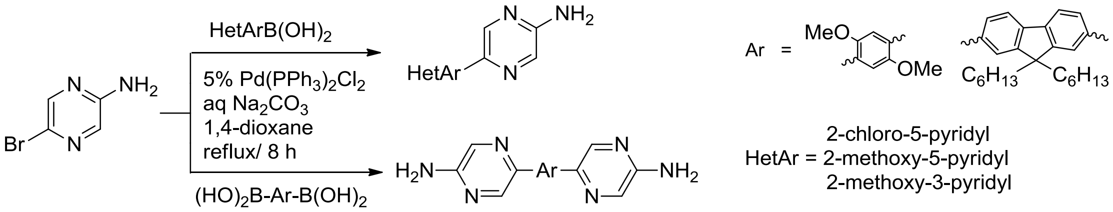
Coupling of highly functionalized bromopyrazines with most of the aryl boronic acids gave the heterobiaryl products in very high yields of >90%. Introduction of an electron-withdrawing group on the aryl boronic acid moiety had no considerable impact on the coupled product yield as well as on the reaction rate. The only exception was thiophene-2-boronic acid, giving only 60% of the coupled product after 48 hours. However, the reaction was still clean forming no side products.[17]

Cavalier *et al.*[18,19] extended the McKillop methodology further and successfully applied this approach for the simultaneous mono- and di-arylation of aminobromopyrazine in 30-80% yields (Scheme 2.3). Remarkably, direct Suzuki coupling of unprotected phenols was also accomplished in moderate to good yields revealing no influence of the phenol group.



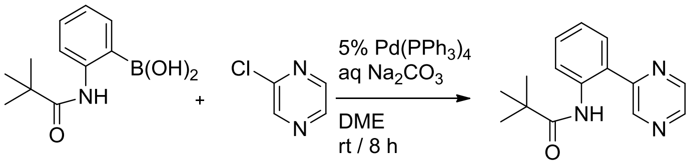
Scheme 2.3. Arylation of aminobromopyrazine and aminodibromopyrazine.

Thompson *et al.*[20] have reported the first systematic study of a Suzuki reaction in the presence of an unprotected amino group on a coupling substrate scaffold. 2-Amino-5-bromopyrazine smoothly reacted with methoxy- and chloropyridyl boronic acids to give the coupled products in moderate yields, independent of the base used. Twofold couplings of 2-amino-5-bromopyrazine with arylene diboronic acid derivatives proceeded in 50-70% yields, demonstrating the general applicability of the protocol developed by McKillop towards not only the synthesis of pyrazine-containing heterobiaryls, but also to extended amino-substituted tri- and tetraarylene systems (Scheme 2.4).



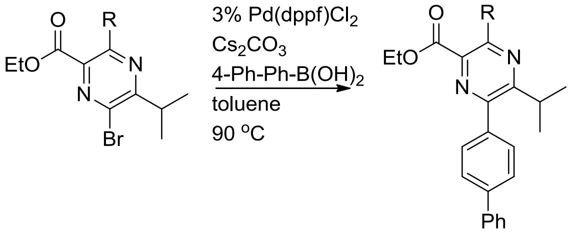
Scheme 2.4. McKillop methodology extended to hetaryl coupling partners.

Tapolcsanyi *et al.*[21] examined the reactivity of chloropyrazine towards 2-pyvaloylaminophenyl boronic acid. In contrast to the results obtained by McKillop, who reported Pd(PPh$_3$)$_4$ to be incapable to catalyze cross-coupling of chloropyrazine with phenyl boronic acid (vide supra), 2-pyvaloylaminophenyl boronic acid reacted with chloropyrazine at room temperature in the presence of $Pd(PPh_3)_4$ affording the coupled product in 53% yield (Scheme 2.5). In this case the apparent reactivity can be ascribed to a higher nucleophilicity of the coupling partner due to the presence of the donor pyvaloylamino group that enhances the polarization of the carbon-boron bond and facilitates transmetallation of the aryl boronic acid.



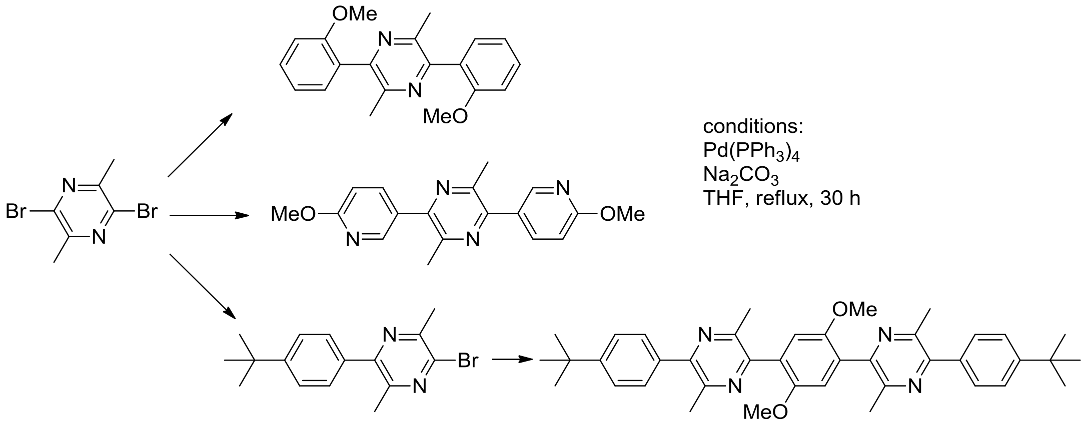
Scheme 2.5. Reaction of 2-pyvaloylaminophenyl boronic acid with chloropyrazine.

Suzuki coupling has also been reported for activated bromopyrazines. Highly functionalized 6-bromopyrazines were subjected to Suzuki coupling conditions. Reaction with biphenyl boronic acid in the presence of cesium carbonate as a base and $Pd(dppf)Cl_2$ as a catalyst gave the 6-arylpyrazines in 85-100% yields (Scheme 2.6). However, the reaction utilizes a high excess of a coupling partner compared to the coupling of regular aromatic halides.[22]



Scheme 2.6. Suzuki coupling of activated bromopyrazines.

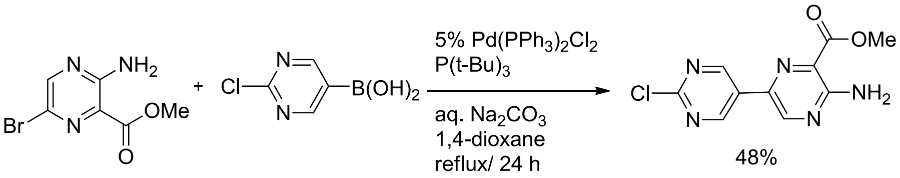
In the course of the preparation of tetra- and pentaarylenes, incorporating a pyrazine core, the Suzuki approach was envisaged. Cross-coupling of 2,5-dibromo-3,6-dimethylpyrazine with 2-methoxybenzeneboronic acid and 4-*tert*-butylbenzeneboronic acid using $Pd(PPh_3)_4$ as catalyst gave the desired coupled products in 76 and 39% yield, respectively (Scheme 2.7).



Scheme 2.7. Cross-coupling of 2,5-dibromo-3,6-dimethylpyrazine.

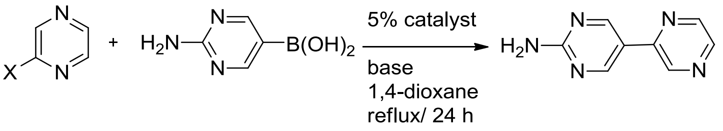
Further reaction of 2-bromo-5-(4-*tert*-butylphenyl)-3,6-dimethylpyrazine with 2,5-dimethoxy-1,4-benzeneboronic acid gave the linear pentaarylene system in 16% yield. The analogous reaction of 2,5-dibromo-3,6-dimethylpyrazine with 2-methoxy-5-pyridylboronic acid afforded the 2,5-dipyridylpyrazine derivative in 73% yield. This last case illustrates that Suzuki reactions enable a range of heteroaryl moieties to be incorporated into the polymer chain.[23] It is worth to note that due to the lability of halogens on the electron-deficient pyrazine core, the monoarylation of 2,5-dibromo-3,6-dimethylpyrazine with 4-*tert*-butylbenzeneboronic acid required a considerable excess of the former.

The same group has explored Suzuki couplings of halopyrazines with pyrimidylboronic acids. In the case of 2-chloro-5-pyrimidylboronic acid the yield of the cross-coupled product was limited to 48% (Scheme 2.8), because of the concurrent formation of byproducts, i.e. the bipyrimidine derivative and higher oligomers derived from competitive self-coupling of boronic acid.



Scheme 2.8. Suzuki coupling of bromopyrazine with 2-chloro-5-pyrimidylboronic acid.

Coupling of chloropyrazine with 2-amino-5-pyrimidylboronic acid gave the desired coupled product in a yield of 60%. The yield was increased to 72% by using iodopyrazine as substrate and $Pd_3(dba)_2$ as catalyst (Scheme 2.9). Protodeboronation of 2-amino-5-pyrimidylboronic acid to give 2-aminopyrimidine was a competing side-reaction. The overall yield of cross-coupled product was improved by subsequent addition of a second equivalent of boronic acid to the reaction mixture after 24 h reflux.[24]

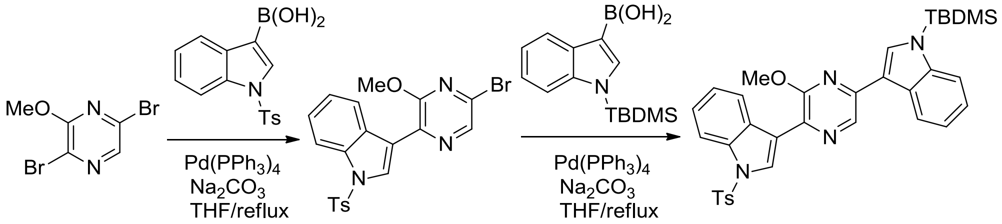


X = I, catalyst = $Pd(PPh_3)_2Cl_2/P(t\text{-}Bu)_3$, base = Na_2CO_3
X = I, catalyst = $Pd_2(dba)_3/PCy_3$, base = K_3PO_4
X = Cl, catalyst = $Pd_2(dba)_3/PCy_3$, base = K_3PO_4

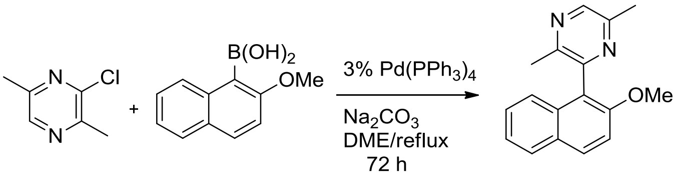
Scheme 2.9. Coupling of chloropyrazine with 2-amino-5-pyrimidylboronic acid.

In an attempt to synthesise the dragmacidin D scaffold, another example of the Suzuki coupling of halogenated pyrazine with hetarylboronic acids was reported. Reacting 2,5-

dibromo-3-methoxypyrazine with tosyl-protected indolylboronic acids solely yielded the 2-arylated product (Scheme 2.10). This regioselectivity can be attributed to the methoxy group “assistance” in the ortho-halogene displacement by coordination towards the palladium catalytical center. Introduction of the second tosyl-protected indole unit by repeating the first Suzuki step failed. Neither worked a large excess of tosyl-protected indolylboronic acid in the first step. No improvement occurred using stronger bases, higher temperature or the more active Pd(dppf)Cl_2 catalyst. On the other hand, coupling of bromoindolylpyrazine with phenylboronic acid under standard Suzuki conditions afforded the desired coupling product in 80% yield. The latter result clearly indicates that the electronic properties of the coupling partner play an important role. Thus employing the more electron-rich TBDMS-protected indolylboronic acid as the coupling partner in the second step afforded the desired *bis*-indolylpyrazine in 80% yield.[25]



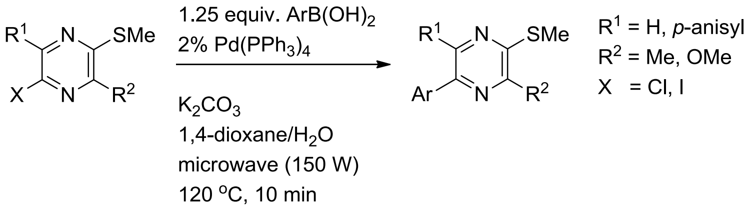
Scheme 2.10. Coupling of 2,5-dibromo-3-methoxypyrazine with protected indolylboronic acids.



Scheme 2.11. Suzuki coupling of 3-chloro-2,5-dimethylpyrazine.

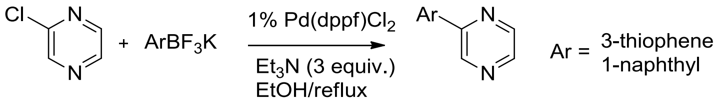
3-Chloro-2,5-dimethylpyrazine was also found to undergo Suzuki coupling (Scheme 2.11). Reaction with 2-methoxynaphthylboronic acid afforded the coupled product in 61% yield. The relatively low yield and relatively long reaction time of 72 h can be explained by the presence of two electron-donating methyl groups, which deactivate the chloropyrazine towards oxidative addition.[26]

In a study on the preparation of asymmetrically tri- and tetrasubstituted pyrazines the application of microwave irradiation during the Suzuki coupling step was found to be highly valuable for substrate activation, speeding up the reaction (reaction time 10 min) (Scheme 2.12). Although significantly inactivated by the presence of multiple donor groups, pyrazines reacted with various arylboronic acids giving coupled products in excellent yields.[27]



Scheme 2.12. Suzuki coupling of 5-halo-2-(methylthio)pyrazines.

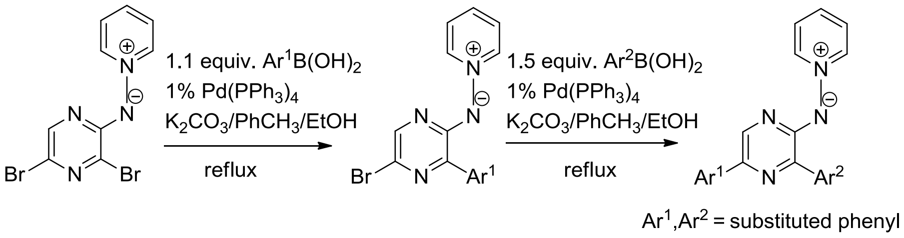
The use of trifluoroborates to improve the cross-coupling was exemplified by the reaction with chloropyrazine (Scheme 2.13).



Scheme 2.13. Chloropyrazine coupling with trifluoroborates.

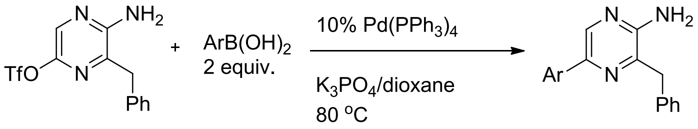
The reaction of chloropyrazine with 1-naphthyl- and 3-thiophenetrifluoroborates afforded the coupled products in >80% yield in 9 h. For comparison, the reactions involving similar boronic acid coupling partners required 3 times higher catalyst load and 5 times longer reaction times and gave lower yields.[26,28] The key advantages of organotrifluoroborates as hetaryl coupling partners over boronic acids include higher reactivity, tolerance to a wide range of electron-withdrawing and electron-donating groups in both coupling partners, and ease of handling. In addition, organotrifluoroborates are less prone to protodeboronation.[29]

Another interesting approach towards regioselective Suzuki coupling was reported by Castillo *et al.*[30] The reaction of pyridinium *N*-(3,5-dibromopyrazinyl)aminide and boronic acids worked effectively under standard conditions with 1 mol% of $Pd(PPh_3)_4$ catalyst to afford mono- and diarylpyrazines in good to excellent yields (Scheme 2.14). The regioselectivity of the monoarylation in the first step was provided by the unshared electron pair of the aminide nitrogen that coordinates to palladium and directs the oxidative addition to the ortho halogen.



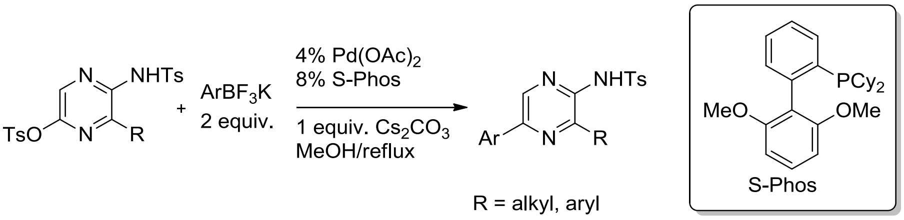
Scheme 2.14. Suziki coupling of pyridinium *N*-(3,5-dibromopyrazinyl)aminide with boronic acids.

The Suzuki coupling was also examined with pyrazine *O*-triflates under standard Suzuki conditions.[31] Reaction of 5-*O*-triflyl-3-benzyl-2-aminopyrazine with different arylboronic acids afforded the coupled products in good yields (Scheme 2.15) showing triflate to be a suitable leaving group. However, the procedure requires a high load (up to 10 mol%) of palladium catalyst.



Scheme 2.15. Reaction of 5-*O*-triflyl-3-benzyl-2-aminopyrazine with different arylboronic acids.

A systematic study on the coupling of pyrazine *O*-tosylates with various organoboron derivatives was recently reported by Makarasen *et al.*[32] In this work *O*-tosylates gave the highest yields reacting with aryltrifluoroborates in the presence of 4 mol% of Pd(OAc)$_2$ and 8 mol% of biarylphosphine ligand (Scheme 2.16) revealing also tosylate to be a good leaving group.



Scheme 2.16. Coupling of pyrazine *O*-tosylates with aryltrifluoroborates.

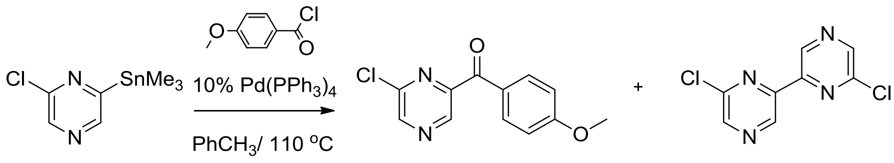
The high electrophilicity of the trifluoroborate group also happened to dominate over the electronic effects of the *para*-substituent in the aromatic ring, providing good to excellent yields in all cases of coupling with aryltrifluoroborates bearing highly electron-donating or

-withdrawing groups at the *para*-position.

In summary, due to its broad scope and high tolerance towards a wide variety of functional groups, the Suzuki reaction of hetaryl organoborons as well as halides or related electrophiles provides one of the most straightforward methods for pyrazine functionalization along with the construction of pyrazine-based heterocyclic frameworks.

2.3. Stille Coupling

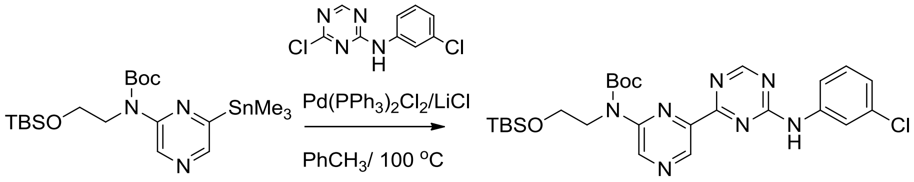
The palladium-catalyzed Stille coupling is a versatile reaction for the formation of C-C bonds between stannanes and halides or pseudohalides.[33] Several examples of the Stille cross-coupling reaction have been reported in pyrazine chemistry. The Stille reaction of stannylated pyrazine and 4-methoxybenzoyl chloride afforded a mixture of the desired compound and the product of homocoupling of the tributylstannylpyrazine in 64% overall yield. The homocoupling, however, was suppressed by simply changing the order of introduction of the reagents. Mixing the aroyl chloride with the palladium catalyst prior to introduction of the stannylated pyrazine yielded 70% of the desired compound without formation of the homocoupling product (Scheme 2.17).[34]



Process A: stannane + aroyl chloride, then catalyst (64%) 70 / 30
Process B: aroyl chloride + catalyst, then stannane (70%) 100 / 0

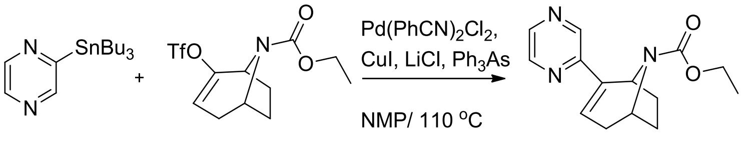
Scheme 2.17. Stille coupling of stannylated pyrazine with 4-methoxybenzoyl chloride.

Bihetaryl Stille coupling with chlorotriazine starting from stannylated pyrazine was accomplished in 47% yield (Scheme 2.18).[35] The reaction occurred selectively at the triazine chlorine leaving the chlorophenyl substituent intact.



Scheme 2.18. Bihetaryl Stille coupling of stannylated pyrazine with chlorotriazine.

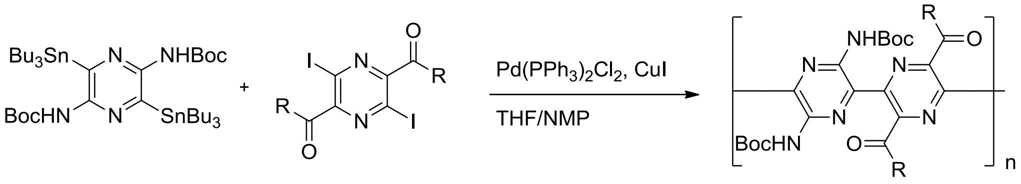
Another example of palladium-catalyzed Stille cross-coupling of the trialkylstannyl pyrazine was reported by Gundisch *et al.*[36] The cross-coupling with azabicycloalkene triflate afforded the coupling product with a slightly reduced yield of 54% (Scheme 2.19).



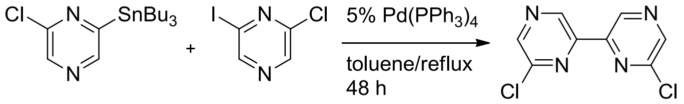
Scheme 2.19. Stille cross-coupling of the trialkylstannyl pyrazine with azabicycloalkene triflate.

Efficient double Stille cross-coupling of distannylated pyrazines with diiododiketopyrazines gave polymers in 65-82% yields (Scheme 2.20). The optimal catalyst system for the polymerization of the pyrazine monomers was $Cl_2Pd(PPh_3)_2$/CuI in a THF/NMP mixture. A slight excess of the stannane, used to achieve the reduction of the Pd(II) to the active Pd(0), apparently lowered the molecular weight of the obtained polymers. The same effect was observed when the PPh_3 ligand was replaced by $AsPh_3$, or when Pd-

(dba)$_2$/PPh$_3$/CuI was used as the catalyst.[37] Stille coupling of stannylated chloropyrazine with chloroiodopyrazine afforded dichlorobipyrazyl in an excellent yield of 95% (Scheme 2.21).[38]



Scheme 2.20. Double Stille cross-coupling of distannylated pyrazines with diiododiketopyrazines.

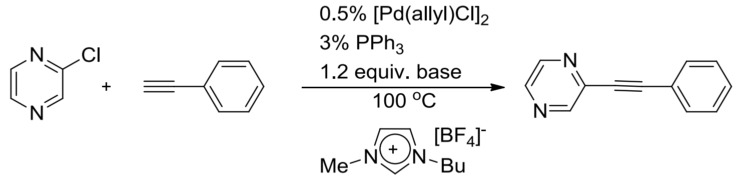


Scheme 2.21. Stille coupling of stannylated chloropyrazine with chloroiodopyrazine.

In conclusion, the Stille cross-coupling is one of the most versatile tools for carbon-carbon bond formation within pyrazines as a result of the air- and moisture-stability of organotin reagents and the excellent functional group compatibility of the reaction. The reaction can be used for the coupling of stannylated pyrazines with a vast variety of partners, i.e. aryl-, acyl-, and vinyl halides as well as triflates.

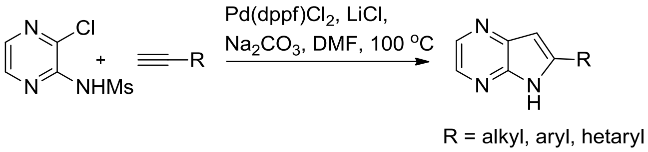
2.4. Sonogashira Coupling

The palladium-catalyzed coupling of terminal alkynes with aryl/vinyl halides/pseudohalides, typically in the presence of a copper cocatalyst, is commonly known as the Sonogashira reaction.[39] These coupling reactions are nowadays well-explored in pyrazine chemistry. Chloropyrazine proved to be an excellent substrate for this cross-coupling reaction. Under $[Pd(allyl)Cl]_2/PPh_3$ catalysis, using a slight excess of phenylacetylene, chloropyrazine was quantitatively converted into the corresponding diarylacetylene[40] (Scheme 2.22).



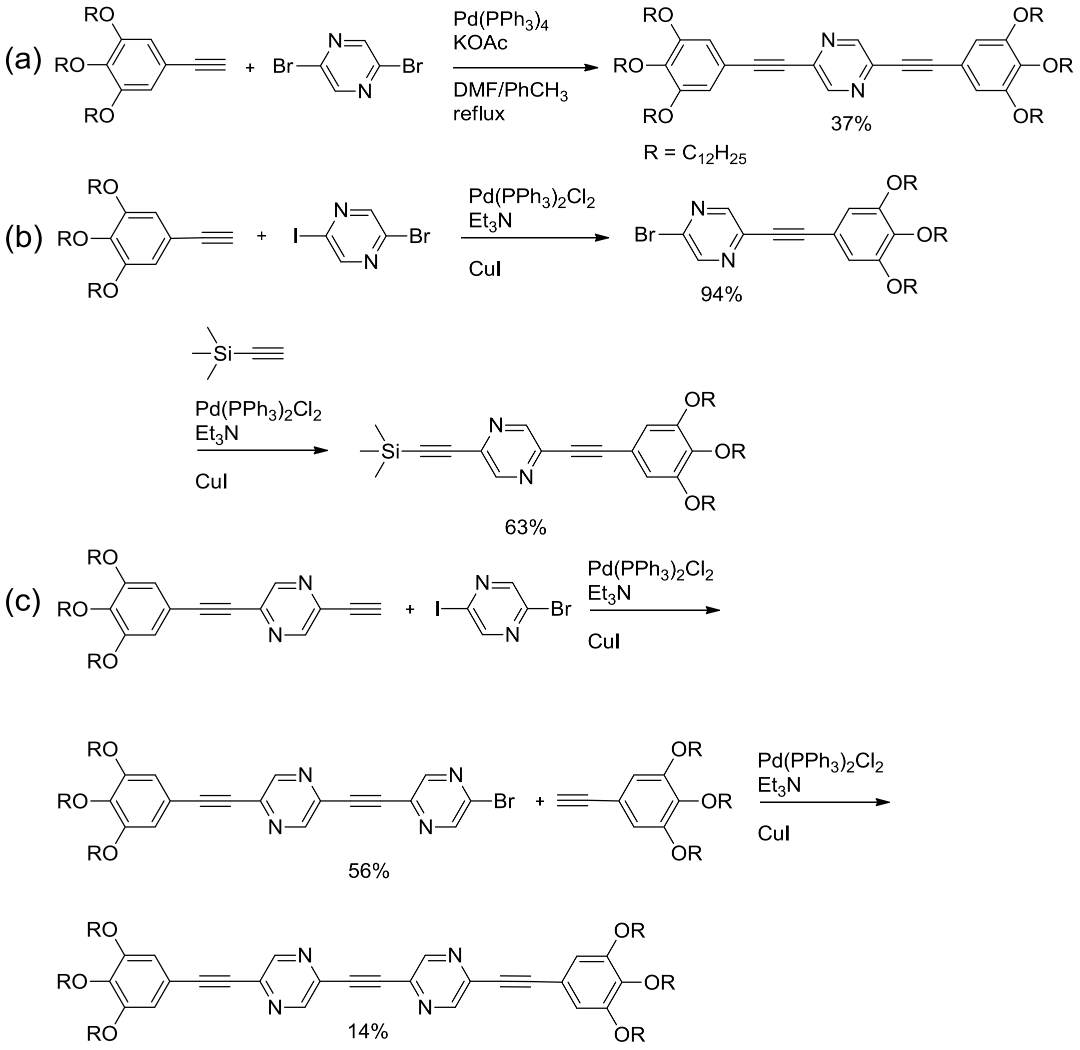
Scheme 2.22. Sonogashira coupling of chloropyrazine with phenylacetylene.

A Sonogashira coupling accompanied by heteroannulation was reported in a synthetic sequence towards 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines. *N*-(3-chloropyrazin-2-yl)-methanesulfonamide was subjected to the classical Sonogashira conditions with various acetylenes followed by base-induced cyclization resulting into the formation of the 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines in 41-67% yields (Scheme 2.23). It is noteworthy that the reaction also tolerates amino groups as well as ketones, ortho-substituents, and carboxylic acids.[41] A similar example using microwave irradiation instead of conventional heating was reported to give higher yields with shorter reaction times.[42]



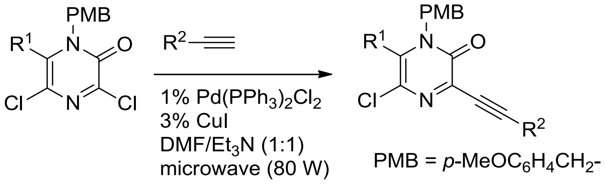
Scheme 2.23. Formation of the 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines under the Sonogashira conditions.

In the course of a route to π-conjugated pyrazine oligomers, which are of great importance for manufacturing various electronic devices, several halogenated pyrazines were reacted with terminal acetylenes under Sonogashira conditions (Scheme 2.24). Since the reaction of 2,5-dibromopyrazine with a stoichiometric amount of 3,4,5-tridodecyloxyphenylacetylene presumably afforded disubstituted pyrazine (Scheme 2.24 (a)), two iterative couplings with different terminal acetylenes were performed on 5-bromo-2-iodopyrazine (Scheme 2.24 (b)). To further elongate the π-conjugated system and finalize the synthetic route towards an oligomer, the afore mentioned pyrazine derivative was deprotected and subsequently coupled to 5-bromo-2-iodopyrazine, followed by a reaction with 3,4,5-tridodecyloxyphenylacetylene to end-cap the oligomer (Scheme 2.24 (c)).[43]



Scheme 2.24. Multiple Sonogashira couplings with halogenated pyrazines.

Ermolat’ev *et al.*[44] have shown the suitability of *N*-4-methoxybenzyl (PMB) protected chlorinated pyrazinones for the Sonogashira reaction (Scheme 2.25). Selective coupling at the reactive 3-position with various acetylenes afforded the corresponding 3-ethynyl-5-chloropyrazin-2-ones in 85-93% yields.

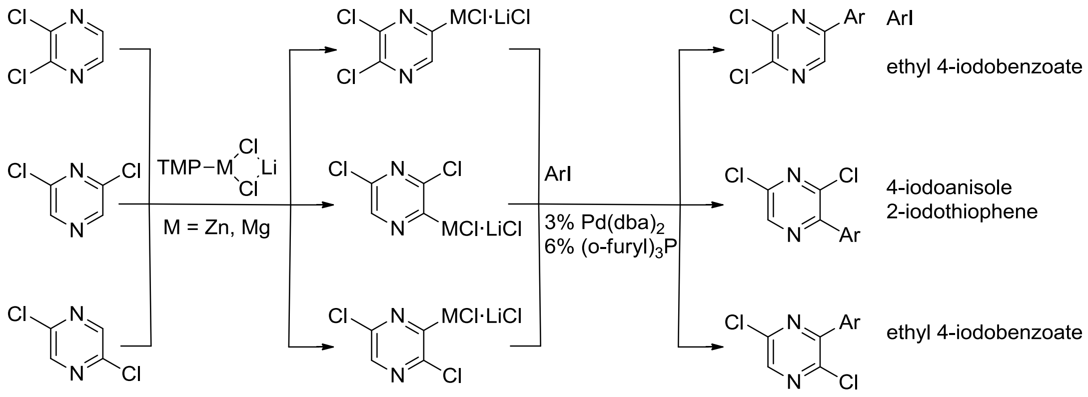


Scheme 2.25. Sonogashira coupling of chlorinated pyrazinones.

In general, the Sonogashira coupling represents an excellent method for the synthesis of elongated pyrazine containing π-conjugated systems. Accompanied by heteroannulation this reaction allows the versatile synthesis of pyrazine-based fused heterocyclics.

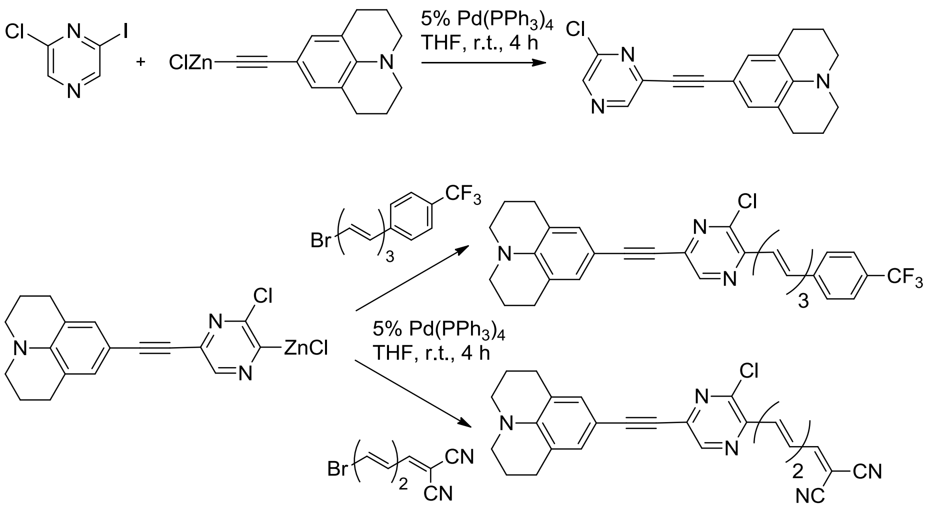
2.5. Negishi Coupling

Nickel- or palladium-catalyzed coupling of organozinc reagents with various halides/pseudohalides, commonly referred to as the Negishi reaction, represents a versatile C-C bond formation tool with a broad scope.[45] Several Negishi cross-coupling examples were reported in pyrazine chemistry. Various dichloropyrazines readily underwent direct metalations using TMPMgCl·LiCl or TMPZnCl·LiCl, where TMP is deprotonated tetramethylpiperidine and DBA is dibenzalacetone. Subsequent cross-coupling with iodobenzenes and iodothiophene gave the coupled products in good yields[46] (Scheme 2.26).

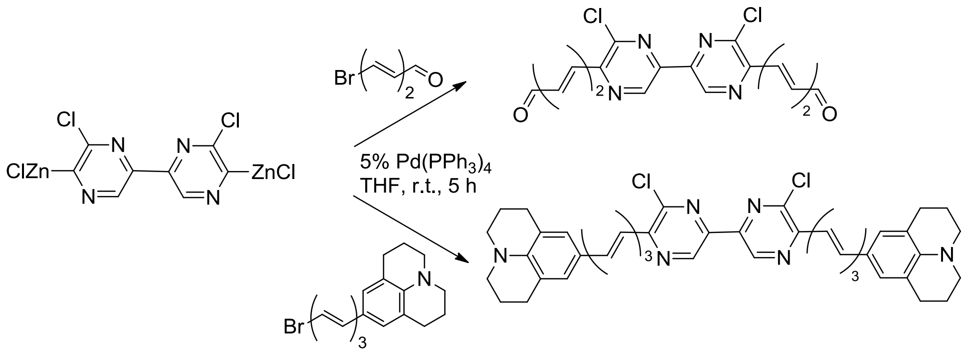


Scheme 2.26. Negishi coupling of various dichloropyrazines.

Hebbar *et al.*[38] reported the Negishi reaction of 2-chloro-6-iodopyrazine with an acetylenic zinc reagent to give the coupling product in 71% yield (Scheme 2.27). The resulting compound was converted into the organozinc intermediate, whereupon reaction with bromopolyenes gave the coupled products in good yields.[47] The same approach was successfully used for the double Negishi coupling of dichlorobipyrazyl with 1-bromo-6-substituted-hexatrienes to give the corresponding coupled products in 64 and 57% yield, respectively (Scheme 2.28).

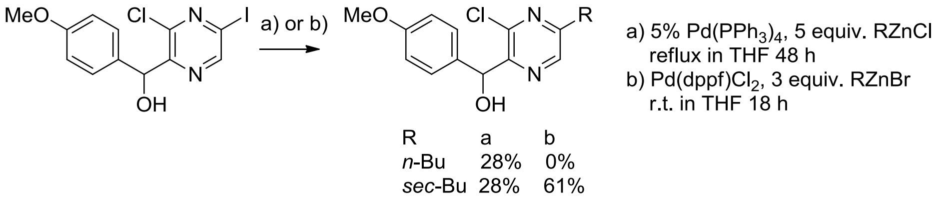


Scheme 2.27. Negishi reactions of 2-chloro-6-iodopyrazine with an acetylenic zinc reagent and zinkated chloropyrazine with bromoalkenes.



Scheme 2.28. Negishi reaction of zinkated dichlorobipyrazyl with 1-bromo-6-substituted-hexatrienes.

Negishi coupling with *sec*-butylzinc halides was investigated by Fruit *et al.*[48] (Scheme 2.29). Using $Pd(PPh_3)_4$ as the catalyst, partial isomerization occurred, resulting into a 1:1 mixture of *n*-Bu and *sec*-Bu pyrazines. However, this was overcome by replacing the catalyst with the more selective $Pd(dppf)Cl_2$, also increasing the overall yield up to 61%.

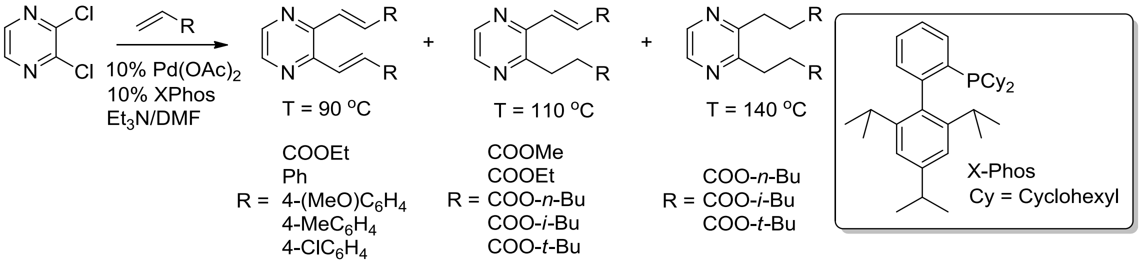


Scheme 2.29. Negishi coupling of halopyrazines with alkylzink halides.

Similar to Suzuki and Stille couplings, the Negishi reaction represents a powerful tool for C-C bond formation. However, the examples of this reaction in the pyrazine series are mainly limited to zinkated pyrazines, which act as a nucleophilic coupling partner.

2.6. Heck Coupling

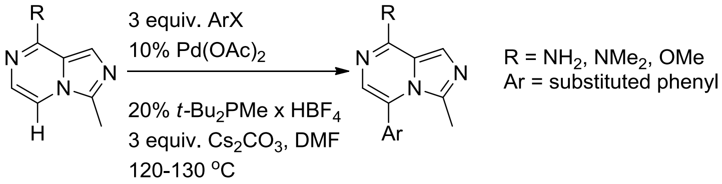
The palladium-catalyzed C-C coupling between aryl or vinyl halides and activated alkenes in the presence of a base is referred to as the Heck reaction.[49] Malik *et al.*[50] explored the Heck cross-coupling of 2,3-dichloropyrazine with various acrylates and styrenes. An interesting dependence of the product formation and distribution on the reaction temperature was found. Reaction of 2,3-dichloropyrazine with 2.5 equivalents of ethyl acrylate, in the presence of $Pd(OAc)_2$ and X-Phos, afforded the corresponding 2,3-dialkenylpyrazine in 83% yield. Partial hydrogenation was observed when the reaction was carried out at higher temperatures (Scheme 2.30).



Scheme 2.30. Heck cross-coupling of 2,3-dichloropyrazine with acrylates and styrenes.

The partial or complete hydrogenation of the double bond of the coupled product could be explained by the presence of the strongly π-deficient pyrazine ring on one side of the double bond and the strongly electron-withdrawing ester group on the other.

A related Heck-type reaction, where pyrazine moiety acts as an "olefin-like" coupling partner, was reported by the group of Snieckus. Thus 8-substituted imidazo[1,5-*a*]pyrazines were successfully arylated with a wide array of aryl halides in 45-92% yields (Scheme 2.31).[51]

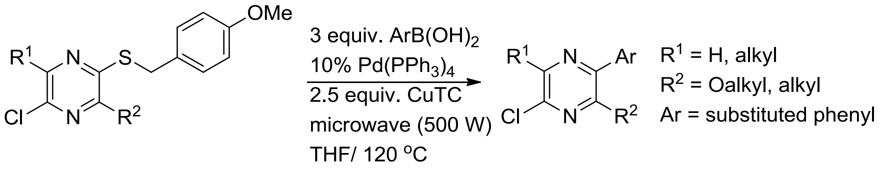


Scheme 2.31. Pyrazine moiety as an "olefin-like" coupling partner in the Heck reaction.

The Heck cross-coupling of pyrazines is scarcely represented in the literature, probably due to the high electrophilicity of the pyrazine ring, which makes Michael addition to the formed alkenylpyrazines very facile.

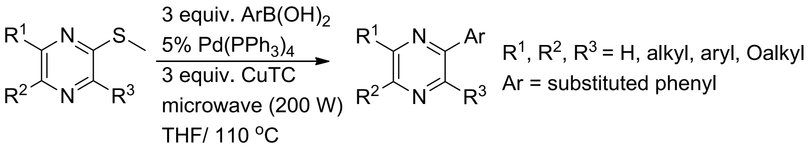
2.7. Liebeskind-Srogl Coupling

The Liebeskind-Srogl coupling is a recently discovered organic reaction that forms a coupled product from a thioester/thioether and a boronic acid using a metal catalyst.[52] Modha *et al.*[53] reported the successful application of Liebeskind-Srogl conditions towards the coupling of *p*-methoxybenzylthiopyrazines with arylboronic acids. Initially, coupling of *p*-methoxybenzylthio-bearing pyrazine with arylboronic acid in the presence of copper(I)-thiophene-2-carboxylate (CuTC) and $Pd(PPh_3)_4$ in THF under conventional heating as well as under microwave irradiation gave poor to average yields, possibly due to decomposition of the reagents during the long reaction time at high temperature. However, the yields of the coupled products were considerably improved up to 69-93% by simple addition of the reagents in two portions (Scheme 2.32).



Scheme 2.32. Coupling of *p*-methoxybenzylthiopyrazines with arylboronic acids.

Earlier the same group reported the Liebeskind-Srogl coupling of methylthiopyrazines with arylboronic acids, which generally gave higher yields, but had a narrower scope being mainly limited to arylboronic reagents with donor groups. Substituted methylthiopyrazines were reacted with various boronic acids, in the presence of $Pd(PPh_3)_4$ and copper thiophene-2-carboxylate, giving the coupled products in yields ranging from 78 to 94% (Scheme 2.33).[27]



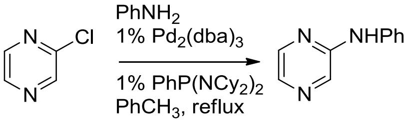
Scheme 2.33. Coupling of methylthiopyrazines with arylboronic acids.

These examples show that the novel Liebeskind-Srogl coupling reaction can be easily accomplished on thioether derivatives of substituted pyrazines, thus representing another method for the preparation of arylpyrazines.

2.8. C-N coupling

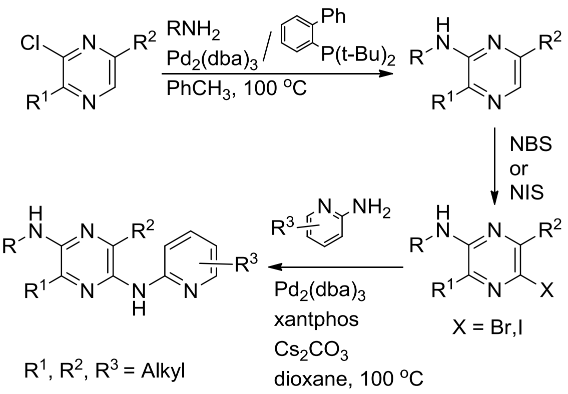
Examples of palladium-catalyzed C-N coupling reactions performed on halogenated pyrazines are rare, since amination of chloropyrazines is readily achievable via aromatic nucleophilic substitution of chlorine by an appropriate primary or secondary amine in the presence of base. Nevertheless, a few interesting reactions of so-called deactivated pyrazines will be described requiring metal catalysis.

An example of the amination of chloropyrazine was recently reported by Kim *et al.*[54] Using $Pd_2(dba)_3$ together with a bulky electron-rich phosphine ligand the corresponding phenylaminopyrazine was obtained in 59% yield (Scheme 2.34).



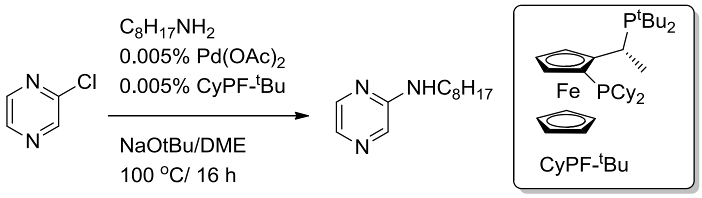
Scheme 2.34. Amination of chloropyrazine.

C-N cross-coupling has also been achieved with deactivated dialkylchloropyrazines (Scheme 2.35). The subsequent halogenation of the aminopyrazines, obtained in the first C-N coupling step, allowed a second amination, affording tetrasubstituted diaminopyrazines in 20-70% yields, demonstrating the generality, wide substrate scope, and tolerance to a variety of functional groups of the method.[55]



Scheme 2.35. C-N cross-coupling with deactivated dialkylchloropyrazines.

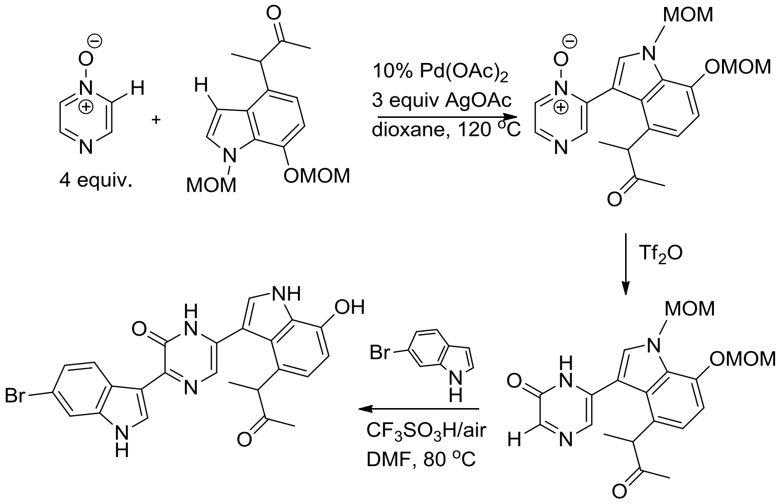
Recently, Hartwig *c.s.*[56] reported the high yield, selective palladium-catalyzed amination of aryl and hetaryl halides with a remarkably low catalyst loading. Chloropyrazine was coupled with *n*-octylamine affording the corresponding aminopyrazine in 82% yield in the presence of 0.005% of a catalyst (Scheme 2.36). In contrast, iodopyrazine required a higher catalyst loading and a longer reaction time. The same tendency was observed for a variety of iodo- and chloroarenes. Parallel studies revealed that the presence of the formed iodide ion considerably slows down the reaction.



Scheme 2.36. C-N cross-coupling with chloropyrazine.

2.9. C-H activation

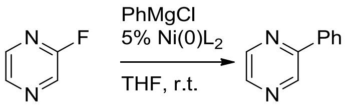
A relatively new method in metal-catalyzed reactions is the direct arylation by C–H activation. In an effort of a total synthesis of the natural alkaloid dragmacidin D a method for the direct arylation of the pyrazine ring was developed. A bis-MOM-protected indole was primed for the Pd-catalyzed C-H/C-H coupling reaction with pyrazine *N*-oxide. Although the yield of this reaction was not superb, a 50% yield was achieved upon recycling. Despite its moderate yield, the reaction furnished the coupling product regioselectively. The second oxidative C-H/C-H coupling reaction of pyrazinone and 6-bromoindole under the influence of CF_3SO_3H afforded the corresponding coupling product in 57% yield with simultaneous removal of the two MOM groups (Scheme 2.37). Notably, the regioselectivity in these subsequent couplings was achieved by elegant employing the “tautomeric switch” between pyrazinone and pyrazine *N*-oxide. Whilst pyrazine *N*-oxide has the most acidic, and hence more susceptible for coupling, carbon atom adjacent to the N-O moiety, the pyrazinone form of the resulting compound has the most acidic carbon atom next to a carbonyl group.[57]



Scheme 2.37. Synthesis of dragmacidin D.

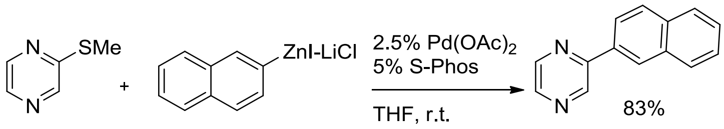
2.10. Miscellaneous couplings

The palladium-catalyzed coupling of aryl halides or triflates with Grignard reagents is generally refered as the Kumada reaction.[58,59] Despite the significance, this reaction has a limited applicability due to the intolerance of Grignards towards many functional groups. An interesting example of a Kumada coupling was reported by Mongin *et al.*[60] reacting fluoropyrazine with phenylmagnesium chloride at very mild conditions under nickel catalysis, giving the coupled product in 81% yield (Scheme 2.38).



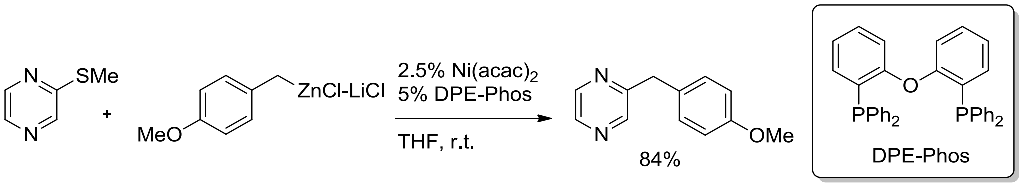
Scheme 2.38. Kumada coupling of fluoropyrazine with phenylmagnesium chloride.

The combination of $Pd(OAc)_2$ and the S-Phos ligand, originally introduced by Buchwald,[61] was successfully applied by the group of Knochel[62] for the coupling of functionalized aryl-, benzylic- and alkylzinc reagents with various thiomethylated *N*-heterocycles and methylthiopyrazine in particular (Scheme 2.39).



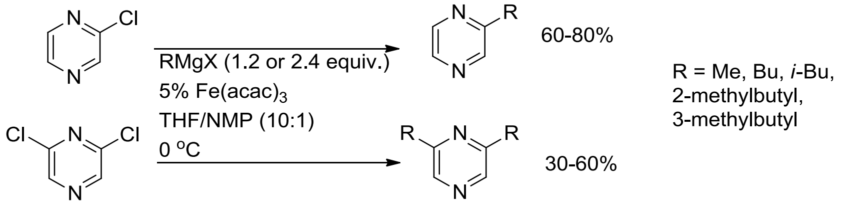
Scheme 2.39. Palladium-catalyzed coupling of organozinc reagents with methylthiopyrazine.

Further development of this reaction showed that methylthiopyrazine can also be cross-coupled with functionalized benzylic zinc reagents under Ni catalysis by using the inexpensive and robust system of $Ni(acac)_2$ and DPE-Phos (Scheme 2.40).



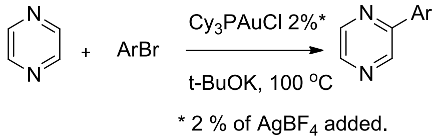
Scheme 2.40. Nickel-catalyzed coupling of functionalized benzylic reagents with methylthiopyrazine.

Chloropyrazines can be monoalkylated with Grignard reagents under $Fe(acac)_3$ catalysis.[63] Dickschat *et al.*[64] reported the synthesis of mono- and dialkylpyrazines reacting chloropyrazines with alkylmagnesium bromides in the presence of $Fe(acac)_3$ (Scheme 2.41).



Scheme 2.41. Fe(III)-catalyzed cross-coupling of chloropyrazines with Grignard reagents.

A variety of arylpyrazines were prepared by cross-coupling of pyrazine with aryl bromides in the presence of Cy_3PAuCl (Scheme 2.42). The corresponding 2-arylated pyrazines were obtained in moderate to good yields, typically between 40 and 90%, however, 2-bromopyridine and 1-bromo-2-(trifluoromethyl)benzene gave only trace amounts of the coupled products. The low yields can be explained by the fact that electron-poor aryl bromides easily undergo hydrodebromination. Therefore, the reaction of pyrazine with electron-poor aryl bromides was performed in the presence of a catalytic amount of $AgBF_4$ to accelerate the desired reaction and to overcome side processes. That gave the corresponding coupled products in better yields of 24 and 31%, respectively.[65]



Scheme 2.42. Gold(I)-catalyzed arylation of pyrazine.

2.11. Conclusions and Outlook

In the past two decades a remarkable progress has been made towards the development of methods for pyrazine functionalization. Starting from the very first attempts of the Suzuki coupling of chloropyrazine, the list of transition metal-catalyzed reactions, applicable for pyrazines, has included practically all coupling reactions known for regular aromatics. Moreover, the unique electronic and structural properties of pyrazine has made possible its direct functionalization via C-H activation. Thus, choosing an appropriate transition metal and ligand proved to be versatile for solving the long-standing challenge of bringing pyrazines into the family of useful substrates for transition metal-catalyzed cross-couplings. However, despite the impressive progress, a number of challenges still remain. Most of the studies described above utilize a relatively high catalyst loading. For industrial applications in particular, it will be highly desirable to develop more effective catalytic systems that require a lower use of precious metals, operate at milder conditions, and have a wider scope.

2.12. References

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Chapter 3

Study on the Pd/C-Catalyzed (Retro-)Michael Addition Reaction of Activated Methylene Compounds to Electron-Poor Styrenes[*]

Palladium on carbon efficiently catalyzes the (retro-)Michael addition of activated methylene compounds, such as malononitrile, to mono- and doubly activated styrenes to give the addition adducts. The scope and limitations are described. The Knoevenagel condensation reaction of arylaldehydes and malononitrile or ethyl cyanoacetate is also catalyzed by 10 % Pd/C. In these cases the Michael adducts can even be prepared in a three-component reaction. A mechanism, with the oxidative addition of C-H acids to Pd^0 as the first step, is proposed.

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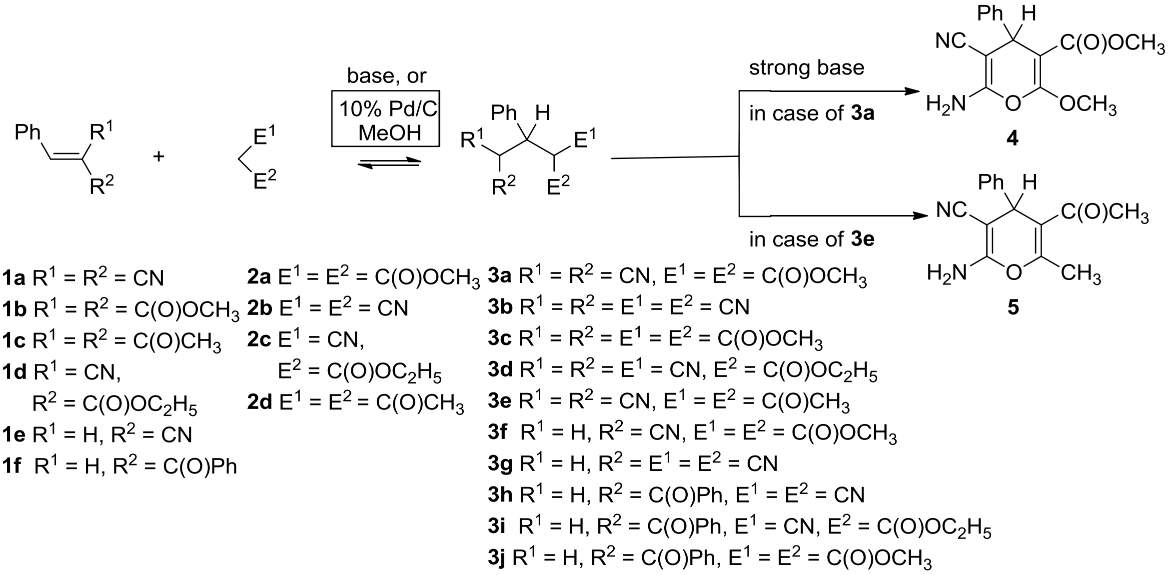
3.1. Introduction

Highly substituted propanes containing two pairs of geminal electron-withdrawing groups at the 1,1- and 3,3-positions are versatile precursors for a large number of heterocyclic compounds, as e.g. 4*H*-pyranes and 4*H*-pyridines,[1,2] that are essential parts of biologically important natural products.[3,4] This type of propanes are usually prepared via a Knoevenagel condensation reaction resulting in symmetrical compounds with identical electron-withdrawing groups. However, non-symmetrical 1,1,3,3-tetrasubstituted propanes can be obtained by a Michael addition of an activated methylene compound to a Knoevenagel adduct. Over the years different studies have appeared to perform the Michael addition reaction under mild reaction conditions, e.g. making use of transition metals. It has been reported that rhodium, iridium and ruthenium polyhydride complexes are excellent catalysts for C-H bond activation of various activated methylene compounds.[5,6,7] Also palladium(0) tetrakis(triphenylphosphine) was reported to give satisfactory results performing the Michael addition of cyanoacetates to alkynes bearing electron-withdrawing substituents.[7] However, soluble polyhydride and low-valent transition metal complexes usually require special reaction conditions, while in addition the catalyst has to be removed from the crude reaction mixture. In this chapter a simple palladium-catalyzed Michael addition of activated methylene compounds to mono- and doubly activated styrenes using catalytic amounts of non-toxic and easily removable palladium on activated carbon (Pd/C) is presented.

3.2. Results and Discussion

First we studied the formation of 1,1,3,3-tetrasubstituted propanes using a base-catalyzed Michael addition reaction (Scheme 3.1). Reaction of benzylidenemalononitrile (**1a**) with one equivalent of dimethyl malonate (**2a**) in the presence of a catalytic amount of a mild base such as triethylamine or pyridine in diethyl ether gave an equilibrium mixture containing 76% of the Michael adduct **3a**. Slow evaporation of the solvent induced crystallization of the product and shifted the equilibrium up to quantitative conversion. When the reaction was carried out with two equivalents of dimethyl malonate (**2a**) the Michael adduct **3a** was obtained in quantitative yield. When a stronger base is being used such as a hydroxide or alkoxide in-situ intramolecular cyclization of the Michael adduct **3a** to the 4*H*-pyran **4** takes place as recently described.[1] In our hands reaction of **1a** and **2a** in the presence of DBU as a base in diethyl ether afforded a 1:1 mixture of Michael adduct **3a** and 4*H*-pyran **4** according to the ^{1}H NMR spectrum. At the same time, base catalysis of a 1:1 mixture of benzylidene dimethyl malonate (**1b)** and **2a** or malononitrile (**2b**) yielded no Michael adduct (**3c** or **3a**) at all.

During our studies on the further functionalisation of tetrasubstituted propanes, we attempted the selective reduction of the cyano groups in the Michael adduct **3a**. Since the ester moieties had to remain unaffected 10% Pd/C-catalyzed hydrogenation was chosen.[8] Upon hydrogenation of **3a** with 10 bar of H_2 the expected amino derivative could not be detected in the ^{1}H NMR spectrum of the crude reaction mixture. Instead the ^{1}H NMR spectrum showed signals at δ 7.80 and 3.40, characteristic for benzylidenemalononitrile (**1a**) and dimethyl malonate (**2a**), respectively. Treatment of a solution of the Michael adduct **3a** in methanol with 10% Pd/C in the absence of H_2 for 15 h resulted, according to the ^{1}H NMR spectrum, in a clean mixture of **1a**:**2a**:**3a** of about 1:1:3. Apparently, a retro-Michael reaction had occurred giving rise to the mixture. Conversely, stirring of a 1:1 mixture of **1a** and **2a** in methanol in the presence of 10% Pd/C gave rise to the same mixture, proving that equilibrium had been reached.



1a $R^1 = R^2 = CN$
1b $R^1 = R^2 = C(O)OCH_3$
1c $R^1 = R^2 = C(O)CH_3$
1d $R^1 = CN$, $R^2 = C(O)OC_2H_5$
1e $R^1 = H$, $R^2 = CN$
1f $R^1 = H$, $R^2 = C(O)Ph$

2a $E^1 = E^2 = C(O)OCH_3$
2b $E^1 = E^2 = CN$
2c $E^1 = CN$, $E^2 = C(O)OC_2H_5$
2d $E^1 = E^2 = C(O)CH_3$

3a $R^1 = R^2 = CN$, $E^1 = E^2 = C(O)OCH_3$
3b $R^1 = R^2 = E^1 = E^2 = CN$
3c $R^1 = R^2 = E^1 = E^2 = C(O)OCH_3$
3d $R^1 = R^2 = E^1 = CN$, $E^2 = C(O)OC_2H_5$
3e $R^1 = R^2 = CN$, $E^1 = E^2 = C(O)CH_3$
3f $R^1 = H$, $R^2 = CN$, $E^1 = E^2 = C(O)OCH_3$
3g $R^1 = H$, $R^2 = E^1 = E^2 = CN$
3h $R^1 = H$, $R^2 = C(O)Ph$, $E^1 = E^2 = CN$
3i $R^1 = H$, $R^2 = C(O)Ph$, $E^1 = CN$, $E^2 = C(O)OC_2H_5$
3j $R^1 = H$, $R^2 = C(O)Ph$, $E^1 = E^2 = C(O)OCH_3$

Scheme 3.1. Palladium-catalyzed (retro-) Michael addition of activated methylene compounds to mono- and doubly activated styrenes.

To study the scope of these Pd/C-catalyzed reactions, the behavior of the tetrafunctionalized propanes **3b,d** towards this catalyst was investigated (Scheme 3.1). In the case of the propanes **3b** and **3d**, according to the ^{1}H NMR spectra, 90% conversion was obtained resulting in an equilibrium mixture of 9:9:1 of **1a** : **2b** : **3b** and **1a** : **2c** : **3d**, respectively. The reverse reaction under identical conditions gave the same ratio.

In case of the retro-reaction of the Michael adducts **3a** and **3d** two different alkenes can be formed. In all cases the retro-Michael reaction occurred with the exclusive formation of the olefin bearing the strongest electron-withdrawing functionalities, hence having the highest thermodynamic stability.

Upon treatment of 1:1 mixtures of benzylidenemalononitrile (**1a**) and acetylacetone (**2d**) and of benzylidene acetylacetone (**1c**) and malononitrile (**2b**) with 10% Pd/C in methanol overnight the expected product **3e** could not be detected. However, a fast tandem intramolecular cyclization of in-situ formed Michael adduct **3e** took place to afford 4*H*-pyran

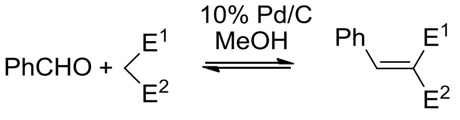
5 in 98% yield (Scheme 3.1). In addition to the correct mass, the formation of 4*H*-pyran **5** could be deduced from characteristic ^{1}H NMR signals at δ 4.40 and 4.60. The corresponding base-catalyzed reaction gives rise to poor yields and requires thorough separation of the crude reaction mixtures containing products due to further based-catalyzed reaction of 4*H*-pyran **5** with **1a,c** to give pyrano[2,3-*b*]pyridines.[9]

Both the character of the olefin and the activated methylene compound considerably influence the rate of the reaction. The Pd/C-catalyzed reaction of benzylidenemalononitrile (**1a**) with dimethyl malonate (**2a**) takes about 20 h before equilibrium is reached. In case of the more acidic malononitrile (**2b**) the equilibrium is already reached within 3 h. Starting from benzylidene dimethyl malonate (**1b**), the reaction is much slower. Treatment with dimethyl malonate (**2a**) did not give any reaction, even after prolonged heating. The Pd/C-catalyzed reaction with malononitrile (**2b**) proceeds very slowly; after 3 days there is about 30% of the Michael adduct **3a** formed which grows to 60% after 6 days and upon about 7 days equilibrium is reached.

To further explore the scope of the Pd/C-catalyzed Michael addition reaction, a series of experiments was performed with mono-β-activated styrenes (Scheme 3.1). Treatment of 1:1 mixtures of cinnamonitrile (**1e**) with dimethyl malonate (**2a**) and malononitrile (**2b**) with 10% Pd/C in refluxing methanol for two days did not give rise to any reaction; the formation of the Michael adducts **3f,g** could not be detected. The addition of one equiv. of DBU was also unsuccessful. However, the reaction of *trans*-chalcone (**1f**) with **2b,c** in the presence of 10% Pd/C in methanol at room temperature gave the corresponding Michael adducts **3h** and **3i** in quantitative yield. Starting from dimethyl malonate (**2a**) the Michael adduct **3j** was only obtained in 35% yield after stirring for 2 days. Refluxing the reaction mixture gave rise to a complicated mixture of products. The described SmI_3-catalyzed reaction for the preparation of **3h,i** gives lower yields and requires chromatographic purification,[10] underlining the suitability of the Pd/C approach.

Aliphatic Michael acceptors such as isopropylidene diethyl malonate, acrylonitrile, isopropylidenemalononitrile, and neopentylidenemalononitrile failed to react with e.g. malononitrile (**2b)** under the 10% Pd/C conditions. Even after refluxing in methanol overnight, no trace of the Michael adducts could be detected in the ^{1}H NMR spectra of the crude reaction products; only starting materials were present. Apparently, the presence of the π-accepting phenyl group is a prerequisite for the reaction.

Assuming that Pd/C catalyzes the Michael addition reaction via C-H bond activation of an activated methylene compound, the influence on the Knoevenagel condensation reaction was investigated. Stirring a solution of benzaldehyde (**6**) and dimethyl malonate (**2a**) or acetylacetone (**2d**) in the presence and absence of 10% Pd/C in methanol overnight did not give rise to any conversion. However, reaction of benzaldehyde (**6**) with ethyl cyanoacetate (**2c**) in the absence and presence of 10% Pd/C in methanol for 19 h resulted in the formation of the condensation product **1d** in 7 and 80%, respectively. The corresponding reactions with malononitrile (**2b**) for 1 h gave benzylidenemalononitrile (**1a**) in 21 and 90%, respectively (Scheme 3.2). These results show that the more acidic the methylene hydrogens are the faster the Knoevenagel reaction proceeds catalyzed by Pd/C.



6 **2b,c** **1a** $E^1 = E^2 = CN$
1d $E^1 = CN$, $E^2 = C(O)OC_2H_5$

Scheme 3.2. Palladium-catalyzed Knoevenagel reaction.

This inspired the investigation of a three-component reaction in which the Knoevenagel condensation product is formed in-situ. Reaction of a mixture of benzaldehyde (**6**) with malononitrile (**2b**) and two equivalents of dimethyl malonate (**2a**) in the presence of 10% Pd/C gave as expected the Michael adduct **3a** in quantitative yield (Scheme 3.3).

$$\mathbf{6} + \mathbf{2b} + 2\ \mathbf{2a} \xrightleftharpoons[\text{MeOH}]{\text{10\% Pd/C}} \mathbf{3a}$$

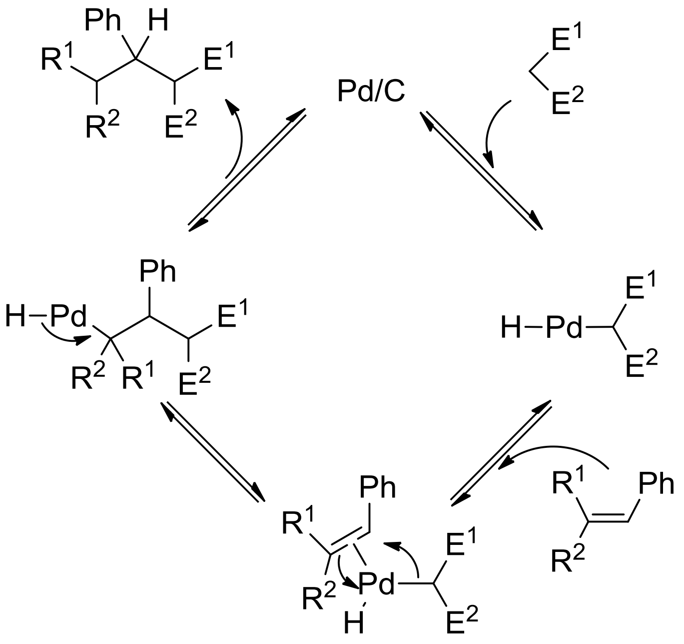
$$\mathbf{6} + \mathbf{2b} + \mathbf{2d} \xrightarrow[\text{MeOH}]{\text{10\% Pd/C}} \mathbf{5}$$

$$\mathbf{6} + \mathbf{2b} + \mathbf{2c} \xrightleftharpoons[\text{MeOH}]{\text{10\% Pd/C}} \mathbf{1a} + \mathbf{1d} + \text{traces of } \mathbf{3b} \text{ and } \mathbf{3d}$$

Scheme 3.3. Palladium-catalyzed three-component reactions.

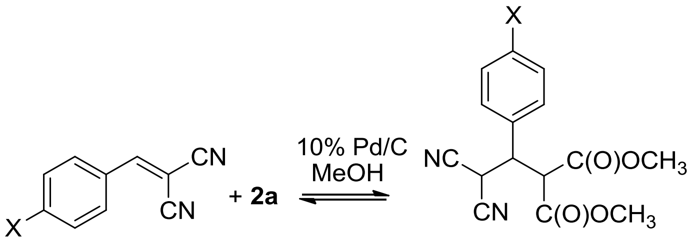
The same reaction in which **2a** was replaced by one equivalent of acetylacetone (**2d**) afforded the 4*H*-pyran **5** in quantitative yield in line with the results described above. The corresponding reaction of a 1:1:1 mixture of benzaldehyde, **2b**, and ethyl cyanoacetate (**2c**) gave a 1:1 mixture of the Knoevenagel adducts **1a,d** and traces of the different Michael adducts. The latter is explainable by the fact that the Michael adducts are in equilibrium with the Knoevenagel adducts in a 1:9 ratio (*vide supra*).

A possible mechanistic rationale that explains this unprecedented catalytic activity of palladium on carbon in a Michael addition reaction is shown in Scheme 3.4. Oxidative addition of an activated methylene compound to Pd(0) will furnish a Pd(II) species. Further coordination of an activated alkene followed by a migratory insertion of the deprotonated Michael-donor into a double bond and subsequent reductive elimination will afford the Michael adduct and recover the active catalyst. The same type of oxidative addition of C-H acids to Pd(0) was also proposed as the key step in catalytic additions to allenes.[11,12]



Scheme 3.4. Proposed catalytic cycle.

To investigate the influence of substituents on the aromatic ring of the Michael acceptor on the formation of the π-complex with palladium (Scheme 3.4), claimed as the prerequisite for this reaction, a series of experiments with 2-(4-nitrobenzylidene)malononitrile (**1g**) and 2-(4-methoxybenzylidene)malononitrile (**1h**), as extreme examples of substrates bearing electron-withdrawing and -donating groups, respectively, was performed (Scheme 3.5).



1g X = NO_2
1h X = OCH_3

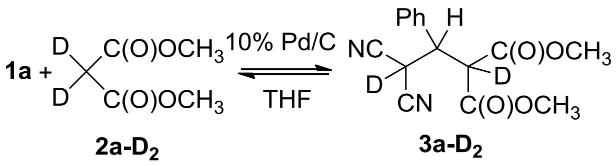
3k X = NO_2
3l X = OCH_3

Scheme 3.5. Palladium-catalyzed Michael reaction with substituted benzylidenemalononitriles.

Upon reaction of **1g** with an equimolar amount of **2a** in the presence of Pd/C (10%) the desired Michael adduct **3k** was formed in 90% yield after stirring for 15 h. However, a different behavior was observed in case of **1h**. Stirring a 1:1 mixture of **1h** and **2a** in the presence of Pd/C (10%), the equilibrium was only set after 4 days; in the reaction mixture 43% of the Michael adduct **3l** was detected. Apparently, the reaction rate was considerably decreased by the presence of the strongly electron-donating methoxy group.

The obtained experimental data clearly show that the presence of a strongly electron-withdrawing group in the aromatic ring of the Michael acceptor facilitates its coordination to the palladium center. This decreases the HOMO-LUMO gap of Michael donor and Michael acceptor and hence significantly increases the reaction rate.

To further support the proposed mechanism the palladium-catalyzed reaction of methylene-deuterated dimethyl malonate (**2a-D$_2$**) with benzylidenemalononitrile (**1a**) in THF as an aprotic solvent was carried out and the deuterated Michael adduct **3a-D$_2$** was obtained (Scheme 3.6). In the ^{1}H NMR spectrum the expected positions of the deuterium atoms in adduct **3a-D$_2$** were confirmed by the absence of two doublets at δ 4.90 and δ 4.14 (in **3a**) and the presence of singlet at δ 3.95 for the benzylic hydrogen atom.



Scheme 3.6. Deuterium-labeled Michael addition reaction.

3.3. Conclusions

In conclusion, an efficient and very simple palladium-on-carbon-catalyzed (retro-)Michael addition reaction of activated methylene compounds to doubly and mono-activated styrenes, that in some cases is superior to base-catalysis, was demonstrated. The catalyst is very robust, not air-sensitive, and can easily be removed.

3.4. Experimental Section

General remarks: The solvents and all reagents were obtained from commercial sources and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity INOVA (300 MHz) spectrometer. ^{1}H NMR chemical shift values (300 MHz) are reported as δ using the residual solvent signal as an internal standard ($CDCl_3$, δ 7.257). ^{13}C NMR chemical shift values (75 MHz) are reported as δ using the residual solvent signal as an internal standard ($CDCl_3$, δ 77.0). Electrospray Ionization (positive mode) mass spectra were recorded on a WATERS LCT mass spectrometer. The styrene derivatives **1b**,[13] **1c**,[14] **1g**,[15] and **1h**[15] and the Michael adducts **3a**,[16] **3c**,[17] **3h**,[10] **3i,**[10] **3j,**[18] **3k**,[19] and **3l**[19] were prepared according to literature procedures.

General Procedure for the Palladium-catalyzed (Retro-)Michael Reactions:

A mixture of a Michael donor (1 mmol), a Michael acceptor (1 mmol), and 10%-Pd/C (0.106 g) in methanol (10 mL) was stirred overnight (unless specified). (In case of the retro-reaction 1 mmol of the Michael adduct was used under the same conditions.) Thereafter the catalyst was filtered off and the solvent removed in vacuo. The residue was analyzed by ^{1}H

NMR spectroscopy. The spectra correspond with those reported for the different compounds in literature. For the 4*H*-pyranes **4** and **5** see refs 1 and 9, respectively.

General Procedure for the Palladium-catalyzed Three-component Reactions:

A mixture of an aromatic aldehyde (1 mmol), two corresponding activated methylene compounds (1 mmol of each), and 10%-Pd/C (0.106 g) in methanol (10 mL) was stirred overnight. The catalyst was filtered off from the resulting mixture and the solvent removed in vacuo. The residue was analyzed by ^{1}H NMR spectroscopy. The spectra correspond with those reported for the different compounds in literature.

1,1-Dicyano-1,3-dideutero-3,3-dimethoxycarbonyl-2-phenylpropane (3a-D_2):

A mixture of methylene-deuterated dimethyl malonate **2a-D_2**[20] (1.34 g, 1 mmol), benzylidenemalononitrile (**1a**) (1.54 g, 1 mmol), and 10%-Pd/C (0.106 g) in dry THF (10 mL) was stirred for 20 h and then filtered. After removal of the solvent the ^{1}H NMR spectrum of the residue showed the formation of 76% of **3a-D_2**. ^{1}H NMR: δ = 7.40 (m, 5 H, Ph), 3.95 (s, 1 H, *H*CPh), 3.86 (s, 3 H, COOMe), 3.50 (s, 3 H, COOMe); ^{13}C NMR: δ = 168.0, 166.6, 134.9, 133.7, 131.0, 129.9, 129.5, 128.6, 111.6, 111.5, 53.8, 53.4, 53.3, 52.8, 45.0, 44.9, 44.8, 27.9.

3.5. References

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Chapter 4

Palladium–Catalyzed Cross-Coupling of Various Phosphorus Pronucleophiles with Chloropyrazines: Synthesis of Novel Am(III)-selective Extractants[*]

Palladium-catalyzed cross-coupling of (di)chloropyrazines with phosphorus pronucleophiles in the presence of base gave the phosphorylated pyrazines in 81-95% yields. Based on this methodology a series of appropriately functionalized pyrazines was prepared as potential extractants of trivalent cations from highly acidic nuclear waste. A few hydrophilic derivatives exhibited a very good selectivity for Am^{3+} *over* Eu^{3+} *with separation factors up to 40 at pH 1 at 0.01 mol/L ligand concentration.*

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4.1. Introduction

Owing to its unique electronic and structural properties pyrazine is of high demand in such areas as construction of multidimensional metal-organic frameworks and supramolecular coordination complexes,[1,2] transition metal catalyzed oxidation,[3,4] soft metal extracting agents, and sensors.[5] However, the functionalization of pyrazines still remains a challenging task. Synthetic strategies leading to substituted pyrazines generally include a direct metallation followed by a subsequent reaction (quenching) with an electrophile,[6] heteroaromatic nucleophilic substitution,[7,8] and different types of transition metal-catalyzed coupling reactions.

The direct metallation of pyrazines is always complicated by side reactions such as nucleophilic addition or intermolecular deprotonation due to the electrophilic nature of this heterocycle.[6] The aromatic nucleophilic substitution of halogenated pyrazines is a rather simple method, but mostly limited to malonate-type substrates or primary/secondary amines and usually is being applied for the introduction of alkyl and amino groups, respectively.[7]

Transition metal-catalyzed couplings are generally used for carbon-carbon bond formation on pyrazines and include classic examples like Sonogashira,[9] Heck,[10] Suzuki,[11] and Stille[12] reactions. However, only a few examples of carbon-phosphorus bond formation in pyrazines are known. Montchamp et al. reported the $Pd(OAc)_2/PPh_3$/dppp-catalyzed reaction of monochloropyrazine with alkyl hypophosphites[13] and dialkyl phosphites[14]. Applying a completely different methodology, based on the thermally induced rearrangement of 2*H*-azirine-2-phosphonates and –phosphine oxides, pyrazine-2,5-diphosphonates and phosphine oxides were synthesized, respectively.[15]

In this chapter a simple, general, and versatile method is reported for the Pd(dppf)Cl_2-catalyzed coupling of chlorinated pyrazines with dialkyl phosphites, secondary phosphines, and secondary phosphine oxides for the synthesis of the until now unknown 2,6-disubstituted pyrazines containing one or two phosphorus substituents. The lanthanide/actinide extraction properties and the complexation behavior of selected *O,N,O*-pyrazine-based ligands will also be demonstrated.

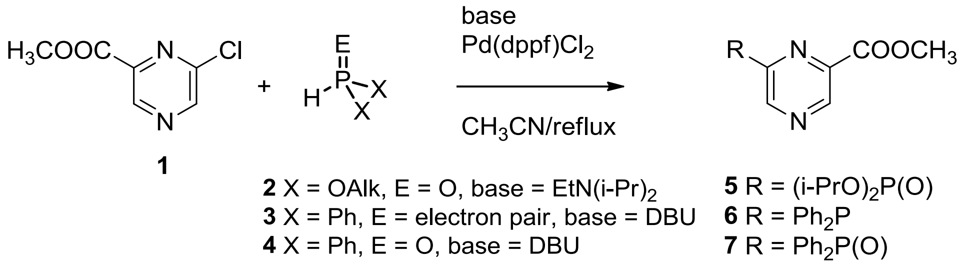
4.2. Results and Discussion

4.2.1. Palladium-catalyzed Cross-coupling Reactions with Chloropyrazines

Palladium–catalyzed P-C cross-coupling of chloropyrazines was performed by reaction of methyl 6-chloropyrazine-2-carboxylate (**1**) with a phosphorus pronucleophile in the presence of a suitable base and 1 mol % of Pd(dppf)Cl_2 in refluxing acetonitrile (Scheme 4.1). Pd(dppf)Cl_2 was the catalyst of choice, since it was previously identified as one of the best second generation catalysts for various carbon-heteroatom couplings that provides high yields of coupled products in cases where most of the palladium complexes with other bidentate phosphine ligands were not successful.[16,17] Also in our case applying other palladium catalysts like $Pd(OAc)_2$/Buchwald ligand, $Pd(PPh_3)_4$, or $Pd(dppe)_2$ did not give rise to any conversion.

Reaction of **1** with 1.05 equiv. of diisopropyl phosphite (**2**) in the presence of 1.05 equiv. of Huenig base and 1 mol % of Pd(dppf)Cl_2 for 15 h afforded methyl 6-(diisopropylphosphono)pyrazine-2-carboxylate (**5**) in 92% isolated yield. In the ^{1}H NMR spectra the signals for the pyrazine protons were shifted from 8.79 and 9.20 ppm in **1** to 9.19 and 9.34 ppm in **5**, respectively. The peak at 9.34 ppm for the proton adjacent to the phosphonate group was split into a doublet (*J* = 3.6 Hz) due to phosphorus-hydrogen coupling. The formation of **5** was also confirmed by the molecular ion peak in the electrospray mass spectrum.

However, under these conditions with diphenylphosphine (**3**) and diphenylphosphine oxide (**4**) no reaction occurred. Apparently, Huenig base is too weak to perform the reaction. In a study carried out in DMSO the pK_a values of diphenylphosphine (**3**) and diphenylphosphine oxide (**4**) were found to be approximately four and two orders of magnitude larger, respectively, than that of dialkylphosphites.[18] Therefore, using DBU as a base, reaction of **1** with **3** and **4** afforded methyl 6-(diphenylphosphino)- (**6**) and methyl 6-(diphenylphosphoryl)pyrazine-2-carboxylate (**7**) in 85 and 90% yield, respectively. In case of the more acidic diphenylphosphine oxide (**4**) the reaction was already completed within 3 h, while starting from diphenylphosphine (**3**) the reaction required 20 h. In the ^{1}H NMR spectra the characteristic peaks of the pyrazine protons of **1** were shifted from 8.79 and 9.20 ppm to 8.40 and 9.11 ppm for **6** and to 9.32 and 9.60 ppm (d, J = 3.0 Hz) for **7**. All compounds showed characteristic $[M+H]^+$ peaks in their electrospray mass spectra.

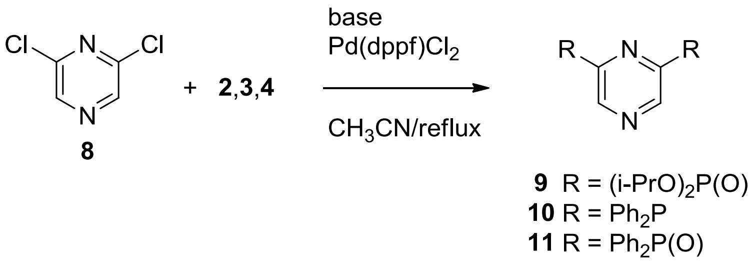


Scheme 4.1. Palladium-catalyzed coupling reactions on 6-chloropyrazine-2-carboxylate (**1**).

To further explore the scope of the palladium–catalyzed cross-coupling of phosphorus pronucleophiles with chloropyrazines, the same series of experiments was performed with

2,6-dichloropyrazine (**8**) (Scheme 4.2). Thus reaction of **8** with 2.1 equiv. of diisopropylphosphite (**2**) in the presence of 2.1 equiv. of Huenig base and 1 mol % of Pd(dppf)Cl_2 in refluxing acetonitrile for 20 h afforded 2,6-bis(diisopropylphosphono)pyrazine (**9**) in 90% yield.

Performing the reaction of **8** under exactly the same conditions with 2 equiv. of diphenylphosphine (**3**) and diphenylphosphine oxide (**4**) in the presence of 2 equiv. of DBU gave the corresponding 2,6-bis(diphenylphosphino)- (**10**) and 2,6-bis(diphenylphosphoryl)-pyrazines (**11**) in 81 and 95% yield, respectively. Also here the difference in reactivity between diphenylphosphine (**3**) and diphenylphosphine oxide (**4**) is reflected in reaction times of 3 h and 24 h, respectively. This significant difference in reaction times can be easily explained considering the lower acidity of **3** on the one hand and the pyrazine ring deactivation towards the second oxidative addition (vide infra) to the palladium catalyst by the introduction of an electron-donating diphenylphosphino group on the other hand.



Scheme 4.2. Palladium-catalyzed coupling reactions on 2,6-dichloropyrazine (**8**).

The ^{1}H NMR spectra of **9**, **10**, and **11** showed a double resonance for the pyrazine protons at 9.18, 8.14, and 9.39 ppm, respectively, as a pair of superimposed doublets. The slight difference in the chemical shifts of the protons is probably due to a different spatial orientation of the substituents and hindered rotation of the bulky (i-PrO)$_2$P(O), Ph_2P, and

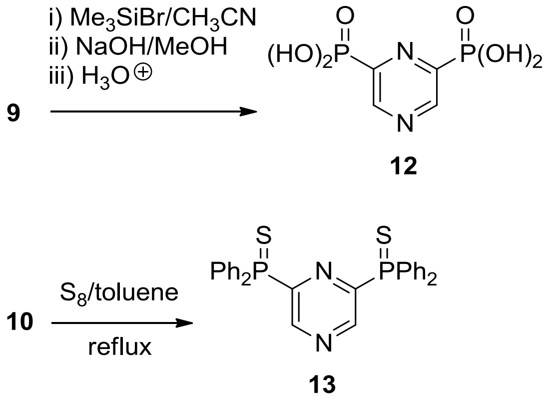
$Ph_2P(O)$ groups. In addition to the ^1H NMR spectra, all compounds exhibited characteristic $[M+H]^+$ peaks in their electrospray mass spectra.

With regards to the mechanism of the reaction, it is assumed that the reaction follows the established mechanism of the palladium-catalyzed coupling of aryl halides and phosphorus nucleophiles.[19] However, no detailed mechanistic study of palladium-catalyzed reactions of phosphorus pronucleophiles with heteroaryl halides has been reported. Nevertheless, kinetic and computational studies on the coupling of aryl halides with dialkyl phosphites and secondary phosphines have been published.[20] Kohler *et al.*[21] synthesized stable arylpalladium intermediates containing a dialkylphosphonate fragment. This study on the ligand influence on the arylpalladium complex stability revealed that the reductive elimination of the corresponding arylphosphonate happens much faster, almost instantaneously, in case of palladium complexes with diphosphine ligands compared to those with bipyridyls, for example. This indicates that the reductive elimination is not the rate-limiting step in the catalytic cycle. At the same time, the presence of an electron-withdrawing group activates the carbon-chlorine bond towards oxidative addition of palladium species and accelerates the reaction as can be concluded from the difference in reactivities between **3** and **4**. This also explains why any attempts to prepare monosubstituted pyrazines starting from 2,6-dichloropyrazine (**8**) were unsuccessful. Even using 1 equiv. of diisopropylphosphite (**2**) or diphenylphosphine oxide (**4**) gave rise to a 50/50 mixture of 2,6-disubstituted product and starting material; in the ^1H NMR spectra of the crude reaction mixtures only minute peaks of possibly monosubstituted product are present.

4.2.2. Synthesis of Pyrazine-based Lanthanide/Actinide Ligands

As part of a project aimed at the design and synthesis of novel extracting agents for actinide/lanthanide separation with improved selectivity for nuclear waste treatment,[22,23] a series of pyrazine-based lipophilic and water-soluble ligands **12, 13, 15, 20,** and **21**, containing amide, phosphinoxide, phosphonate and in one case phosphine sulfide moieties were developed. The lipophilic ligands are typically used to extract f-block elements from highly acidic radioactive waste solutions, while the water-soluble complexants are applied to strip metal ions back.[24] Pyridine-based ligands, picolinamides for instance, are known to lose their extraction ability significantly at a pH < 3, due to protonation of the pyridine nitrogen.[25] Pyrazine will be less acid sensitive, since the pyrazine nitrogen ($pK_{b,\ \mathrm{pyrazine}} = 13.8$) is much less basic than that of pyridine ($pK_{b,\ \mathrm{pyridine}} = 8.8$).[25] It was anticipated that the introduction of phosphinoxides or phosphonates will further decrease the basicity of the pyrazine nitrogens, hence increasing the affinity towards actinides over lanthanides, the first ones being slightly softer cations than the lanthanides. In general, picolinamides show a reasonable extraction selectivity of Am(III) over lanthanides, although the amide substituents and the diluent play an important role.[26] The well known carbamoylphosphinoxides are highly efficient extractants among the bidentate organophosphorus compounds for the recovery of trivalent actinides and lanthanides from highly acidic nuclear waste solutions.[22,23]

The synthesis of the pyrazine-based ligands **12, 13, 15, 20,** and **21** is mainly based on the above described methodology. Pyrazine-2,6-diyldiphosphonic acid (**12**) was synthesized in 98% yield (Scheme 4.3) performing phosphonate ester cleavage of **9** with trimethylbromosilane in acetonitrile and subsequent hydrolysis with NaOH in methanol.

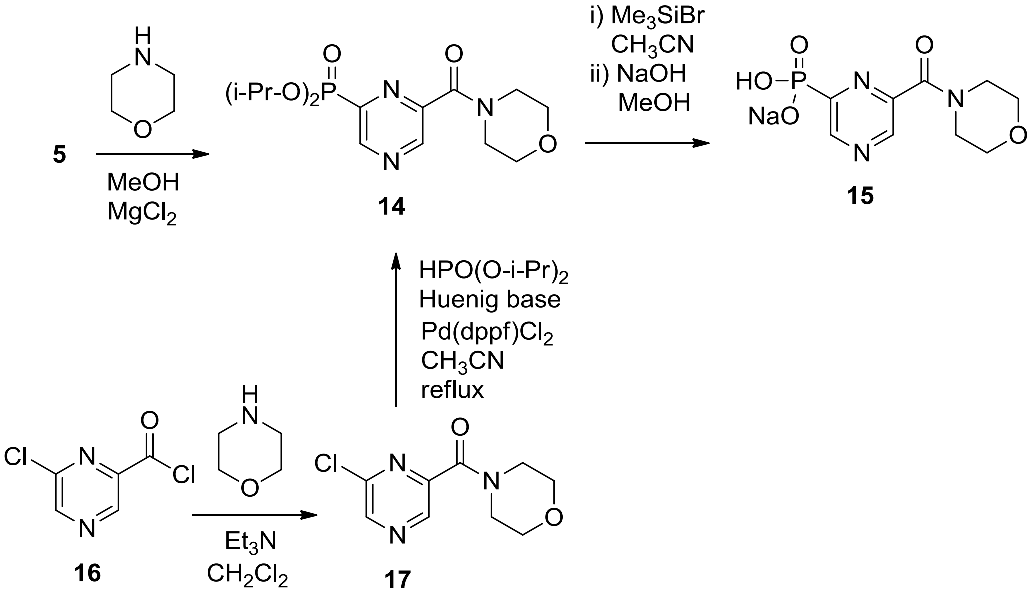


Scheme 4.3. Synthesis of ligands **12** and **13**.

The ^{1}H NMR spectrum of **12** shows a triplet (*J* = 1.8 Hz) for the pyrazine protons at 8.89 ppm, and complete disappearance of the characteristic phosphonate isopropyl group signals. The electrospray mass spectrum of **12** gave the correct $[M+H]^+$, $2[M+H]^+$, and $3[M+H]^+$ peaks.

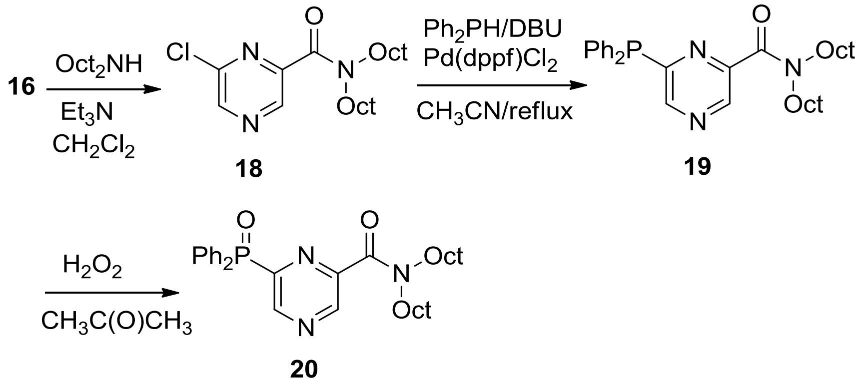
Simple oxidation of diphosphine **10** with 2 equiv. of elementary sulphur in refluxing toluene gave pyrazine-2,6-diylbis(diphenylphosphine sulfide) (**13**) in quantitative yield (Scheme 4.3). In addition to the correct peak of the molecular ion in the electrospray mass spectrum, the ^{1}H NMR spectrum of **13** reveals two overlapped doublets for the pyrazine protons at 9.79 ppm, which is 0.40 ppm higher, than in case of diphosphorylpyrazine **11**, with a negative spin-coupling constant (*J* = -4.2 Hz), as can be concluded from the decreased intensity of the inner lines of the multiplet.[27]

Initially, sodium hydrogen(6-(morpholine-4-carbonyl)pyrazin-2-yl)phosphonate (**15**) was prepared in 59% yield in two steps starting by amidation of ester **5** with morpholine in the presence of $MgCl_2$[28] in methanol and followed by phosphonate cleavage of the resulting product **14** with trimethylbromosilane (Scheme 4.4). However, due to the modest reactivity of ester **5**, amidation of it required a 3-fold excess of the amine, which in its turn promoted morpholine alkylation by diisopropyl phosphonate, complicating the purification and significantly decreasing the yield of **14**. Therefore, the synthetic sequence was altered. Starting from 6-chloropyrazine-2-carbonyl chloride (**16**), the corresponding amide **17** was obtained in quantitative yield upon reaction with morpholine. Performing P-C coupling of **17** with **2**, following the established procedure, afforded **14** in 90% yield. The ^{1}H NMR spectrum reveals two singlets for the pyrazine protons at 8.66 and 8.87 ppm, also displaying characteristic signals for the diisopropylphosphonate group at 4.73 (m) and 1.38 ppm (d). Treatment of **14** with trimethylbromosilane in acetonitrile and subsequent hydrolysis with NaOH in methanol gave amidophosphonate **15** in 96% yield. In its ^{1}H NMR spectrum, the characteristic peaks of the pyrazine protons did not undergo a significant shift compared to **14**, however, the successful cleavage of the phosphonate ester group was proven by the complete absence of the isopropyl signals as present in **14**. The electrospray mass spectrum of **15** demonstrated the molecular ion peak.



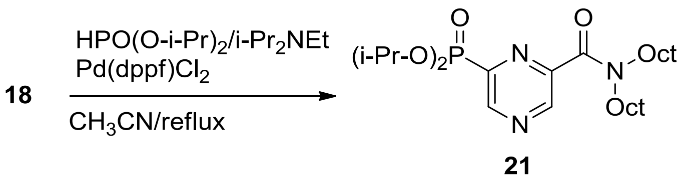
Scheme 4.4. Synthesis of amidophosphonate **15**.

Surprisingly, pyrazine ester **7** proved to be completely unreactive towards dioctylamine, hence it was decided to apply the same approach, as described for **15**, and to perform amidation prior to P-C coupling. Treatment of pyrazine acid chloride **16** with dioctylamine gave pyrazine dioctylamide **18** in quantitative yield. Reaction of **18** with 1 equiv. of diphenylphosphine (**3**) in the presence of 1 equiv. of DBU and 1 mol % of Pd(dppf)Cl_2 in refluxing acetonitrile overnight, followed by oxidation of the diphenylphosphino group with hydrogen peroxide in acetone, afforded 6-(diphenylphosphoryl)-*N*,*N*-dioctylpyrazine-2-carboxamide (**20**) in 75% yield (Scheme 4.5). In the ^{1}H NMR spectrum the signals for the pyrazine protons of **18** at 8.60 and 8.80 ppm were shifted to 8.24 and 8.72 ppm, respectively, for **19** and to 8.95 and 9.41 ppm (d, *J* = 3.3 Hz), after oxidation of the phosphine, for **20**. The electrospray mass spectrum confirmed the formation of **20**, exhibiting the molecular ion peak.



Scheme 4.5. Synthesis of ligand **20**.

Diisopropyl (6-(dioctylcarbamoyl)pyrazin-2-yl)phosphonate (**21**) was obtained by reaction of **18** with 1.05 equiv. of diisopropyl phosphite (**2**) in the presence of 1.05 equiv. of Huenig base and 1 mol % of Pd(dppf)Cl_2 in refluxing acetonitrile overnight in 87% yield (Scheme 4.6). In the ^{1}H NMR spectrum the signals for the pyrazine protons of **18** at 8.60 and 8.80 ppm were shifted to 8.98 ppm (d, *J* = 3.6 Hz) and 9.08 ppm, respectively, for **21**. The formation of **21** was also confirmed by the molecular ion peak in the electrospray mass spectrum.



Scheme 4.6. Synthesis of ligand **21**.

4.2.3. Extraction Results

Lipophilic ligands

Preliminary solvent extraction experiments were carried out to determine the ability of the new lipophilic ligands **11**, **13**, **20**, and **21** to extract f-block elements from highly acidic radioactive solutions into an organic phase. Therefore, organic solutions of the ligands were contacted with nitric acid solutions (0.01 mol/L – 4 mol/L) containing ^{241}Am and ^{152}Eu radiotracers. These conditions are commonly used for testing the extraction properties of extractants relevant for nuclear waste treatment.

The metal distribution ratio D_M was calculated according to equation 1 and the percentage of metal ions retained in the water phase after extraction using equation 2.

$$D_M = \frac{[M]_{org}}{[M]_{aq}} \tag{1}$$

$$\%M_{eq,\, aq} = \frac{1}{1+D_M} \times 100\% \tag{2}$$

The separation factor (*SF*) between Am(III) and Eu(III) was calculated using equation 3.

$$SF_{\frac{Eu}{Am}} = \frac{D_{Eu}}{D_{Am}} \qquad (3)$$

The extraction results of ligand **11** are presented in Figure 4.1. It shows that ligand **11** is a poor extractant under the tested conditions. The distribution ratios for Am(III) and Eu(III) are below 1 in the region between 0.01 and 4 mol/L nitric acid. Since the *D*-values decrease with increasing acidity, it is assumed that **11** is protonated at the central N atom, and the poor extraction of Am(III) (D_{Am} = 0.5 at 0.01 mol/L HNO_3) can be explained by ion-pair extraction.

The solubility of **11** in the hydrocarbon diluent TPH (Total Petroleum Hydrocarbon/hydrogenated tetrapropene) was moderate. Solubility problems were also encountered with ligand **13**, in which the two phosphoryl oxygens were replaced by sulphur-donor atoms. Ligand **13** shows no extraction efficiency for both Am(III) and Eu(III); distribution ratios were below 0.01 in the entire HNO_3 region tested.

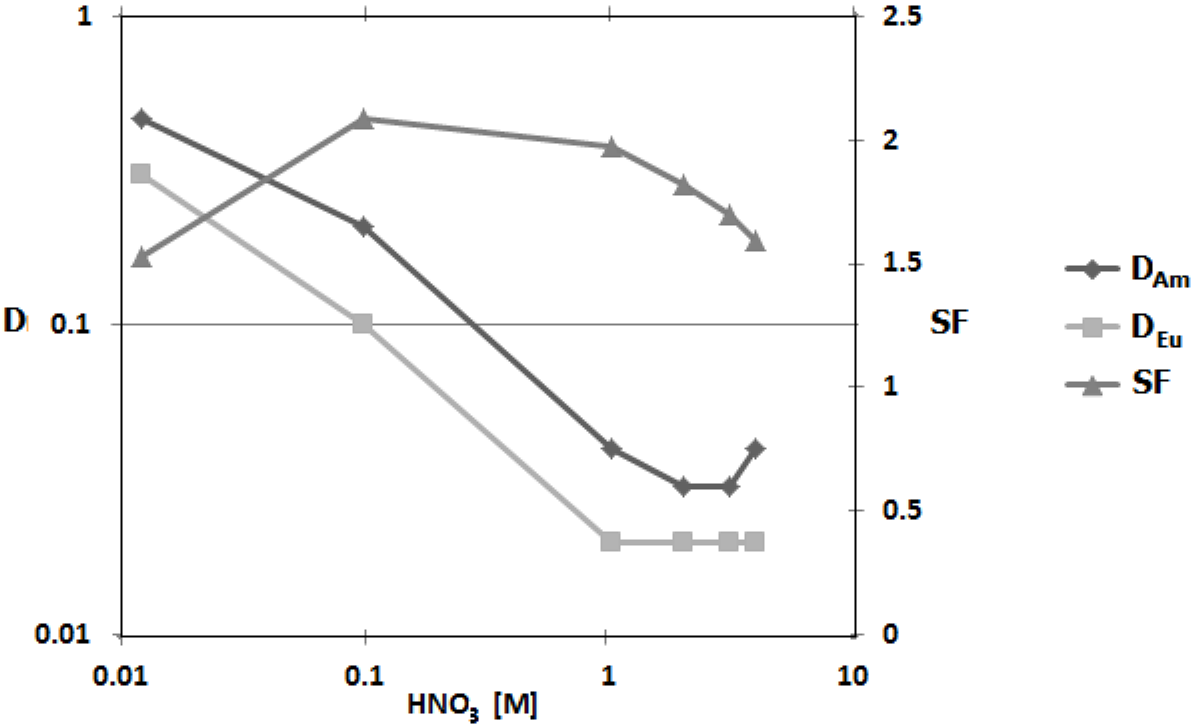


Figure 4.1. *D* ratios of ^{241}Am(III) and ^{152}Eu(III) as a function of the initial HNO_3 concentration by ligand **11**. Organic phase: 0.05 mol/L **11** in TPH. Aqueous phase: variable concentrations of HNO_3, tracers: ^{241}Am, ^{152}Eu, mixing time: 60 min, T = 22 °C ± 1 °C.

To increase the solubility and possibly the affinity for trivalent actinides with the new pyrazine-based ligands, two modifications were realized: a) one phosphoryl group was replaced by an amide moiety containing two lipophilic *n*-octyl groups (ligand **20**) and b) the residual phosphoryl was replaced by a phosphonate group bearing isopropoxy moieties (ligand **21**). The extraction results showed, however, that the ligands **20** and **21** are not able to extract f-block elements like Am(III) and Eu(III) from highly acidic radioactive waste solutions; 95% up to 100% of the radionuclides Am and Eu were still remaining in the aqueous phase.

Water-soluble ligands

Actinide separation processes developed over the last 20 years are predominantly based on multi-cycle processes i.e. the combined extraction of actinides (An(III)) and lanthanides (Ln(III)) from the PUREX raffinate (Plutonium Uranium Recovery by Extraction) followed by their subsequent group separation. In single-cycle processes, on the other hand, An(III) + Ln(III) are also simultaneously separated. Following an An(III)/Ln(III) co-extraction step, the trivalent actinides are selectively back-extracted (stripped) from the loaded organic phase, e.g. using a hydrophilic polyaminocarboxylic acid such as diethylenetriaminepentaacetic acid (DTPA). However, they have a limited solubility, which also greatly depends on the pH of the aqueous solution. Among the most important developments of this process, in Europe the so-called "innovative SANEX" (Selective ActiNide EXtraction) concept is being studied.[29,30]

In the present study the new hydrophilic ligands **12** and **15** were tested for selective stripping of Am(III) from loaded organic solutions into an aqueous phase. An organic solution containing TODGA (*N,N,N',N'*-tetra-*n*-octyl diglycolamide) (0.2 mol/L) and 5 vol-% 1-octanol in TPH was used as solvent.[31] The TODGA molecule is known to efficiently extract trivalent lanthanides and actinides from moderate to high nitric acid concentrations.[32,33] A weighted amount of the hydrophilic ligand was dissolved in an aqueous NH_4NO_3 (0.5 mol/L) solution followed by pH adjustment (HNO_3 or NaOH) and addition of traces of ^{241}Am(III) and ^{152}Eu(III). The nitrate ion was used as a salting-out agent to compensate the metal charge, since TODGA extracts metals only as neutral species (solvating extraction mechanism).[34]

The higher the $SF_{Eu/Am}$ is, the better the selectivity of the water-soluble for Am(III) *versus* Eu(III) is.

Figure 4.2 displays the distribution ratios as a function of the initial pH of different concentrations of ligand **12**. For comparison, the results of the reference system (TODGA) are expressed by the dotted lines in Figure 4.2. TODGA shows a slightly higher affinity for Eu(III) over Am(III). In case of **12** high distribution ratios for Am(III) and Eu(III) were obtained and they were not affected by the initial pH of the aqueous phase due to the salting-out effect of NO_3^-. The *D* values for Am are between 34 and 76, whereas higher *D* values (250–323) were obtained for Eu, resulting in $SF_{Eu/Am}$ values between 4.5 and 7.2.

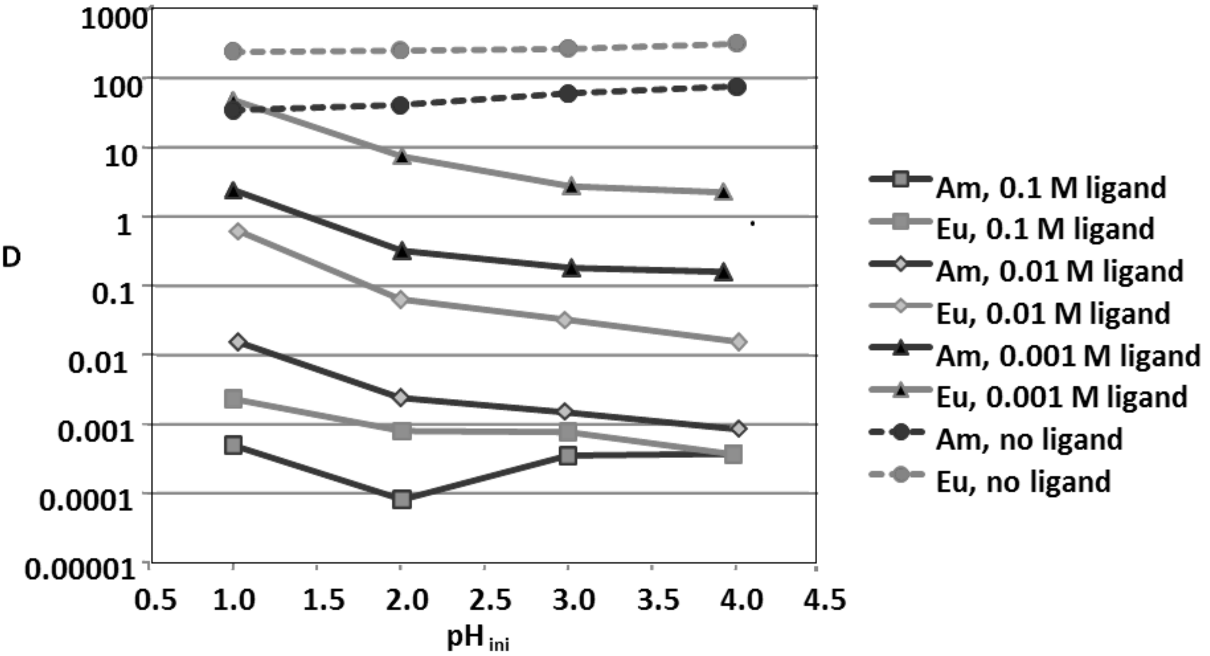


Figure 4.2. *D* ratios of ^{241}Am(III) and ^{152}Eu(III) as a function of the initial pH and the influence of the concentration of ligand **12**. Organic phase: 0.2 mol/L TODGA + 5 vol % 1-octanol in TPH. Aqueous phase: 0.5 mol/L NH_4NO_3, variable pH_{ini}, variable concentrations of ligand **12**, tracers: ^{241}Am, ^{152}Eu, mixing time: 60 min, T = 22 °C ± 1 °C.

Ligand **12** exhibits a very strong extractability for ^{241}Am and ^{152}Eu. At a ligand concentration of 0.1 mol/L nearly 100 % of Am(III) and Eu(III) are complexed in the aqueous phase (Table 1). As expected, the distribution ratios increase with decreasing ligand concentration. However, the one of ^{152}Eu increases at a much higher rate than that of ^{241}Am.

Therefore, it becomes possible to separate Am over Eu at lower ligand concentrations. The separation factor $SF_{Eu/Am}$ of Eu over Am at an initial pH of 1 increases from 4.6 to 40, upon decreasing the ligand concentration from 0.1 mol/L to 0.01 mol/L (Table 4.1). While decreasing the ligand concentration to 0.001 mol/L the distribution ratios increase further.

Table 4.1. Percentages of retained ions in the aqueous phase and Eu/Am separation factors using ligands **12** and **15**. Calculated using equations 2 and 3 using the distribution ratios from Figures 2 and 3, respectively.

Ligand conc. [mol/L]		Ligand **12**			Ligand **15**		
	initial pH	%Am$_{\mathrm{aq,eq}}$	%Eu$_{\mathrm{aq,eq}}$	$SF_{\mathrm{Eu/Am}}$	%Am$_{\mathrm{aq,eq}}$	%Eu$_{\mathrm{aq,eq}}$	$SF_{\mathrm{Eu/Am}}$
0	1	2.83	0.40	7.2	2.83	0.40	7.2
	2	2.38	0.39	6.3	2.38	0.39	6.3
	3	1.64	0.37	4.5	1.64	0.37	4.5
	4	1.31	0.31	4.3	1.31	0.31	4.3
0.001	1	29.26	2.02	20.1	2.31	0.32	7.4
	2	75.77	11.79	23.4	3.38	0.49	7.2
	3	84.67	26.35	15.4	5.65	1.05	5.6
	4	86.26	30.26	14.5	5.27	1.26	4.3
0.01	1	98.49	62.04	40.0	2.05	0.31	6.7
	2	99.76	94.11	26.1	10.30	1.03	11.1
	3	99.85	96.90	21.3	22.85	3.18	9.0
	4	99.92	98.50	18.0	24.88	4.47	7.1
0.1	1	99.95	99.77	4.6	8.47	0.87	10.6
	2	99.99	99.92	9.9	61.39	10.34	13.8
	3	99.97	99.93	2.2	87.03	35.15	12.4
	4	99.96	99.96	1.0	84.18	30.51	12.1

It is possible to adjust conditions, which are of a great interest for the innovative-SANEX concept.[29] At a ligand concentration of 0.001 mol/L and an initial pH between 2 and 4, Eu(III) is held back preferentially in the organic phase, whereas Am(III) is complexed selectively in the aqueous phase. The D_{Am} values are between 0.3 and 0.2 (Figure 4.2), which expresses that 76% to 86% of the metal is retained in the aqueous phase. However, the D_{Eu}

values are between 2 and 7, which means that >70% of the metal is kept in the organic phase. In a multi-step counter-current extraction process these conditions can be used for a complete group separation. As the ligand concentration is very low, the system may be very sensitive to loading effects.

The back extraction results with ligand **15** are depicted in Figure 4.3 and also summarized in Table 4.1. At a low ligand concentration of 0.01 mol/L or 0.001 mol/L, the extraction of Am and Eu is less pronounced, compared to ligand **12**; only a moderate amount (< 50%) of the radionuclides is extracted into the aqueous phase (Table 4.1). However, at a ligand concentration of 0.1 mol/L, the conditions are again interesting for the innovative-SANEX concept. The D_{Am} values are < 1 in the initial pH-range between 2 and 4, but those of Eu are > 1, which makes a selective separation of both radionuclides possible. Although the observed separation factors are lower than those of ligand **12** ($SF_{Eu/Am}$ ~ 10-14), due to the higher ligand concentrations, the process will be less sensitive to metal loading effects. This makes this ligand an excellent candidate for the innovative SANEX process.

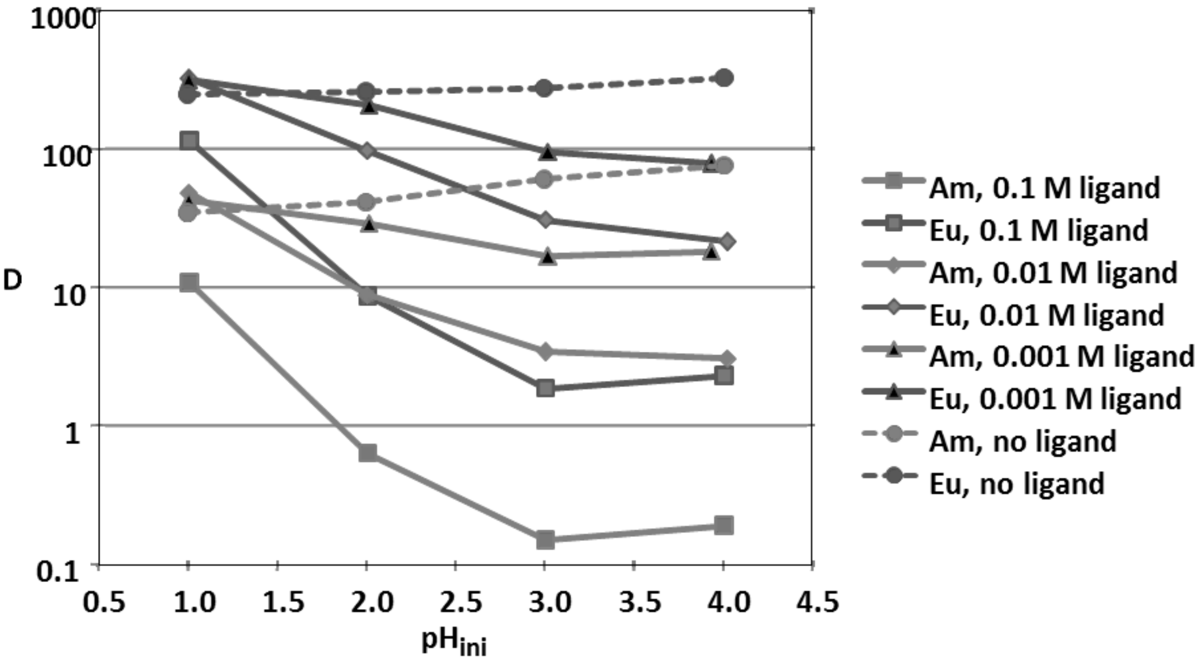


Figure 4.3. *D* ratios of ^{241}Am(III) and ^{152}Eu(III) as a function of pH_{ini} and the influence of the concentration of ligand **15**. Organic phase: 0.2 mol/L TODGA + 5 vol-% 1-octanol in TPH. Aqueous phase: 0.5 mol/L NH_4NO_3, variable pH_{ini}, variable concentrations of ligand **15**, tracers: ^{241}Am, ^{152}Eu, mixing time: 60 min, T = 22 °C ± 1 °C.

4.3. Conclusions

A simple method has been developed for the preparation of a novel class of compounds, viz. 2,6-disubstituted pyrazines bearing ore or two phosphorus substituents, comprising the Pd(dpppf)Cl_2-catalyzed coupling of (di)chloropyrazines with phosphorus-containing pronucleophiles. The introduction of an electron-withdrawing group enhances the rate of the second coupling step in case of dichloropyrazines. From a series of pyrazine-based lipophilic and water-soluble ligands, prepared according to this methodology and by fine-tuning the basicity of the pyrazine nitrogens, the latter ones exhibit a very good selectivity for Am^{3+}, used as a typical representative of the minor actinides, over lanthanides. This underlines the importance of further development of pyrazine-based ligands. On the other hand, its relatively simple synthesis, the extraction behavior and the reduced sensitivity towards acid compared to pyridine-containing ligands make them very suitable candidates to be applied in the innovative SANEX process.

4.4. Experimental Section

General

The solvents, catalyst, and all reagents were obtained from commercial sources and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity INOVA (300 MHz) spectrometer. ^{1}H NMR chemical shift values (300 MHz) are reported as δ using the residual solvent signal as an internal standard ($CDCl_3$, $\delta = 7.257$). ^{13}C NMR chemical shift values (75 MHz) are reported as δ using the residual solvent signal as an internal standard ($CDCl_3$, $\delta = 77.0$ ppm). Electrospray ionization (positive mode) mass spectra were recorded on a WATERS LCT mass spectrometer. All reactions were performed under nitrogen atmosphere.

General procedure for the palladium catalyzed P-C coupling of monochloropyrazines 1, 17 and 18 with diisopropyl phosphite. Formation of 5, 14, and 21.

To a solution of chloropyrazines **1**, **17**, **18** (10 mmol) and Pd(dppf)Cl_2 (0.073 g, 1 mol %) in CH_3CN (50 mL) were subsequently added HPO(O-*i*-Pr)$_2$ (1.7 mL, 10.5 mmol) and *i*-Pr_2NEt (1.8 mL, 10.5 mmol). The resulting mixture was refluxed for 3 h and then all the volatiles were removed in vacuo. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and the solution was passed through a short plug of silica. The resulting solution was dried in vacuo yielding the coupled products as oils.

Tetraisopropyl pyrazine-2,6-diylbis(phosphonate) (5): Yield 2.78 g, 92%. ^{1}H NMR ($CDCl_3$): δ = 9.33 (d, 1 H, $^3J_{HP}$ = 3.6 Hz, PyzH), 9.20 (s, 1 H, PyzH), 4.92-4.82 (m, 2 H, $C\mathit{H}(CH_3)_2$), 4.02 (s, 3 H, $CH_3OC(O)$), 1.42 and 1.36 (d, 6 H, J = 6.0 Hz, $CH(C\mathit{H}_3)_2$). ^{13}C NMR: δ = 164.2, 150.3 (d, J_{CP} = 4.2 Hz), 149.9 (d, J_{CP} = 4.2 Hz), 147.6 (m), 147.5 (m), 73.3 (t, $^2J_{CP}$ = 6.8 Hz), 53.4, 24.2-24.8 (set of doublets). HRMS-TOF (*m/z*): $[M + H]^+$ calcd 303.1110, found 303.1108.

Diisopropyl (6-(morpholino-4-carbonyl)pyrazin-2-yl)phosphonate (14): Yield 3.22 g, 90%. ^{1}H NMR ($CDCl_3$): δ = 9.34 (d, 1 H, $^3J_{HP}$ = 3.0 Hz, PyzH), 9.20 (s, 1 H, PyzH), 4.90-4.80 (m, 2 H, $C\mathit{H}(CH_3)_2$), 3.85-3.80 (m, 4 H, $OC\mathit{H}_2CH_2N$), 3.75-3.64 (m, 4 H, $OCH_2C\mathit{H}_2N$), 1.43 and 1.36 (d, 6 H, J = 6.0 Hz, $CH(C\mathit{H}_3)_2$). ^{13}C NMR: δ = 165.8, 149.2, 148.5, 147.8 (d, $^1J_{CP}$ = 16.2 Hz), 147.1 (d, $^2J_{CP}$ = 4.3 Hz), 73.3 (d, $^2J_{CP}$ = 3.0 Hz), 73.2 (d, $^2J_{CP}$ = 3.0 Hz), 67.9, 67.0, 48.1, 43.5, 25.6-25.0 (set of doublets, $^3J_{CP}$ = 1.5 Hz). HRMS-TOF (*m/z*): $[M + H]^+$ calcd 358.1532, found 358.1536.

Diisopropyl (6-(dioctylcarbamoyl)pyrazin-2-yl)phosphonate (21): Yield 4.45 g, 87%. ^{1}H NMR ($CDCl_3$): δ = 9.07 (s, 1 H, PyzH), 8.99 (d, 1 H, $^3J_{HP}$ = 3.0 Hz, PyzH), 4.86-4.76 (m, 2 H, $C\mathit{H}(CH_3)_2$), 3.50 and 3.40 (t, 2 H, J = 7.5 Hz, CH_2N), 1.15-1.75 (m, 36 H, AlkH), 0.86 (t, 6 H, J = 6.0 Hz, CH_3). ^{13}C NMR: δ =163.2, 149.0, 148.6, 147.7 (d, $^1J_{CP}$ = 16.5 Hz), 147.2 (d, $^2J_{CP}$ = 4.5 Hz), 73.2 (d, $^2J_{CP}$ = 3.0 Hz), 73.1 (d, $^2J_{CP}$ = 3.0 Hz), 32.1, 31.8, 29.8, 29.6, 29.5, 28.4, 28.0, 27.3, 26.5, 22.8, 21.9, 20.8, 14.3. HRMS-TOF (*m/z*): $[M + H]^+$ calcd 512.3617, found 512.3621.

Methyl 6-(diphenylphosphoryl)pyrazine-2-carboxylate (7)

To a solution of **1** (1.74 g, 10 mmol), Pd(dppf)Cl_2 (0.073 g, 1 mol %) and HP(O)Ph_2 (2.02 g, 10 mmol) in CH_3CN (50 mL) was added DBU (1.5 mL, 10 mmol). The resulting mixture was refluxed for 3 h and then all the volatiles were removed in vacuo. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and the solution was passed through a short plug of silica. The resulting solution was dried in vacuo yielding **7** as an amber oil (3.04 g, 90%). ^{1}H NMR ($CDCl_3$): δ = 9.59 (s, 1 H, PyzH), 9.34 (d, 1 H, $^3J_{HP}$ = 3.0 Hz, PyzH), 7.97-7.90 (m, 4 H, ArH), 7.53-7.40 (m, 6 H, ArH), 4.02 (s, 3 H, $CH_3OC(O)$). ^{13}C NMR: δ = 166.8, 151.2 (d, $^1J_{CP}$ = 17.3 Hz), 148.6, 148.3, 146.9, 133.1, 132.5, 132.4, 131.3, 131.0, 129.6, 129.0, 128.8, 128.7, 128.6, 128.5, 128.3, 56.5. HRMS-TOF (*m/z*): $[M + H]^+$ calcd 339.0899, found 339.0898.

General procedure for the palladium catalyzed P-C coupling of monochloropyrazines 1 and 18 with diphenylphosphine. Formation of 6 and 19.

To a solution of monochloropyrazines **1** and **18** (10 mmol) and Pd(dppf)Cl_2 (0.073 g, 1 mol %) in CH_3CN (50 mL) were subsequently added HPPh_2 (1.7 mL, 10 mmol) and DBU (1.5 mL, 10 mmol). The resulting mixture was refluxed for 20 h and then the solvent was removed in vacuo. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and all the volatiles were removed in vacuo. The resulting crude phosphines **6** and **19** were characterized as their phosphine oxides.

6: ^{1}H NMR ($CDCl_3$): δ = 9.12 (s, 1 H, PyzH), 8.39 (d, 1 H, $^3J_{HP}$ = 1.5 Hz, PyzH), 7.41-7.35 (m, 10 H, ArH), 3.99 (s, 3 H, $CH_3OC(O)$).

2,6-Bis(diisopropylphosphono)pyrazine (9)

To a solution **8** (1.49 g, 10 mmol) and Pd(dppf)Cl_2 (0.146 g, 2 mol %) in CH_3CN (50 mL) were subsequently added HPO(O-*i*-Pr)$_2$ (3.5 mL, 21.0 mmol) and *i*-Pr_2NEt (3.7 mL, 21.0 mmol). The resulting mixture was refluxed for 3 h and then all the volatiles were removed in vacuo. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and the solution was passed through a short plug of silica. The resulting solution was dried in vacuo to give **9** (3.67 g, 90%). ^{1}H NMR ($CDCl_3$): δ = 9.12 (d, 2 H, $^3J_{HP}$ = 4.5 Hz, PyzH), 4.86-4.76 (m, 4 H, CH(CH_3)$_2$), 1.37 and 1.31 (d, 12 H, J = 6.0 Hz, CH(CH_3)$_2$). ^{13}C NMR: δ = 151.1 (d, $^1J_{CP}$ = 17.3 Hz), 149.3 (t, $^2J_{CP}$ = 4.1 Hz), 148.9 (t, $^2J_{CP}$ = 4.1 Hz), 148.1 (d, $^1J_{CP}$ = 17.3 Hz), 73.2 (d, $^2J_{CP}$ = 3.0 Hz), 73.1 (d, $^2J_{CP}$ = 3.0 Hz), 73.0 (d, $^2J_{CP}$ = 3.0 Hz), 72.9 (d, $^2J_{CP}$ = 3.0 Hz), 24.0-24.5 (set of doublets, $^3J_{CP}$ = 1.5 Hz). HRMS-TOF (*m/z*): $[M + H]^+$ calcd 409.1657, found 409.1654.

2,6-Bis(diphenylphosphino)pyrazine (10)

To a solution of **8** (1.49 g, 10 mmol) and Pd(dppf)Cl_2 (0.146 g, 2 mol %) in CH_3CN (50 mL) were subsequently added $HPPh_2$ (3.4 mL, 20 mmol) and DBU (3.0 mL, 20 mmol). The resulting mixture was refluxed for 24 h and then all the volatiles were removed in vacuo. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and the solution was passed through a short plug of silica. The resulting solution was dried in vacuo. The crude product was crystallized from toluene-hexane affording pure **10** (3.63 g, 81%). Mp 116–118 °C. ^{1}H NMR ($CDCl_3$): δ = 8.14 (d, 2 H, $^3J_{HP}$ = 3.0 Hz, PyzH), 7.28-7.24 (m, 20 H, ArH). ^{13}C NMR: δ = 153.4 (d, $^1J_{CP}$ = 13.5 Hz), 151.8 (d, $^1J_{CP}$ = 13.5 Hz), 149.5 (d, $^2J_{CP}$ = 3.0 Hz), 149.2 (d, $^2J_{CP}$ = 3.0 Hz), 132.9, 132.8, 132.6, 132.3, 132.1, 131.5, 130.1, 129.1, 129.0, 128.9, 128.7, 128.5. HRMS-TOF (*m/z*): $[M + H]^+$ calcd 449.1336, found 449.1335.

2,6-Bis(diphenylphosphoryl)pyrazine (11)

To a solution of **8** (1.49 g, 10 mmol) and Pd(dppf)Cl_2 (0.146 g, 2 mol %) and HP(O)Ph_2 (4.04 g, 20 mmol) in CH_3CN (50 mL) was added DBU (3.0 mL, 20 mmol). The resulting mixture was refluxed for 3 h and then then all the volatiles were removed in vacuo. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and the solution was passed through a short plug of silica. The resulting solution was dried in vacuo. The crude product was crystallized from toluene-hexane to give **11** (4.56 g, 95%). Mp 206–208 °C. ^{1}H NMR ($CDCl_3$): $\delta = 9.39$ (dd, 2 H, $^3J_{HP} = 3.6$ Hz, $^5J_{HP} = -3.3$ Hz, PyzH), 7.57-7.50 (m, 12 H, ArH), 7.29-7.25 (m, 8 H, ArH). ^{13}C NMR: $\delta = 149.3$ (d, $^1J_{CP} = 22.5$ Hz), 148.6, 132.8-132.0 (m), 131.5, 130.1, 129.1-128.2 (m), 123.0. HRMS-TOF (*m/z*): $[M + H]^+$ calcd 481.1235, found 481.1231.

General procedure for phosphonate 9 and 14 deprotection. Formation of 12 and 15.

To a solution of dialkylphosphonates **9** and **14** (5 mmol) in CH_3CN (50 mL) was added Me_3SiBr (3 equiv. per phosphonate group). The resulting mixture was refluxed for 18 h and all the volatiles were removed in vacuo. The residue was dissolved in CH_3OH (50 mL), whereupon NaOH (0.2 g, 5 mmol) was added. The resulting solution was stirred for 1 h and then acidified with 1M HCl and dried in vacuo affording the corresponding amidophosphonic acids **12** and **15**.

Pyrazine-2,6-diyldiphosphonic acid (12): Yield 2.35 g, 98%. Mp 205–206 °C. ^{1}H NMR ($(CD_3)_2SO$): $\delta = 8.91$ (t, 2 H, $^3J_{HP} = 2.1$ Hz, PyzH). ^{13}C NMR: $\delta = 154.3$ (d, $^1J_{CP} = 15.8$ Hz), 151.4 (d, $^1J_{CP} = 15.8$ Hz), 147.6 (t, $^2J_{CP} = 4.5$ Hz), 147.3 (t, $^2J_{CP} = 4.5$ Hz). HRMS-TOF (*m/z*): $[M + H]^+$ calcd 240.9779, found 240.9772.

(6-(Morpholino-4-carbonyl)pyrazin-2-yl)phosphonic acid (15): Yield 2.63 g, 96%. ^{1}H NMR ((CD$_3$)$_2$SO): δ = 8.95 and 8.85 (s, 1 H, PyzH), 3.65 (bs, 4 H, OCH_2CH$_2$N), 3.55 and 3.44 (t, 2 H, J = 3.0 Hz, OCH$_2$CH_2N). ^{13}C NMR: δ = 163.7, 148.1, 147.4, 145.7 (d, $^1J_{\mathrm{CP}}$ = 3.8 Hz), 143.6 (d, $^1J_{\mathrm{CP}}$ = 5.3 Hz), 67.0, 66.9, 47.9, 43.1. HRMS-TOF (*m/z*): [M + H]$^+$ calcd 274.0593, found 274.0585.

2,6-Bis(diphenylthiophosphoryl)pyrazine (13)

A suspension of **10** (4.48 g, 10 mmol) and elementary sulfur (0.64 g, 20 mmol) in toluene (100 mL) was refluxed overnight forming a brown solution. Then all the volatiles were removed in vacuo. The residue was recrystallized from hot EtOH giving **13** as orange crystals (4.51 g, 88%). Mp 154–157 °C. ^{1}H NMR: δ = 9.79 (dd, 2 H, $^3J_{\mathrm{HP}}$ = 3.6 Hz, $^5J_{\mathrm{HP}}$ = -4.2 Hz, PyzH), 7.56-7.45 (m, 12 H, ArH), 7.33-7.26 (m, 8 H, ArH). ^{13}C NMR: δ = 151.9 (d, $^1J_{\mathrm{CP}}$ = 11.3 Hz), 150.5 (d, $^1J_{\mathrm{CP}}$ = 11.3 Hz), 149.5 (d, $^2J_{\mathrm{CP}}$ = 3.8 Hz), 149.2 (d, $^2J_{\mathrm{CP}}$ = 3.8 Hz), 132.5, 132.4, 132.2, 131.6, 130.4, 128.8, 128.7, 128.6. HRMS-TOF (*m/z*): [M + H]$^+$ calcd 513.0778, found 513.0775.

(6-Chloropyrazin-2-yl)(morpholino)methanone (17)

To a solution of acid chloride **16** (5.3 mmol) in dry CH$_2$Cl$_2$ (25 mL) was added dropwise a solution of morpholine (0.48 mL, 5.5 mmol) and Et$_3$N (1.5 mL, 10 mmol) in dry CH$_2$Cl$_2$ (25 mL). The resulting mixture was stirred for 2 h and then all the volatiles were removed in vacuo. The residue was partitioned between H$_2$O (30 mL) and EtOAc (70 mL). The organic phase was dried over Na$_2$SO$_4$ and the solvent was removed in vacuo, giving **17** in quantitative yield as a pale yellow oil. ^{1}H NMR: δ = 8.88 and 8.66 (s, 1 H, PyzH), 3.83-3.78 (m, 4 H, OCH_2CH$_2$N), 3.75-3.64 (m, 4 H, OCH$_2$CH_2N). ^{13}C NMR: δ = 163.7, 148.2, 147.5, 145.8, 143.7, 67.1, 47.9, 43.2. HRMS-TOF (*m/z*): [M + H]$^+$ calcd 200.0591, found 200.0599.

6-Chloro-*N,N*-dioctylpyrazine-2-carboxamide (18)

To a solution of acid chloride **16** (10 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise a solution of di-*n*-octylamine (3.0 mL, 10 mmol) and Et_3N (3.0 mL, 20 mmol) in dry CH_2Cl_2 (50 mL). The resulting mixture was stirred overnight and then all the volatiles were removed in vacuo. The residue was partitioned between H_2O (30 mL) and EtOAc (70 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo, to afford **18** in quantitative yield as a yellow oil. ^{1}H NMR: δ = 8.80 and 8.62 (s, 1 H, PyzH), 3.48 and 3.32 (t, 2 H, J = 7.5 Hz, CH_2N), 1.65-1.55 (m, 4 H, AlkH), 1.39-1.15 (m, 20 H, AlkH), 0.88-0.78 (m, 6 H, CH_3). ^{13}C NMR: δ = 162.8, 148.1, 147.3, 144.9, 143.5, 32.0, 31.9, 29.6, 29.5, 29.4, 29.3, 29.0, 27.3, 26.5, 23.0, 22.6, 21.3, 14.1. HRMS-TOF (*m/z*): $[M + H]^+$ calcd 382.2625, found 382.2632.

6-(Diphenylphosphoryl)-*N,N*-dioctylpyrazine-2-carboxamide (20)

A solution of the crude phosphine **19** (2.23 g, 5 mmol) and H_2O_2 (30% aqueous, 0.8 mL) in acetone (25 mL) was stirred for 12 h and then 1 M HCl (10 mL) was added. After stirring the reaction mixture for 30 min all the volatiles were removed in vacuo and the residue was partitioned between H_2O (30 mL) and $CHCl_3$ (30 mL). The organic phase was dried over Na_2SO_4 and passed through a short plug of silica, giving **20** after evaporation of the solvent as a yellow oil (2.05 g, 75%). ^{1}H NMR: δ = 9.40 (s, 1 H, PyzH), 8.97 (d, 1 H, $^3J_{HP}$ = 3.0 Hz, PyzH), 7.85-7.75 (m, 4 H, ArH), 7.60-7.35 (m, 6 H, ArH), 3.46 and 3.11 (t, 2 H, J = 7.5 Hz, CH_2N), 1.70-0.70 (m, 30 H, AlkH). ^{13}C NMR: δ = 165.8, 150.1 (d, $^1J_{CP}$ = 17.3 Hz), 148.3, 147.3, 145.8, 133.0, 132.4, 132.2, 131.3, 130.9, 129.5, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 32.0, 31.9, 29.6, 29.5, 29.4, 29.3, 29.0, 27.2, 26.6, 22.9, 22.8, 20.8, 14.3. HRMS-TOF (*m/z*): $[M + H]^+$ calcd 548.3406, found 548.3405.

Solvent extraction studies

The batch experiments were performed in 2 mL glass vials. Organic and aqueous phases (500 μL) were prepared as described below, spiked with 10 μL of radiotracer (^{241}Am, ^{152}Eu, approx. 25 kBq/mL) and shaken by a vortex mixer for 60 minutes. The radiotracers were supplied by Isotopendienst M. Blaseg GmbH, Waldburg (Germany). Separation of the phases by centrifugation was followed by sampling 200 μL of each phase for analysis using a high-purity germanium spectrometer system obtained from EG&G Ortec, München, Germany, and equipped with the gamma vision software. The γ-lines at 59.5 and 121.8 keV were examined for ^{241}Am and ^{152}Eu, respectively. The distribution ratio D_M was measured as the ratio between the radioactivity of an isotope in the organic and the aqueous phases. Distribution ratios between 0.1 and 100 exhibit a maximum error of ± 5%. The error may be up to ± 20% for smaller and larger values.

Lipophilic ligands

All the lipophilic ligands should have been dissolved in TPH to a preferable concentration of 0.1 mol/L. But due to their low solubility, ligands **11** and **13** had been dissolved in a mixture of 1-octanol and toluene to a concentration of 0.05 mol/L.

The obtained organic solvent was contacted with nitric acid of variable concentrations (0.01 - 4 mol/L) containing traces of Am(III) and Eu(III). Nitric acid solutions were prepared by diluting concentrated nitric acid (Merck KGa, Darmstadt, Germany) with ultrapure water (resistivity, 18 MΩcm). The acidity was checked by titration with NaOH.

Water-soluble ligands

All the aqueous solutions were prepared by dissolution of weighted amounts of the ligand in ultrapure water (resistivity, 18 MΩcm) containing 0.5 mol/L NH_4NO_3 (salting-out agent). The initial pH of the aqueous phase was adjusted using ammonia or diluted nitric acid. The organic solvent consisted of 0.2 mol/L TODGA (extractant) and 5 vol % 1-octanol dissolved in TPH. The organic phase was not loaded with Am and Eu followed by stripping as TODGA extracts significant amounts of HNO_3 which would prevent obtaining reasonable results at pH > 1 without using a buffer. Instead, each of the aqueous phases (500 µL) were spiked with the radiotracers and contacted with the organic solvent (500 µL). The acidities of the initial aqueous solutions were determined using a 691 Metrohm pH meter (3 mol/L KCl).

4.5. References and Notes

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Chapter 5

Pyrazine-functionalized Calix[4]arenes: Synthesis by Palladium–catalyzed Cross-coupling with Phosphorus Pronucleophiles and Metal Ion Extraction Properties[*]

A series of pyrazine-based calix[4]arene extractants was prepared by a stepwise functionalization, comprising palladium-catalyzed exhaustive cross-coupling of di- and tetrasubstituted calix[4]arenes bearing chloropyrazine moieties. The extraction behavior of the synthesized ligands was studied on Am/Eu mixtures under acidic feed conditions similar to those prevailing in nuclear wastes. Phosphorylpyrazine-bearing extractants exhibited a very high acid resistivity and a high affinity for americium giving D values as high as 794 at pH 1. The synergistic effect of the chlorinated cobalt bis(dicarbollide) anion $[(B_9C_2H_8Cl_3)_2Co]^-$ *(CCD-anion), as well as the effect of the calix[4]arene platform compared to monovalent ligands, were investigated. The presence of 1 mM CCD resulted into a* 10^5 *times increase in D value.*

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5.1. Introduction

Since their discovery, calixarenes have become widely employed as platforms for molecular and ionic recognition, enzyme mimicking, and in many other domains of supramolecular chemistry.[1] The high level of preorganization and the well understood conformational behavior of calix[4]arenes have boosted the development of highly efficient and selective calixarene-based extracting agents.[2] The attachment of monovalent ligating units to a rigid scaffold (such as calix[4]arene) is known to give a certain degree of preorganization to a resulting multivalent ligand favoring metal complexation. On the other hand, ligand multivalency[3] results into a stronger binding than is expected from the same number of monovalent units. The use of the multivalency effect to improve the extractant's properties has become quite popular in the field of actinide (An(III))/lanthanide (Ln(III)) separation for nuclear waste remediation. A large enhancement of the metal ion extractability was observed for CMPO-,[4] DGA-,[5,6,7] phosphoryl-,[8,9,10] and diamide[11]-functionalized calix[4]arenes compared to the respective monovalent ligands.

Recently, a solvent extraction process based on heterocyclic polynitrogen ligands,[12] called Selective ActiNide EXtraction (SANEX), has been proposed and successfully tested for An(III)/Ln(III) separation from 1 mol/L nitric acid solutions.[13] Moreover, it was found that supramolecular calixarene-based ligands incorporating heterocyclic N-donor units are generally the most efficient in the extraction of both actinides and lanthanides.[11,12] However, pyridine-based ligands, such as picolinamide-bearing calixarenes, being good extractants, display moderate to low selectivities towards actinides over lanthanides.[14] Due to the decreased basicity of nitrogen in pyrazine compared to pyridine one should expect more pronounced discrimination of lanthanides over actinides in the extraction process, since the latter are known to be the softer cations.[15] In the work presented in Chapter 4 it was found that appropriately functionalized monovalent water-soluble pyrazine-based ligands exhibit a very good selectivity and affinity towards americium over europium in the back-extraction process. At the same time, pyrazine-based ligands with lipophilic diphenylphosphoryl and dioctylcarbamoyl groups failed to extract trivalent f-block metal cations into a non-polar organic phase, presumably due to the lack of lipophilicity. The idea of the work, presented in this chapter, to employ the *p*-*tert*-butylcalix[4]arene platform comprises two presumable improvements: to enhance the ligand binding via multivalency and to increase the extractant lipophilicity.

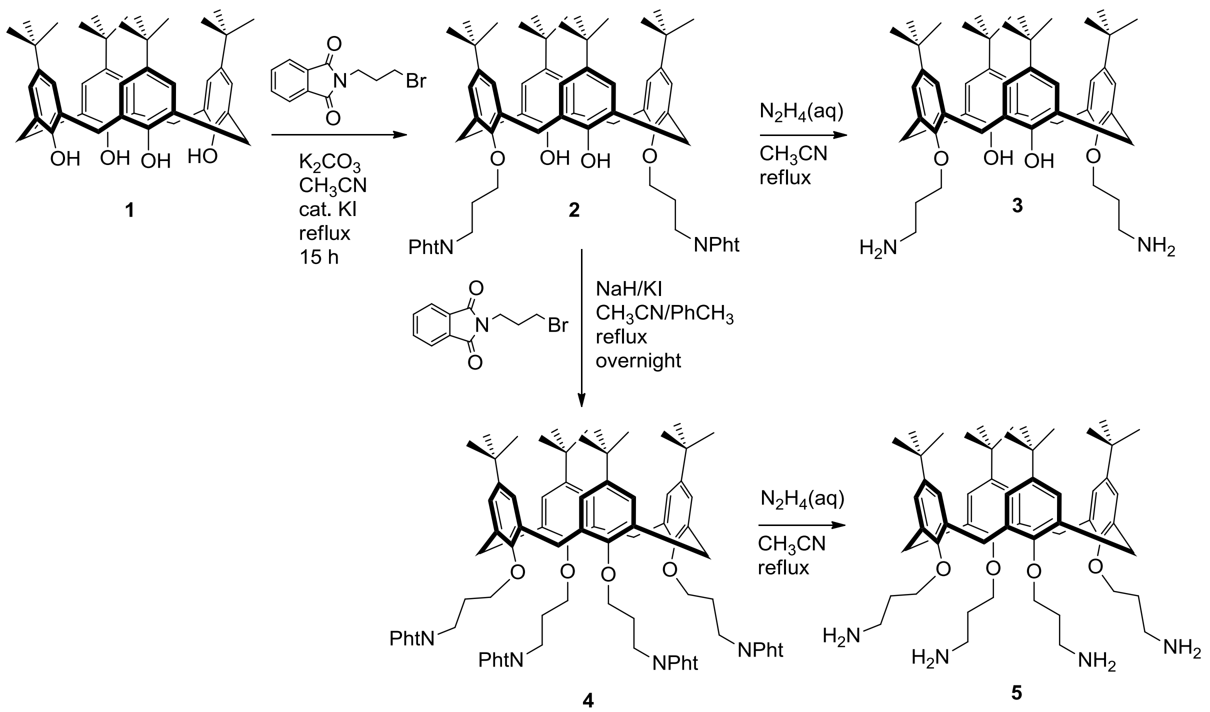
The traditional approach to obtain functionalized calix[4]arenes bearing ionophores focuses on a convergent synthesis strategy that involves the independent synthesis of an ionophore fragment followed by coupling it to the calixarene platform in the final step. However, the convergent strategy is simply not applicable to the synthesis of most of the presented extractants due to incompatibility of the functional groups of the reactants. Bearing various functionalities that are reactive towards both amines and phenols, makes it impossible to achieve the desired selectivity. On the other hand, a divergent synthesis is typically associated with problems such as incomplete reaction and the use of a vast excess of reagents to accomplish full functionalization, that complicate the purification of the final product.

In this chapter the synthesis of novel calix[4]arene-based extractants is reported employing a divergent strategy based on a stepwise build-up of the ionophore groups on the platform. The drawbacks of the divergent synthesis, described above, were mostly overcome by employing (or *in situ* generating) highly reactive alkylating and acylating agents. Special attention is paid to the palladium-catalyzed exhaustive cross-coupling of di- and tetrafunctionalized calix[4]arenes, bearing a chloropyrazine moiety, with diphenylphosphine as a remarkable example of autocatalysis. The extraction behavior and acid resistivity of the new multivalent ligands compared to the corresponding monovalent ones is studied to probe their potential applicability in nuclear waste treatment.

5.2. Results and Discussion

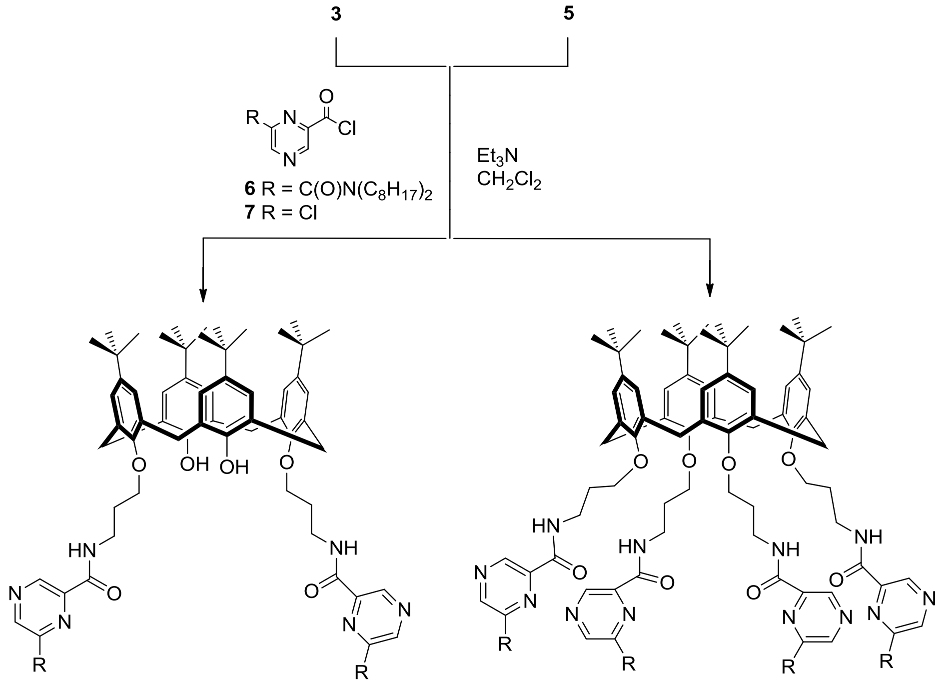
5.2.1. Synthesis

Narrow rim-difunctionalized calix[4]arenes are readily accessible via the standard procedure for selective 1,3-dialkylation of calix[4]arenes, developed in our group previously.[16] Dialkylated calixarene **2** was prepared by reaction of calix[4]arene **1** with bromopropylphthalimide in the presence of K_2CO_3. Interesting to note is that simple addition of a catalytic amount of KI decreased the reported[16] reaction time from 2 days to 15 h and at the same time increased the yield from 54% to almost quantitative. In order to obtain tetraalkylated *p*-*tert*-butylcalix[4]arene **4** in the cone conformation the second dialkylation of calix[4]arene **2** with bromopropylphthalimide was performed in the presence of NaH. Using also in this case Finkelstein conditions by the addition of KI, the reaction time decreased drastically, from 4 days to 20 h, and the yield of the tetraalkylated product **4** increased from 34 to 83%, compared to the procedure reported by Vatsouro *et al.*[17] Following a standard procedure for phthalimide deprotection with hydrazine, 1,3-bis(aminopropyl)-*p*-*tert*-butylcalix[4]arene (**3**) and tetrakis(aminopropyl)-*p*-*tert*-butylcalix[4]arene (**5**) were obtained in 95 and 87% yield, respectively (Scheme 5.1). The spectral characteristics of the obtained compounds were consistent with those reported in literature.[18]



Scheme 5.1. Synthesis of aminoalkylated calix[4]arenes.

The resulting aminopropylcalixarenes **3** and **5** were successfully acylated with 6-(dioctylcarbamoyl)pyrazine-2-carbonyl chloride (**6**) in the presence of 2 equivalents of Et_3N affording bis-diamide **8** and tetrakis-diamide **10** in 65 and 72% yield, respectively (Scheme 5.2). The formation of **8** was established by the appearance of two singlets at 9.38 and 8.90 ppm characteristic for the pyrazine protons, a triplet of the amido hydrogen at 8.13 ppm (J = 6.0 Hz) and a singlet of the phenolic proton at 7.71 ppm in the ^{1}H NMR spectrum. Tetrakis-diamide **10** revealed signals at 9.37, 8.87, and 8.11 ppm in the ^{1}H NMR spectrum corresponding to the two pyrazine and one amido protons, respectively, the only difference being the absence of the phenolic proton signal. The corresponding acylation of **3** and **5** with 6-chloropyrazine-2-carbonyl chloride (**7**) under identical conditions gave calix[4]arenes **9** and **11**, bearing two and four 6-chloropyrazine-2-carboxamide moieties, in 87 and 92% yield, respectively. The ^{1}H NMR spectra of **9** and **11** revealed an identical set of signals as **8** and **10** with a slightly larger difference in the chemical shifts. Thus **9** gave two singlets at 9.21 and 8.61 ppm for the pyrazine protons, a triplet of the amido hydrogen at 8.36 ppm (*J* = 6.0 Hz) and a singlet of the phenolic proton at 7.70 ppm. Compound **11** showed only two pyrazine singlets at 9.33 and 8.65 ppm and an amido triplet at 8.41 ppm (*J* = 6.0 Hz). In addition to the ^{1}H NMR spectra, the formation of **8-11** was confirmed by the respective molecular ion peaks for all products in the electrospray mass spectra. The somewhat lower yield of acylated products in case of the difunctionalized calixarenes may be attributed to the presence of unprotected phenol groups.



8 R = $C(O)N(C_8H_{17})_2$
9 R = Cl

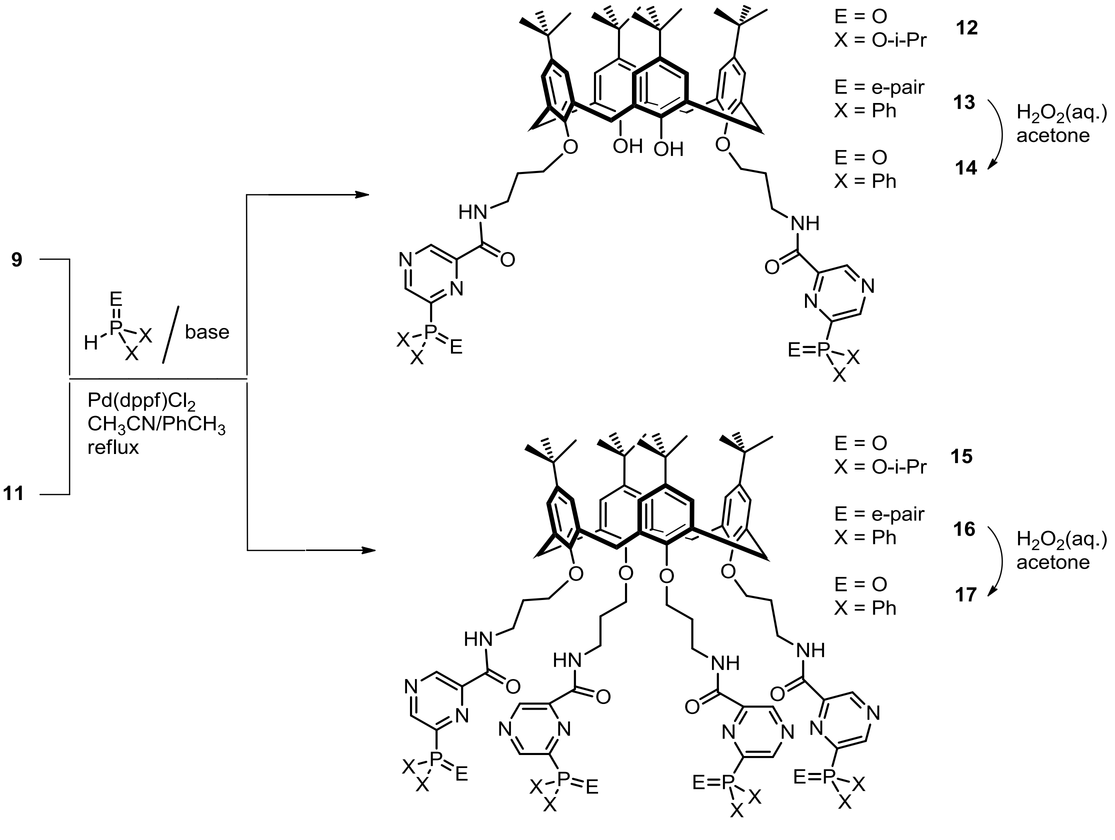
10 R = $C(O)N(C_8H_{17})_2$
11 R = Cl

Scheme 5.2. Acylation of aminopropylcalix[4]arenes **3** and **5**.

The pyrazine-containing calix[4]arenes **9** and **11** were subjected to further functionalization involving palladium-catalyzed coupling with various phosphorus pronucleophiles.

5.2.2. Palladium-catalyzed cross-coupling reactions with chloropyrazine bearing calix[4]arenes

The palladium-catalyzed P-C cross-coupling reaction, described earlier (Chapter 4), was successfully performed on the bis- (**9**) and tetrakis(chloropyrazine)-functionalized calix[4]arenes **11**. To the best of our knowledge it involves the first example of a cross-coupling reaction implemented on calix[4]arenes and presenting a versatile method for the terminal functionalization of platform molecules with multiple reacting sites. Reaction of **9** and **11** with a phosphorus coupling partner in the presence of a suitable base and a catalyst (1 mol% per chloropyrazine moiety) in a refluxing 1:1 mixture of acetonitrile and toluene afforded calix[4]arenes **12**, **13**, **15**, and **16** (Scheme 5.3).



Scheme 5.3. Palladium-catalyzed P-C cross-coupling performed on calixarenes bearing chloropyrazine moieties.

$Pd(dppf)Cl_2$ was selected as the catalyst, since it was previously found to be the best catalyst for the coupling of simple chloropyrazines with dialkylphosphites that provides high yields of coupled products in cases where most of the other palladium phosphine complexes were not successful. Reaction of **9** with 2.2 equivalents of diisopropyl phosphite in the presence of 2.2 equivalents of Huenig base and 2 mol % of $Pd(dppf)Cl_2$ for 72 h afforded calix[4]arene **12** in 79% yield. In the ^1H NMR spectra the signals for the pyrazine protons were shifted from 9.21 and 8.61 ppm in **9** to 9.47 and 9.16 ppm, respectively, in **12**. The peak at 9.47 ppm for the proton adjacent to the phosphonate group was split into a doublet (J = 3.6 Hz) due to phosphorus-hydrogen coupling. The formation of **12** was also confirmed by the correct molecular ion peak in the electrospray mass spectrum. Performing the reaction of **11** under exactly the same conditions with 4.2 equivalents of diisopropyl phosphite in the presence of 4.2 equivalents of Huenig base and 4 mol % of $Pd(dppf)Cl_2$ for 8 days afforded calix[4]arene **15** in 61% yield.[19] The ^1H NMR spectra revealed shifts of the characteristic pyrazine proton peaks from 9.33 and 8.65 ppm of **11** to 9.47 (d, J = 3.5 Hz) and 9.14 ppm, respectively, for **15**. The electrospray mass spectrum of **15** exhibited the molecular ion peak.

Using DBU as a stronger base for the less acidic diphenylphosphine (1.05 equivalents of both per chloropyrazine moiety), and $Pd(OAc)_2$ as a catalyst (1 mol% per chloropyrazine moiety) the coupling reaction of **9** and **11** was accomplished in 30 h giving diphosphine **13** and tetraphosphine **16**. The ^1H NMR spectra showed two resonances for the pyrazine protons at 9.17 and 8.39 ppm for **13**, and at 9.13 and 8.32 ppm for **16**. In these particular cases phosphorus-hydrogen coupling was not observed. Subsequent oxidation of the phosphines **13** and **16** with hydrogen peroxide (1.5 equivalents per diphenylphosphino group) in acetone afforded the corresponding phosphine oxides **14** and **17** in 79 and 71% yield, respectively, calculated on **9** and **11**. In the ^1H NMR spectra the signals for the pyrazine protons of **13** and

16 considerably shifted upon oxidation of the phosphine groups showing resonances at 9.40 (d, *J* = 3.3 Hz) and 9.38 ppm for **14** and 9.29 (d, *J* = 3.0 Hz) and 9.24 ppm for **17**. The electrospray mass spectra exhibited the correct molecular ion peaks for both compounds.

In contrast to simple chloropyrazines, chloropyrazine-bearing calix[4]arenes exhibited a much higher reactivity towards diphenylphosphine than towards diisopropyl phosphite, displaying reaction times of 30 h and 8 days, respectively. Moreover, the yields of the corresponding bis- and tetrakis(diphenylphosphinopyrazine)-bearing calixarenes **13** and **16** were much higher than is expected from statistical probability, which would provide 52% yield at maximum as calculated from the 85% yield of the coupling reaction of non-tethered chloropyrazine carboxamide. In addition, it was found that cross-coupling reactions with diphenylphosphine proceed with the same high rate in the presence of bare $Pd(OAc)_2$ as the catalyst without extra phosphine ligand. This increased reactivity may be attributed to an autocatalytic effect of the partially phosphine-functionalized calix[4]arene, which most probably complexes palladium, bringing the active catalyst into close proximity of the reacting functionality. In such a scenario, the interaction between substrate and the catalytic center is better described as an intramolecular reaction, which is generally much faster than an intermolecular one because of the higher effective molarity, and which becomes possible after the first site has been functionalized.

A series of monovalent pyrazines **18**, **19**, and **20**, mimicking the ligating units of the described calix[4]arenes, was prepared to compare the extraction behavior (Chart 5.1).

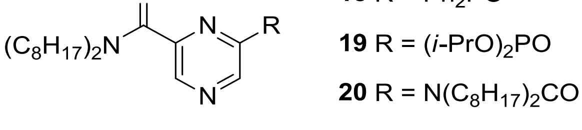
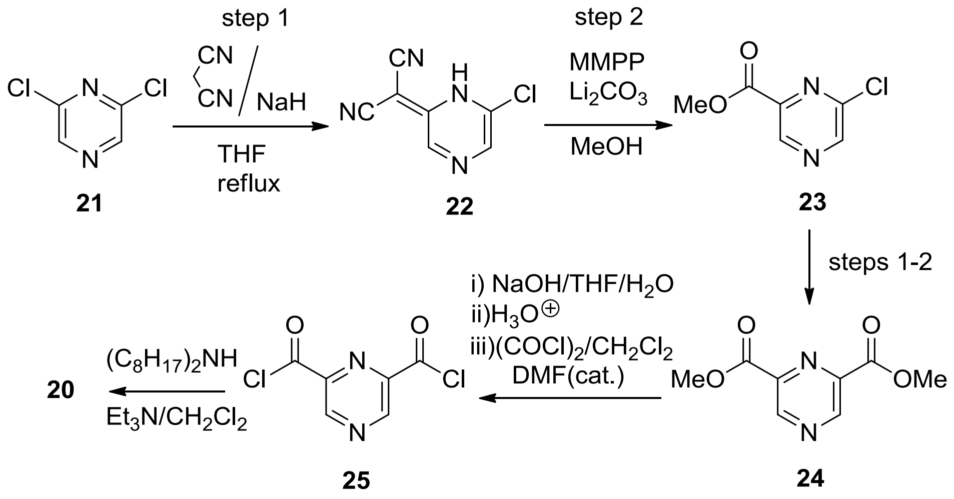


Chart 5.1. Monovalent pyrazines.

The synthesis of pyrazines **18** and **19** has already been described in Chapter 4. However, it was found that the reaction conditions can be simplified. The palladium-catalyzed P-C cross-coupling of simple chloropyrazines with diphenylphosphine can also be catalyzed by $Pd(OAc)_2$ without additional ligand with the same yield as in the presence of the DPPF ligand. This indicates that diphenylphosphine acts as a ligand itself forming the active palladium catalyst *in situ*.

Diamidopyrazine **20** was prepared starting from 2,6-dichloropyrazine (**21**) (Scheme 5.4). Dimethyl pyrazine-2,6-dicarboxylate (24) can be prepared in one step by palladium-catalyzed carbonylative coupling in methanol at 40 atm of CO and 150 ^{o}C.[20] However, to avoid these conditions, a simple stepwise procedure consisting of an aromatic nucleophilic substitution reaction and subsequent mild oxidation[21] of the resulting arylated malononitrile **22** was developed. Treatment of **21** with 2 equivalents of malononitrile in the presence of NaH in THF under reflux conditions, using Colbon's procedure for malonate compounds,[22] gave 2-(6-chloropyrazin-2(1*H*)-ylidene)malononitrile (**22**) in 95% yield. Oxidation of **22** with magnesium monoperoxophthalate (MMPP) as a mild oxidant in the presence of Li_2CO_3 occurred selectively at the malononitrile carbon instead of pyrazine nitrogen with formation of corresponding carbonyl cyanide which was methanolized upon reaction conditions affording methyl 6-chloropyrazine-2-carboxylate (**23**) in 76% yield. Subsequent repetition of the above steps on **23** afforded dimethyl pyrazine-2,6-dicarboxylate (**24**) in 56% yield. The diester **24** was successfully converted into N^2,N^2,N^6,N^6-tetraoctylpyrazine-2,6-dicarboxamide (**20**) via pyrazine-2,6-dicarbonyl dichloride (**25**) in 92% yield. The ^{1}H NMR spectrum of **25** exhibits a singlet at 8.87 ppm for the pyrazine hydrogens and two triplets at 3.28 and 3.49 (J = 9.0 Hz) for the amide methylenes.



Scheme 5.4. Synthesis of diamidopyrazine **20**.

5.2.3. Solvent Extraction

Though *n*-dodecane is widely used for actinide separation studies, the pyrazine-based extractants are not expected to be soluble in non-polar diluents such as *n*-dodecane. Therefore a variety of polar diluents were evaluated for the solubility and extraction studies. The ligands were not freely soluble in many diluents and the results of the solubility study using **17** (in view of its superior extraction properties as compared to the other extractants; *vide infra*) is given in Table 5.1.

Table 5.1. Solubility data of several pyrazine-based ligands.

Diluent	Ligand	Remarks
Nitrobenzene	**8**	Freely soluble
Nitrobenzene	**14**	Freely soluble
Nitrobenzene	**15**	Freely soluble
Nitrobenzene	**17**	Freely soluble
Chloroform	**17**	Freely soluble
PTMS	**17**	Sparingly soluble
1-Decanol	**17**	Sparingly soluble
30% *i*-decanol / *n*-dodecane	**17**	Soluble after 30 min of ultrasonication
n-dodecane	**17**	Insoluble
NPOE	**17**	Soluble

As indicated, the ligand is freely soluble in chloroform and nitrobenzene, while it is sparingly soluble in phenyl trifluoromethyl sulphone (PTMS) and 1-decanol. Though the ligand was insoluble in *n*-dodecane, it was soluble in the diluent in the presence of 30% *iso*-decanol (added to enhance the polarity of the medium) after prolonged ultrasonication. Although the extractant was soluble in 2-nitrophenyloctyl ether (NPOE), emulsion formation during the extraction studies prohibited the further use of this diluent. It is interesting to note that although significant metal ion extraction was observed with phosphoryl derivative **17** of the pyrazine ligands, those with other substituents such as diisopropylphosphonate and dioctylcarbamoyl resulted in poor extraction of both the trivalent lanthanides and actinides (Table 5.2).

Table 5.2. Distribution ratios of Am(III) and Eu(III) for extractions by pyrazine-bearing calix[4]arene ligands **8**, **10**, **12**, **14**, **15**, and **17** and monovalent pyrazine ligands **18**, **19**, and **20** (5.0 mM in nitrobenzene) from aqueous HNO_3.

Ligand	D_{Am}			D_{Eu}		
	0.01 M HNO_3	1 M HNO_3	3 M HNO_3	0.01 M HNO_3	1 M HNO_3	3 M HNO_3
8	0.001	0.001	0.001	0.001	0.001	0.001
10	0.001	0.001	0.001	0.001	0.001	0.001
12	0.09	0.01	0.01	0.06	0.01	0.01
14	0.48	0.03	0.19	0.46	0.03	0.17
15	0.001	0.001	0.05	0.001	0.001	0.03
17	0.06	0.44	13.5	0.06	0.45	14.0
18	0.06	0.01	0.002	0.03	0.002	0.003
19	0.001	0.001	0.001	0.01	0.02	0.006
20	0.01	0.001	0.001	0.12	0.002	0.003

Ligands **18**, **19**, and **20** hardly showed any extraction of the metal ions (Table 5.2). Use of chlorinated cobalt dicarbollide (CCD) as the auxilliary extractant to enable a synergistic effect on metal ion extraction was successful at 0.01 M HNO_3 (Table 5.3) (*vide infra*).

The extraction data presented in Table 5.2 indicate a reasonably high extraction with nitrobenzene as the diluent and moderate extraction with PTMS (commercially known as FS-13), while almost no extraction was seen with the remaining diluents. Surprisingly, both Am(III) as well as Eu(III) extraction decreased substantially to almost zero when the substituent was changed from phosphoryl to either dioctylcarbamoyl (**8**) or diisopropyl phosphonate (**15**) (Table 5.2). It is also interesting to note that even with the pyrazine-bearing calix[4]arenes with two side arms containing phosphoryl groups (**14**), the extraction was significantly higher as compared to the other ligands (Table 5.2).

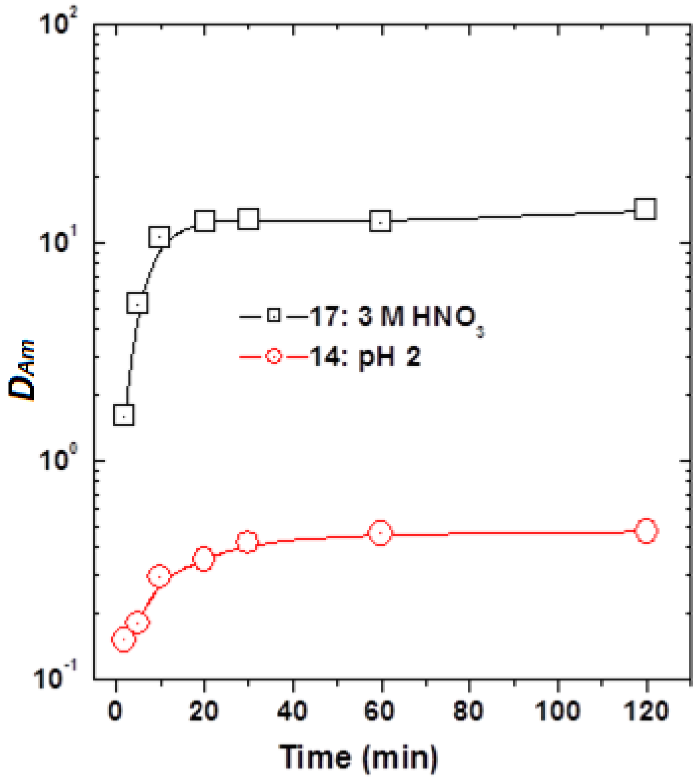


Figure 5.1. Distribution constants for Am(III), D_{Am}, vs. time for the Am(III) extraction using 5.0 mM ligand in nitrobenzene at the given acidity.

Extraction kinetics studies

The effect of the equilibration time on the Am(III) extraction was studied for both **14** and **17**. As will be discussed below, the extraction of Am(III) with **14** was higher at 0.01 M than at 3 M HNO_3 as the feed. Therefore, while 3 M HNO_3 was taken as the aqueous phase for **17**, 0.01 M HNO_3 was used for **14**. As shown in Figure 5.1, the extraction kinetics was relatively slow and about 60 and 20 minutes were required for attaining equilibrium D_{Am} values with **14** and **17**, respectively. The complexation stoichiometry of f-block metal trivalent cations with monovalent tridentate ligands, such as TODGA,[23] typically requires 3 to 4 ligands per metal cation. On the other hand, complexation with divalent calix[4]arenes involves two ligand molecules.[24] Based on these findings a possible conclusion may be that the extraction in case of divalent ligand **14** requires coordination of two ligand molecules, compared to the tetravalent ligand **17** and hence takes more time. However, conformational changes or a difference in extraction mechanism may also play a role. The possible reason has not been investigated further.

Effect of aqueous phase acidity

The effect of aqueous phase acidity was also investigated by carrying out extraction studies with all six pyrazine-bearing calix[4]arene ligands (**8**, **10**, **12**, **14**, **15**, and **17**) at three different acidities viz., 0.01 M, 1 M, and 3 M HNO_3 and the results for Am(III) and Eu(III) extraction are listed in Table 5.2.

As discussed before, the extraction with the phosphoryl-substituted pyrazine-bearing calix[4]arenes resulted in significant extraction at 3 M HNO_3 and the calix[4]arene **14** with two side arms resulted in significantly lower *D* values than calix[4]arene **17** with four side arms. This is understandable, since **17** contains four pendent arms for complexation and consequently has a higher affinity for the metal ion than **14**, which has only two pendent arms. However, it is rather surprising that, although the *D* values of **14** decreased on changing the feed acidity from 3 M to 1 M HNO_3, an increase was observed when the acidity was further decreased to 0.01 M HNO_3 (Table 5.2). This can only be explained by the ion-pair extraction mechanism, by which metal cations are extracted into an organic phase accompanied by anions, and thus, effective extraction is achieved under highly acidic conditions. On the other hand, the higher metal ion extraction at lower acidity may be attributed to a contribution of the phenolic OH groups.

Nature of the extracted species

The nature of the extracted species was studied by carrying out Am(III) as well as Eu(III) extractions at varying concentrations of the extractants **14** and **17** at 0.01 M HNO_3 and 3 M HNO_3, respectively, as the aqueous phase. As shown in Figure 5.2a, linear plots with slope values close to 1 were obtained for both Am(III) as well as Eu(III) extraction, when the concentration of **17** was varied from 5.0×10^{-4} to 5.0×10^{-3} M. These results suggest that 1:1 M:L complexes are formed with possibly three co-extracted nitrate ions acting as the counter anions. In view of the high dielectric constant of nitrobenzene (ε_{20} = 35.7), ion-pair complexed species are expected to be extracted and the following extraction equilibrium can be predicted:

$$M^{3+}_{aq} + L_{org} + 3NO_3^-{}_{aq} \leftrightarrow (ML)^{3+}\cdot(NO_3^-)_{3org} \qquad (1)$$

where M and L represent the metal (Am or Eu) and ligand, respectively, and the subscripts ‘aq’ and ‘org’ refer to the aqueous and the organic phases, respectively.

The ligand concentration variation studies carried out with **14** indeed proved the association of three ligand units in the extracted species (Figure 5.2b). pH variation experiments showed a sharp rise in the extraction profile for Am(III) at lower acidities (*vide supra*).

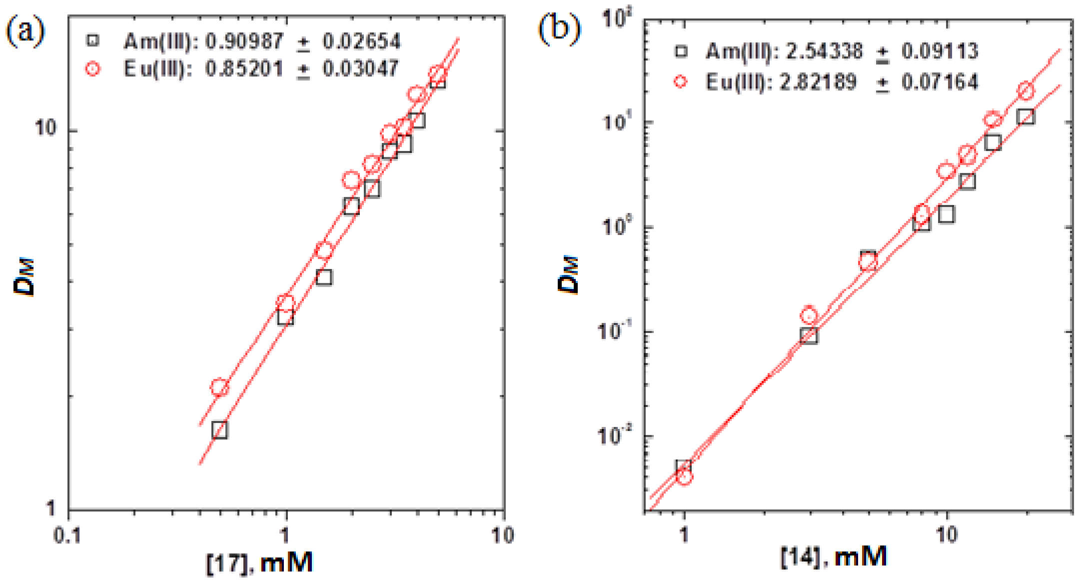


Figure 5.2. Distribution ratios for Am(III) and Eu(III) vs. ligand concentration at the given acidities (a) extractant **17** at 3 M HNO_3 and (b) extractant **14** at 0.01 M HNO_3.

A pH variation experiment using 5.0 mM **14** gave a linear extraction profile with a slope of 2.61±0.13 (Fig. 5.3). This can only be explained by the following extraction equilibrium:

$$M^{3+}_{aq.} + 3HL_{org.} \leftrightarrow (ML_3)_{org.} \quad + 3H^{+}_{aq} \qquad (2)$$

The ligand concentration and pH dependencies on the Am extraction with fractional slope values indicate extraction of 1:3 metal:ligand species with a partial contribution from the 1:2 species.

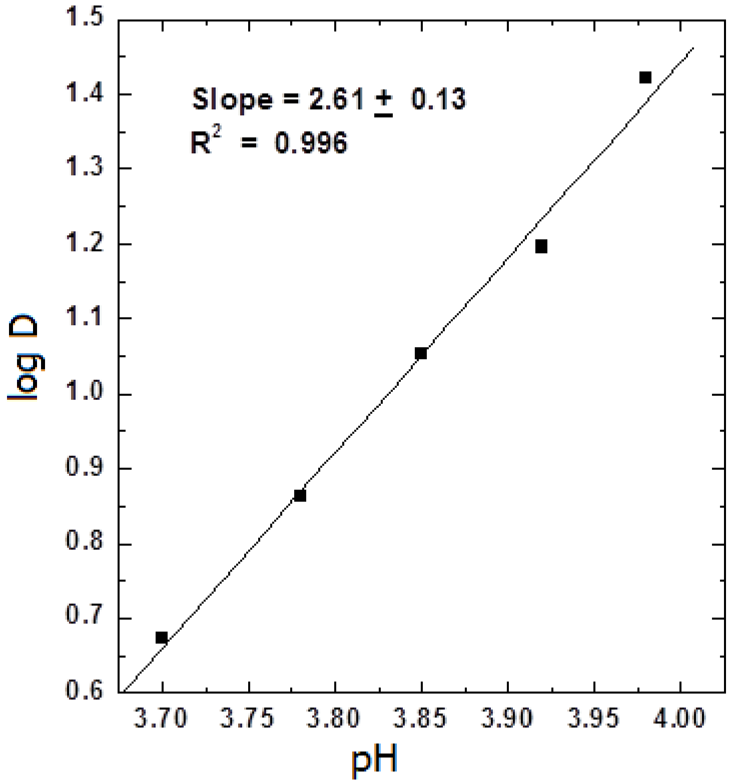


Fig. 5.3. Distribution ratios for Am(III) and Eu(III) vs. aqueous phase pH using 5.0 mM of extractant **14**.

Studies carried out with CCD as the auxiliary ligand

Studies with calixarene-based picolinamide extractants have shown a promising extraction of Am(III) and Eu(III) in the presence of Br-Cosan in nitrophenyl hexyl ether (NPHE) as the diluent.[25] In another recent study,[14] calix[6]arene picolinamide extractants with Br-Cosan in a mixture of NPHE and acetophenone as the diluent resulted in a much higher metal ion extraction, although the separation factor (SF) values have become lower, compared to those in the previous report. The separation factors depended on the Br-Cosan concentration. Similar extraction studies were carried out in the present work in nitrobenzene as the diluent. Solvent extraction studies were carried out using a mixture of the pyrazine-bearing calix[4]arenes **10**, **15**, **17** and monovalent ligands **18**, **19,** and **20** along with chlorinated cobalt dicarbollide (CCD) as the auxiliary ligand. The D_{Am} values obtained with the synergistic extraction system are listed in Table 5.3. The D_{Am} values show a significant enhancement (about 3 times) in the presence of CCD at 3 M HNO_3 with **17** as the primary extractant, while there was no change in the D_{Am} values with both **10** and **15**. On the other hand in all cases, a very high, about 10^4 to 10^5 times, enhancement in the extraction of Am(III) was seen when the experiments were carried out at 0.01 M HNO_3 in the presence of 1.0 mM CCD. The role of the CCD concentration on the metal ion extraction was investigated at 0.1 M HNO_3 and the results for both Am(III) and Eu(III) extraction along with the separation factor values are presented in Figure 5.4. It shows an increasing trend for the extraction of both metal ions with increasing CCD concentration. The *SF* values, however, depend on the nature of the primary extractant. The *SF* values changed marginally with the CCD concentration when **15** was used as the primary extractant (Figure 5.4b). On the other hand, while an increasing trend in *SF* with increasing CCD concentration was seen for **10** (Figure 5.4a), there is an opposite trend when **17** (Figure 5.4c) was used as the primary extractant. The results are in line with those of the calix-picolinamide ligands mentioned above.

Table 5.3. Distribution constants of Am(III), D_{Am}, for extractions using calix-pyrazine-based ligands **10**, **15**, and **17** and monovalent pyrazine ligands **18**, **19**, and **20**, containing 5.0 mM of the extractant in nitrobenzene in the absence or presence (1.0 mM) of CCD.

Ligand	D_{Am} at 3 M HNO_3		D_{Am} at 0.1 M HNO_3		D_{Am} at 0.01 M HNO_3	
	Without CCD	With CCD	Without CCD	With CCD	Without CCD	With CCD
10	0.001	0.002	-	0.5	0.001	360
15	0.05	0.01	-	173	0.001	350
17	13.5	39.8	-	794	0.06	450
18	0.002	0.001			0.06	370
19	0.001	0.001			0.001	335
20	0.001	0.002			0.01	280

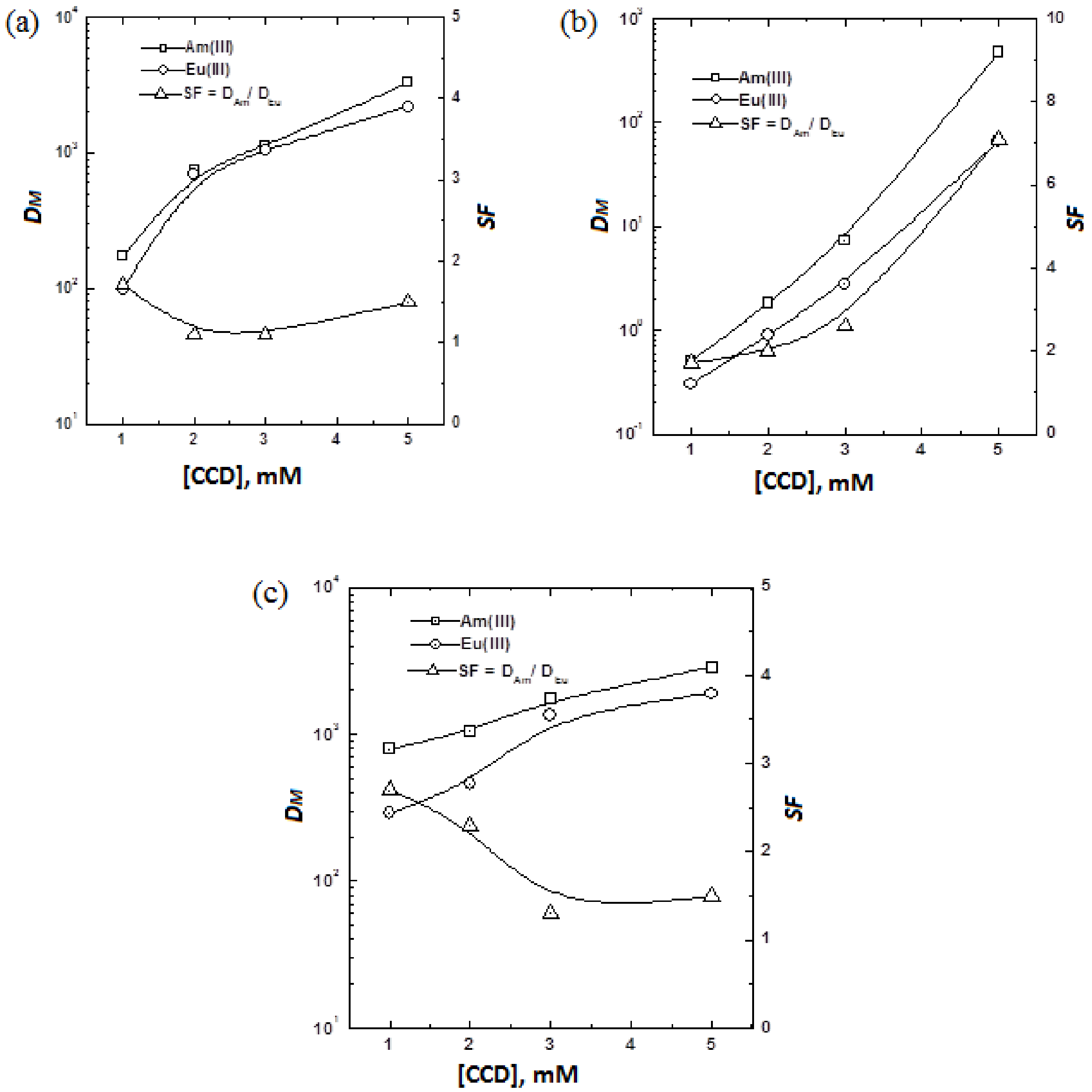


Figure 5.4. Distribution ratios of Am(III), D_{Am}, and Eu(III), D_{Eu}, and separation factors, $SF_{Am/Eu}$, for extractions using 5.0 mM ligand in the presence of CCD; Diluent: nitrobenzene; Aqueous phase: 0.1 M HNO_3; (a) **10**; (b) **15**; (c) **17**.

5.3. Conclusions

An effective and versatile stepwise synthetic strategy has been developed for the preparation of a novel class of multivalent pyrazine-based calix[4]arene extractants, including palladium-catalyzed exhaustive cross-coupling. The reaction rate in the particular case of coupling with $HPPh_2$, being much higher than expected from statistical probability, indicates an autocatalytic effect of the substrate molecule, that is able to coordinate an active catalyst species. The newly synthesized multivalent ligands revealed a very high affinity towards f-block metal ions and a good selectivity for Am(III) with *SF* ~ 10 in the presence of a synergist (CCD), preserving a good extractability even in highly acidic solutions up to 3 M HNO_3 (in case of **17**). In the case of **17** the effect of grouping together the ligating sites on the calix[4]arene platform was reflected in the exceptionally high enhancement of 10^4 to 10^5 times in metal ion extraction, compared to the corresponding monovalent ligands, demonstrating that multivalency is a powerful way of making more potent extractants.

5.4. Experimental Section

The solvents, catalyst, and all reagents were obtained from commercial sources and used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Unity INOVA (300 MHz) spectrometer. ^1H NMR chemical shift values (300 MHz) are reported as δ using the residual solvent signal as an internal standard ($CDCl_3$, $\delta = 7.257$). ^{13}C NMR chemical shift values (75 MHz) are reported as δ using the residual solvent signal as an internal standard ($CDCl_3$, $\delta = 77.0$ ppm). Infrared spectra were taken on a Thermo Scientific spectrometer. Electrospray ionization (positive mode) mass spectra were recorded on a WATERS LCT mass spectrometer. Silicagel-60 (mesh 230-400 ASTM) was used for column chromatography. Calixarenes **8**, **10**, **12**, and **15**, purified by column chromatography, were additionally dried from the residual solvent by azeotropic distillation of CH_2Cl_2 from a solution of a compound.

Bis(3-*N*-phthalimidopropyl)-*p*-*tert*-butylcalix[4]arene (2). (Improved procedure)

To a suspension of *p*-*tert*-butylcalix[4]arene (**1**) (13.0 g, 20 mmol), anhydrous K_2CO_3 (5.6 g, 40 mmol), and *N*-(bromopropyl)phthalimide (12.1 g, 45 mmol) in CH_3CN (500 mL) a small pinch of KI was added and the resulting mixture was refluxed for 15 h. After evaporation of the solvent, the mixture was taken up in $CHCl_3$ (500 mL) and washed with 1 M HCl (2 x 100 mL) and brine (2 x 100 mL). The crude reaction mixture was recrystallized from $CHCl_3$/MeOH to afford pure **2** as a white solid (20.1 g, 98%). The spectral characteristics of the obtained compound were consistent with those reported in literature.[24]

Tetrakis(3-*N*-phthalimidopropyl)-*p*-*tert*-butylcalix[4]arene (4). (Improved procedure)

A suspension of calix[4]arene **2** (10.2 g, 10 mmol) and NaH (60% in oil, 0.9 g, 22 mmol) in dry toluene (200 mL) was stirred for 1 h, and then a solution of *N*-(bromopropyl)phthalimide (5.6 g, 21 mmol) in dry CH_3CN (200 mL) and a small pinch of KI were added to the reaction mixture. The resulting mixture was refluxed for 20 h. After evaporation of the solvent, the mixture was taken up in $CHCl_3$ (200 mL), washed with 1 M HCl (100 mL) and brine (100 mL). The crude reaction mixture was recrystallized from $CHCl_3$/MeOH to afford pure **4** as a white solid (11.6 g, 83%). The spectral characteristics of the obtained compound were consistent with those reported in literature.[18]

Bis(3-(6-dioctylcarbamoylpyrazine-2-carboxamido)propyl)-*p*-*tert*-butylcalix[4]arene (8).

A solution of bis(aminopropyl)calix[4]arene (**3**) (2.3 g, 3 mmol) and Et_3N (1.8 mL, 12 mmol) in CH_2Cl_2 (60 mL) was added dropwise to a solution of 6-dioctylcarbamoylpyrazine-2-carbonyl chloride (**6**; 6 mmol), freshly prepared from 6-dioctylcarbamoylpyrazine-2-

carboxylic acid (2.1 g, 6.0 mmol) and oxalyl chloride, in CH_2Cl_2 (60 mL) at vigorous stirring. The resulting mixture was stirred for 15 h and then all the volatiles were removed in vacuo. The residue was partitioned between H_2O (50 mL) and hexanes (50 mL). The organic phase was dried over Na_2SO_4 and the solution was passed through a short plug of silica and the solvent was removed in vacuo. The crude product was purified by column chromatography ($EtOAc/CHCl_3$, 40:60) affording pure **8** as an amber oil (3.0 g, 65%). Mp 59-62 ^oC. ^1H NMR: δ = 9.38 (s, 2 H, PyzH), 8.90 (s, 2 H, PyzH), 8.13 (t, 2 H, *J* = 6.0 Hz, NH), 7.71 (s, 2 H, ArOH), 7.04 (s, 4 H, ArH), 6.86 (s, 4 H, ArH), 4.25 (d, 4 H, *J* = 12.9 Hz, $ArCH_2Ar$), 4.07 (t, 4 H, *J* = 6.2 Hz, $ArOC\mathit{H}_2CH_2$), 3.96 (q, 4 H, *J* = 6.2 Hz, $CH_2C\mathit{H}_2NH$), 3.40 (t, 4 H, *J* = 7.7 Hz, $NC\mathit{H}_2C_7H_{15}$), 3.32 (d, 4 H, *J* = 12.9 Hz, $ArCH_2Ar$), 3.14 (t, 4 H, *J* = 7.7 Hz, $NC\mathit{H}_2C_7H_{16}$), 2.36 (quintet, 4 H, *J* = 6.2 Hz, $OCH_2C\mathit{H}_2CH_2N$), 1.66 (m, 4 H, octyl), 1.50-0.80 (m, 56 H, octyl), 1.28 and 1.01 (s, 18 H, *t*-Bu). ^{13}C NMR: δ = 165.9, 163.2, 156.6, 149.7, 148.6, 147.5, 142.6, 142.0, 132.9, 127.9, 126.1, 125.9, 125.6, 125.4, 73.4, 46.5, 46.3, 34.3, 34.1, 32.1, 31.9, 31.3, 29.6, 29.5, 29.4, 29.3, 26.8, 22.9, 22.8, 14.4. IR (ν_{max}/cm^{-1}): 2953, 2925, 2855, 1676, 1635, 1522, 1499, 1461, 1362, 1298, 1193, 1167, 1123, 1019, 909, 871, 732, 669. HRMS-TOF (*m/z*): $[M + H]^+$ calcd 1511.0906, found 1511.4041.

Bis(3-(6-chloropyrazine-2-carboxamido)propyl)-*p*-*tert*-butylcalix[4]arene (9).

A solution of bis(aminopropyl)calix[4]arene (**3**) (2.3 g, 3 mmol) and Et_3N (1.8 mL, 12 mmol) in CH_2Cl_2 (60 mL) was added dropwise to a solution of 6-chloropyrazine-2-carbonyl chloride (**7**; 6 mmol), freshly prepared from 6-chloropyrazine-2-carboxylic acid (0.8 g, 6.0 mmol) and oxalyl chloride, in CH_2Cl_2 (60 mL) at vigorous stirring. The resulting mixture was stirred for 2 h and then all the volatiles were removed in vacuo. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4, the solution was passed through a short plug of silica and then all the volatiles were removed in vacuo. The crude product was crystallized from CH_2Cl_2-hexane affording pure **9** (2.8 g, 87%).

Mp 115-120 °C. ^{1}H NMR: δ = 9.21 (s, 2 H, PyzH), 8.61 (s, 2 H, PyzH), 8.36 (t, 2 H, J = 6.0 Hz, NH), 7.70 (s, 2 H, ArOH), 7.01 and 6.80 (s, 4 H, ArH), 4.21 (d, 4 H, J = 12.0 Hz, $ArCH_2Ar$), 4.05 (t, 4 H, J = 6.0 Hz, $ArOCH_2CH_2$), 3.93 (q, 4 H, J = 6.0 Hz, CH_2CH_2NH), 3.30 (d, 4 H, J = 12.0 Hz, $ArCH_2Ar$), 2.39 (quintet, 4 H, J = 6.0 Hz, $OCH_2CH_2CH_2N$), 1.25 and 0.97 (s, 18 H, *t*-Bu). ^{13}C NMR: δ = 162.5, 150.6, 148.6, 147.8, 147.5, 147.4, 144.4, 142.0, 132.9, 129.0, 127.8, 125.9, 125.8, 125.5, 125.3, 34.3, 34.1, 31.9, 31.8, 31.3, 31.2, 31.1. IR (ν_{max}/cm^{-1}): 2954, 2868, 1670, 1521, 1484, 1362, 1298, 1193, 1168, 1124, 1011, 909, 872, 731, 669. HRMS-TOF (*m/z*): [M + H]$^+$ calcd 1044.5002, found 1044.9526.

Tetrakis(3-(6-dioctylcarbamoylpyrazine-2-carboxamido)propyl)-*p-tert*-butyl calix[4]arene (10).

A solution of tetrakis(aminopropyl)calix[4]arene (**3**) (2.6 g, 3 mmol) and Et_3N (3.6 mL, 24 mmol) in CH_2Cl_2 (120 mL) was added dropwise to a solution of 6-dioctylcarbamoylpyrazine-2-carbonyl chloride (**6**; 12 mmol), freshly prepared from 6-dioctylcarbamoylpyrazine-2-carboxylic acid (4.2 g, 12.0 mmol) and oxalyl chloride, in CH_2Cl_2 (120 mL) at vigorous stirring. The resulting mixture was stirred for 15 h and then all the volatiles were removed in vacuo. The residue was partitioned between H_2O (50 mL) and hexanes (50 mL). The organic phase was dried over Na_2SO_4, the solution was passed through a short plug of silica and then all the volatiles were removed in vacuo. The crude product was purified by column chromatography (EtOAc/$CHCl_3$, 40:60) affording pure **10** as an amber oil (5.1 g, 72%). ^{1}H NMR: δ = 9.37 (s, 4 H, PyzH), 8.87 (s, 4 H, PyzH), 8.11 (t, 4 H, J = 5.8 Hz, NH), 6.76 (s, 8 H, ArH), 4.36 (d, 4 H, J = 12.4 Hz, $ArCH_2Ar$), 3.98 (t, 8 H, J = 6.9 Hz, $ArOCH_2CH_2$), 3.67 (q, 8 H, J = 6.9 Hz, CH_2CH_2NH), 3.43 and 3.22 (t, 8 H, J = 7.2 Hz, $NCH_2C_7H_{15}$), 3.13 (d, 4 H, J = 12.4 Hz, $ArCH_2Ar$), 2.35 (quintet, 4 H, J = 6.9 Hz, $OCH_2CH_2CH_2N$), 1.68-0.80 (m, 120 H, octyl), 1.07 (s, 36 H, *t*-Bu). ^{13}C NMR: δ = 166.0, 162.9, 153.4, 148.5, 144.9, 143.0, 133.7, 125.9, 125.4, 125.2, 73.1, 34.0, 32.1, 31.9, 31.6, 29.6, 29.5, 29.4, 29.3, 26.9, 22.9, 22.8, 14.4. IR (ν_{max}/cm^{-1}): 2923, 2854, 1670, 1636, 1522, 1487, 1376, 1362, 1299, 1196, 1167, 1122, 1019, 912, 870, 721, 669. HRMS-TOF (*m/z*): [M + H]$^+$ calcd 2372.7555, found 2372.7666.

Tetrakis(3-(6-chloropyrazine-2-carboxamido)propyl)-*p*-*tert*-butylcalix[4]arene (11).

A solution of tetrakis(aminopropyl)calix[4]arene (**3**) (2.6 g, 3 mmol) and Et_3N (3.6 mL, 24 mmol) in CH_2Cl_2 (120 mL) was added dropwise to a solution of 6-chloropyrazine-2-carbonyl chloride (**7**; 12 mmol), freshly prepared from 6-chloropyrazine-2-carboxylic acid (1.6 g, 12.0 mmol) and oxalyl chloride (2.4 mL) in CH_2Cl_2 (15 mL), in CH_2Cl_2 (120 mL) at vigorous stirring. The resulting mixture was stirred for 15 h and then all the volatiles were removed in vacuo. The residue was partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL) three times. The organic phase was dried over Na_2SO_4, the resulting solution was passed through a short plug of silica and the solvent was removed in vacuo. The crude product was crystallized from CH_2Cl_2-hexane affording pure **11** (4.0 g, 92%). ^{1}H NMR ($CDCl_3$): δ = 9.33 (s, 4 H, PyzH), 8.65 (s, 4 H, PyzH), 8.41 (t, 4 H, *J* = 6.0 Hz, NH), 6.73 (s, 8 H, ArH), 4.31 (d, 4 H, *J* = 12.0 Hz, $ArCH_2Ar$), 3.92 (t, 8 H, *J* = 6.0 Hz, $ArOC\mathit{H_2}CH_2$), 3.68 (q, 8 H, *J* = 6.0 Hz, $CH_2C\mathit{H_2}NH$), 3.14 (d, 4 H, *J* = 12.0 Hz, $ArCH_2Ar$), 2.39 (quintet, 8 H, *J* = 6.0 Hz, $OCH_2C\mathit{H_2}CH_2N$), 1.07 (s, 36 H, *t*-Bu). ^{13}C NMR: δ = 162.4, 162.3, 153.4, 147.8, 147.7, 144.5, 142.5, 142.4, 133.8, 133.7, 133.6, 133.5, 125.4, 125.3, 125.2, 123.0, 73.1, 72.8, 34.1, 31.6. IR (ν_{max}/cm^{-1}): 2954, 2868, 1668, 1533, 1481, 1390, 1362, 1298, 1193, 1168, 1131, 1011, 912, 871, 733, 669. HRMS-TOF (*m/z*): [M + H]$^+$ calcd 1440.5684, found 1440.5892.

General procedure for the palladium-catalyzed P-C coupling of bis- and tetrakis(3-(6-chloropyrazine-2-carboxamido)propyl)-*p*-*tert*-butylcalix[4]arenes with HPO(O-*i*-Pr)$_2$. Formation of 12 and 15.

To a solution of bis- or tetrakis(3-(6-chloropyrazine-2-carboxamido)propyl)calix[4]arene (1 mmol) and Pd(dppf)Cl$_2$ (1 mol % per chloropyrazine moiety) in a CH$_3$CN/toluene (1:1) mixture (50 mL) were subsequently added HPO(O-*i*-Pr)$_2$ (1.1 equiv. per chloropyrazine moiety) and *i*-Pr$_2$NEt (1.1 equiv. per chloropyrazine moiety). The resulting mixture was refluxed for 3 (**12**) and 8 days (**15**), respectively, and then the solvent was removed in vacuo. The residue was partitioned between H$_2$O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na$_2$SO$_4$ and all the volatiles were removed in vacuo to give the crude **12** and **15**. The crude products were purified by column chromatography (neat EtOAc) affording pure compounds as brown oils which solidified upon standing.

Bis(3-(6-(diisopropylphosphono)pyrazine-2-carboxamido)propyl)-*p*-*tert*-butylcalix[4]arene (12): Yield 1.0 g, 79%. ^{1}H NMR: δ = 9.47 (d, 2 H, $^3J_{HP}$ = 3.6 Hz, PyzH), 9.16 (s, 2 H, PyzH), 8.24 (t, 2 H, J = 5.9 Hz, NH), 7.52 (s, 2 H, ArOH), 7.04 (s, 4 H, ArH), 6.84 (s, 4 H, ArH), 4.92-4.79 (m, 4 H, CH(CH$_3$)$_2$), 4.26 (d, 4 H, J = 12.9 Hz, ArCH$_2$Ar), 4.09 (t, 4 H, J = 6.6 Hz, ArOCH_2CH$_2$), 3.94 (q, 4 H, J = 6.6 Hz, CH$_2$CH_2NH), 3.34 (d, 4 H, J = 12.9 Hz, ArCH$_2$Ar), 2.40 (quintet, 4 H, J = 6.6 Hz, OCH$_2$CH_2CH$_2$N), 1.38 and 1.28 (d, 12 H, J = 6.2 Hz, CH(CH_3)$_2$), 1.27 and 0.98 (s, 18 H, *t*-Bu). ^{13}C NMR: δ = 162.9, 153.3, 147.3, 146.2, 133.4, 132.9, 127.9, 123.0, 122.0, 73.5-72.0 (multiplet), 34.2, 32.0, 31.9, 31.3, 31.2, 24.5-23.8 (multiplet). IR (ν_{max}/cm^{-1}): 2962, 1671, 1541, 1485, 1387, 1376, 1362, 1298, 1249, 1197, 1124, 1102, 990, 910, 872, 731, 669. HRMS-TOF (*m/z*): [M + Na]$^+$ calcd 1326.6806, found 1326.6843.

Tetrakis(3-(6-(diisopropylphosphono)pyrazine-2-carboxamido)propyl)-*p-tert*-butylcalix[4]arene (15): Yield 1.2 g, 61%. ^{1}H NMR: δ = 9.47 (d, 4 H, $^3J_{HP}$ = 3.5 Hz, PyzH), 9.14 (s, 4 H, PyzH), 8.26 (t, 4 H, J = 6.0 Hz, NH), 6.75 (s, 8 H, ArH), 4.92-4.80 (m, 8 H, $CH(CH_3)_2$), 4.36 (d, 4 H, J = 12.4 Hz, $ArCH_2Ar$), 3.98 (t, 8 H, J = 7.2 Hz, $ArOCH_2CH_2$), 3.71 (q, 8 H, J = 7.2 Hz, CH_2CH_2NH), 3.13 (d, 4 H, J = 12.4 Hz, $ArCH_2Ar$), 2.36 (quintet, 8 H, J = 7.2 Hz, $OCH_2CH_2CH_2N$), 1.37 and 1.28 (d, 24 H, J = 6.1 Hz, $CH(CH_3)_2$), 1.06 (s, 36 H, *t*-Bu). ^{13}C NMR: δ = 162.6, 153.5, 153.4, 148.3, 144.9, 144.7, 144.5, 133.7, 133.6, 125.4, 125.2, 123.0, 73.0-72.3 (multiplet), 37.4, 34.0, 31.8, 31.4, 31.2, 30.7, 30.6, 24.6-23.5 (multiplet). IR (ν_{max}/cm^{-1}): 2963, 1670, 1541, 1485, 1387, 1362, 1299, 1250, 1198, 1136, 1123, 1103, 989, 730, 669. HRMS-TOF (*m/z*): $[M + 2H]^{2+}$ calcd 979.4864, found 979.5500.

General procedure for the palladium catalyzed P-C coupling of bis- and tetrakis(3-(6-chloropyrazine-2-carboxamido)propyl)calix[4]arenes with $HPPh_2$. Formation of 13 and 16.

To a solution of bis- or tetrakis(3-(6-chloropyrazine-2-carboxamido)propyl)calix[4]arene (1 mmol) and $Pd(OAc)_2$ (1 mol % per chloropyrazine moiety) in a CH_3CN/toluene (1:1) mixture (50 mL) were subsequently added $HPPh_2$ (1 equiv. per chloropyrazine moiety) and DBU (1 equiv. per chloropyrazine moiety). The resulting mixture was refluxed for 30 h and then the solvent was removed in vacuo. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and all the volatiles were removed in vacuo. The resulting crude phosphines **13** and **16** were fully characterized as their phosphine oxides **14** and **17**, respectively.

Bis(3-(6-(diphenylphosphino)pyrazine-2-carboxamido)propyl)-*p-tert*-butylcalix[4]arene (13): ^{1}H NMR: δ = 9.17 (s, 2 H, PyzH), 8.39 (s, 2 H, PyzH), 8.08 (t, 2 H, J = 6.0 Hz, NH), 7.80 (s, 2 H, ArOH), 7.39-7.22 (m, 20 H, Ph), 7.01 and 6.88 (s, 4 H, ArH), 4.15 (d, 4 H, J = 12.0 Hz, $ArCH_2Ar$), 3.92 (t, 4 H, J = 6.0 Hz, $ArOCH_2CH_2$), 3.80 (q, 4 H, J = 6.0 Hz, CH_2CH_2NH), 3.21 (d, 4 H, J = 12.0 Hz, $ArCH_2Ar$), 2.22 (quintet, 4 H, J = 6.0 Hz, $OCH_2CH_2CH_2N$), 1.23 and 1.04 (s, 18 H, *t*-Bu).

Tetrakis(3-(6-(diphenylphosphino)pyrazine-2-carboxamido)propyl)-*p*-*tert*-butylcalix[4]arene (16): ^{1}H NMR: δ = 9.13 (s, 4 H, PyzH), 8.32 (s, 4 H, PyzH), 8.05 (t, 4 H, J = 6.0 Hz, NH), 7.40-7.15 (m, 40 H, Ph), 6.73 (s, 8 H, ArH), 4.21 (d, 4 H, J = 12.0 Hz, $ArCH_2Ar$), 3.79 (t, 8 H, J = 6.0 Hz, $ArOCH_2CH_2$), 3.48 (q, 8 H, J = 6.0 Hz, CH_2CH_2NH), 3.05 (d, 4 H, J = 12.0 Hz, $ArCH_2Ar$), 1.99 (quintet, 8 H, J = 6.0 Hz, $OCH_2CH_2CH_2N$), 1.07 (s, 36 H, *t*-Bu).

Oxidation of phosphines 13 and 16. Formation of 14 and 17.

A solution of the crude phosphine and H_2O_2 (30% aqueous, 1.5 equiv., per PPh_2 group) in acetone (25 mL) was stirred for 12 h and then 1 M HCl (10 mL) was added. After stirring the reaction mixture for 30 min all the volatiles were removed in vacuo and the residue was partitioned between H_2O (30 mL) and $CHCl_3$ (30 mL). The organic phase was dried over Na_2SO_4, giving the corresponding phosphine oxides after evaporation of the solvent as yellow oils. The crude products were purified by numerous crystallizations from CH_2Cl_2-hexane affording the desired compounds as pale yellow powders.

Bis(3-(6-(diphenylphosphoryl)pyrazine-2-carboxamido)propyl)-*p*-*tert*-butylcalix[4]arene (14): Total yield (based on **9**) 1.1 g, 79%. Mp 63-66 ^{o}C. ^{1}H NMR: δ = 9.40 (d, 2 H, $^3J_{HP}$ = 3.3 Hz, PyzH), 9.38 (d, 2 H, $^5J_{HP}$ = 1.2 Hz, PyzH), 7.83 (t, 2 H, J = 6.1 Hz, NH), 7.80-7.70 (m, 8 H, Ph), 7.52-7.30 (m, 14 H, Ph + ArOH), 6.98 (s, 4 H, ArH), 6.80 (s, 4 H, ArH), 4.15 (d, 4 H, J = 12.8 Hz, $ArCH_2Ar$), 3.97 (t, 4 H, J = 6.1 Hz, $ArOCH_2CH_2$), 3.86 (q, 4 H, J = 6.1 Hz, CH_2CH_2NH), 3.18 (d, 4 H, J = 12.8 Hz, $ArCH_2Ar$), 2.27 (quintet, 4 H, J = 6.1 Hz, $OCH_2CH_2CH_2N$), 1.25 and 0.99 (s, 18 H, *t*-Bu). ^{13}C NMR: δ = 162.6, 150.6, 149.6, 149.1, 147.5, 146.0, 144.5, 144.3, 142.0, 133.0, 132.9, 132.8, 132.3, 131.4, 129.9, 129.1, 128.9, 128.8, 128.7, 127.7, 126.0, 125.8, 125.5, 125.4, 34.3, 34.1, 31.9, 31.3. IR (ν_{max}/cm^{-1}): 2955, 1677, 1522, 1485, 1437, 1393, 1362, 1298, 1178, 1120, 1099, 1016, 908, 873, 731, 696, 669. HRMS-TOF (*m/z*): $[M + H]^+$ calcd 1375.6530, found 1375.6530.

Tetrakis(3-(6-(diphenylphosphoryl)pyrazine-2-carboxamido)propyl)-*p*-*tert*-butyl-calix[4]arene (17): Total yield (based on **11**) 1.5 g, 71%. Mp 70 ^{o}C (dec). ^{1}H NMR: δ = 9.29 (d, 4 H, $^3J_{HP}$ = 3.0 Hz, PyzH), 9.24 (s, 4 H, PyzH), 7.95 (t, 4 H, J = 6.1 Hz, NH), 7.82-7.66 (m, 16 H, Ph), 7.53-7.30 (m, 24 H, Ph), 6.76 (s, 8 H, ArH), 4.25 (d, 4 H, J = 8.3 Hz, $ArCH_2Ar$), 3.83 (t, 8 H, J = 6.0 Hz, $ArOCH_2CH_2$), 3.52 (q, 8 H, J = 6.0 Hz, CH_2CH_2NH), 3.05 (d, 4 H, J = 8.3 Hz, $ArCH_2Ar$), 2.19 (quintet, 8 H, J = 6.0 Hz, $OCH_2CH_2CH_2N$), 1.07 (s, 36 H, *t*-Bu). ^{13}C NMR: δ = 162.5, 153.3, 149.1, 145.1, 144.8, 144.6, 133.7, 133.1, 133.0, 132.9, 132.8, 132.7, 132.6, 132.5, 132.3, 131.2, 129.8, 129.2, 129.1, 129.0, 128.7, 125.4, 125.3, 34.1, 31.6. IR (ν_{max}/cm^{-1}): 2960, 1669, 1527, 1481, 1437, 1392, 1362, 1299, 1247, 1178, 1120, 1100, 1016, 909, 871, 730, 693, 669. HRMS-TOF (*m/z*): $[M + H]^+$ calcd 2101.8803, found 2101.0251.

Synthesis of pyrazine-based ligands 18 and 19.

The synthesis of ligands **18** and **19** is described elsewhere. However, a slight modification was applied for compound 18, for which the coupling with $HPPh_2$ was performed under $Pd(OAc)_2$ catalysis without the introduction of an extra ligand to the reaction mixture.

2-(6-Chloropyrazin-2(1*H*)-ylidene)malononitrile (22)[26]

To a solution of malononitrile (5.3 g, 80 mmol) in dry THF (500 mL) NaH (50% oil suspension, 1.6 g) was added in small portions. After stirring the mixture for 30 min a solution of **21** (6.0 g, 40 mmol) in dry THF (100 mL) was added dropwise. The resulting mixture was refluxed for 20 h and then acidified with HCl (1 M, 90 mL). The organic phase was separated and all the volatiles were removed in vacuo. The residue was partitioned between H_2O (150 mL) and Et_2O (150 mL) to wash away all the inorganic salts and excess of malononitrile, yielding 6.8 g (95%) of **22** as dark red crystalline material. Mp 180 ^oC (dec). ^1H NMR (CD_3SOCD_3): $\delta = 7.80$ (s, 1 H), 7.57 (s, 1 H). ^{13}C NMR: $\delta = 163.2$, 155.3, 132.4, 110.6, 100.8, 58.6, 56.4. IR (ν_{max}/cm^{-1}): 1697, 1647, 1445, 1369, 1235.

Methyl 6-chloropyrazine-2-carboxylate (23)

To a solution of **22** (6.8 g, 38 mmol) in MeOH (400 mL) was added Li_2CO_3 (4.2 g, 57 mmol). After stirring the mixture for 30 min magnesium monoperoxyphthalate hexahydrate (80% tech., 17.6 g, 28.5 mmol) was added at 0 ^oC in small portions. The resulting mixture was stirred for 3 h and then filtered. The filtrate was dried in vacuo and the residue was partitioned between H_2O (150 mL) and $CHCl_3$ (150 mL). The organic phase was dried over Na_2SO_4, filtered through a short plug of silica and all the volatiles were removed in vacuo to give **23** as a pale yellow oil that crystallized upon standing. Yield 5.0 g, 76%. The spectral characteristics of the obtained compound were consistent with those reported in literature.[27]

Subsequently, repeating two synthetic procedures, described above, on methyl 6-chloropyrazine-2-carboxylate (**23**), the diester **24** was obtained. The spectral characteristics of the obtained compound were consistent with those reported in literature.[20]

N^2,N^2,N^6,N^6-tetraoctylpyrazine-2,6-dicarboxamide (20)

To a solution of **24** (2.0 g, 10 mmol) in THF (50 mL) an aqueous solution of NaOH (2 M, 10 mL) was added. After stirring for 1 h the resulting mixture was acidified with aqueous HCl (1 M, 21 mL) and all the volatiles were removed in vacuo. The residue was dissolved in acetone (100 mL), dried over Na_2SO_4 and all the volatiles were removed in vacuo to give pyrazine-2,6-dicarboxylic acid as white crystalline material in quantitative yield. Subsequently, it was converted into pyrazine-2,6-dicarbonyl dichloride (**25**) by stirring it with an excess of oxalyl chloride (3.6 equiv., 36 mmol, 3 mL) in CH_2Cl_2 (100 mL) in the presence of a catalytical amount of DMF. After the complete dissolution of the crystalline material in CH_2Cl_2, the solvent was distilled off from the reaction mixture and the residue was dried under high vacuum to remove the residual oxalyl chloride from the crude product. The crude **25** was dissolved in CH_2Cl_2 (100 mL) and the resulting solution was added dropwise to a mixture of $(C_8H_{17})_2NH$ (6 mL, 20 mmol) and Et_3N (6 mL, 40 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred for 2 h and then washed with H_2O (2 x 50 mL). The organic phase was dried over Na_2SO_4, filtered through a short plug of silica and all the volatiles were removed in vacuo to give **20** as a yellow oil. Yield 5.7 g, 92%. ^{1}H NMR: δ = 8.87 (s, 2 H, PyzH), 3.49 and 3.28 (t, 4 H, J = 9.0 Hz, $NCH_2C_7H_{15}$), 1.75-0.75 (m, 60 H, octyl). ^{13}C NMR: δ = 162.7, 148.6, 145.9, 32.0, 31.9, 29.6, 29.5, 29.4, 29.3, 29.0, 27.3, 26.5, 23.0, 22.6, 21.3, 14.1. IR (ν_{max}/cm^{-1}): 2924, 2855, 1636, 1454, 669. HRMS-TOF (*m/z*): $[M + H]^+$ calcd 615.5577, found 615.5585.

Reagents and radiotracers

n-Dodecane (Lancaster, UK), nitrobenzene (Fluka, Switzerland), chloroform (Merck, Germany), 1-decanol (Merck, Germany), isodecanol (Merck, Germany), 2-nitrophenyloctyl ether (Fluka, Switzerland) were used as received, while PTMS was prepared as reported earlier.[28] CCD was obtained from Katchem, Czech Republic and was converted to the H^+-form as reported previously.[28] While suprapur nitric acid (Merck, Germany) was used for making dilute acid solutions for the extraction experiments, all the other reagents were of AR grade. A laboratory stock solution of ^{241}Am tracer was used after freshly purifying, following a reported procedure and its purity was checked by both gamma as well as alpha spectrometric analysis.[29] ^{152,154}Eu was purchased from the Board of Radiation & Isotope Technology, India and its radiochemical purity was checked by gamma spectrometry using a HPGe detector coupled to a multi-channel analyzer. Radiometric assay of ^{241}Am and ^{152,154}Eu was done by gamma counting using a NaI(Tl) scintillation detector (Para Electronics, India).

Solvent extraction studies

Usually, 5.0 mM solutions of the ligands were prepared in the respective diluents, which were subsequently used for the solvent extraction studies. Pyrex glass tubes containing aqueous phases (usually 1 mL) containing the desired nitric acid concentration and spiked with the required radiotracers (concentration of metal ion in the range of $1.0\text{x}10^{-6}$ to $1.0\text{x}10^{-7}$ M) were equilibrated with equal volumes of the ligand solutions in a rotary thermostated water bath for an hour at 25.0±0.1 ^{o}C. The tubes were subsequently centrifuged and assayed radiometrically by taking suitable aliquots from both the phases and measuring the radioactivity by gamma ray counting using a NaI(Tl) scintillation counter interphased with a multi-channel analyzer. The distribution ratio (D) is defined as the ratio of the concentration of a metal ion in the organic phase to that in the aqueous phase. pH measurements of the aqueous phases were carried out using a pH meter (Lab India, Mumbai), which was freshly calibrated using commercial buffer solutions (Merck). The pH measurement of the aqueous phases of the two-phase systems was carried out after equilibration and after carefully removing the organic phases. The extraction experiments were carried out in triplicate and the reproducibility of the mass balance was within $\underline{+}$5%.

5.5. References and Notes

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Chapter 6

Hydrophilic Pyrazine-based Phosphine Ligands: Synthesis and Application in Asymmetric Hydride Transfer and H_2-Hydrogenation of Acetophenone

*A series of pyrazine-based hydrophilic phosphines was prepared by a straightforward two-step procedure. The activity of these ligands was tested for the ruthenium and rhodium-catalyzed hydrogenations of acetophenone under hydride transfer and dihydrogen conditions. The effect of alcohol additives on the catalytic, enantioselective aqueous hydrogenation of acetophenone was examined with the newly developed (*R,R*)-DAMPYPHOS as a ligand and* $Rh_2(norbornadiene)_2Cl_2$ *as the catalyst precursor. A significant increase in conversion, from 73 to 100%, was observed when 1 equiv. of isopropanol was present, but more importantly, the enantiomeric excess of the reaction product 1-phenylethanol increased from 75% to 95%, both effects being attributed to alcohol coordination to the catalytically active rhodium species.*

6.1. Introduction

The design and development of novel catalysts that can operate in aqueous medium is of high importance, since water is the most ecologically benign solvent for chemical reactions and transition metal-catalyzed processes. In addition, water offers many other advantages such as nontoxicity, nonflammability and in many cases ease of product separation or catalyst recovery from the reaction mixture.

The most frequently used methods for ketone reduction are transfer hydrogenation[1,2] from a hydrogen donor molecule, usually isopropanol, and direct H_2-hydrogenation.[3,4,5] Common catalysts, employed by the former method involve a vast variety of Ru, Rh, and Ir complexes with polydentate phosphines and amines.[6,7] However, despite excellent enantioselectivities, outstanding yields, and robustness given by these catalytic systems under hydride-transfer conditions, the direct H_2-hydrogenation is generally preferred by industry.

H_2-hydrogenation was one of the first transition metal-catalyzed processes studied in aqueous medium and continues to attract interest.[8,9] Sulfonated triarylphosphines were reported for alkene hydrogenation in aqueous biphasic systems,[10,11,12] however, generally revealing modest or low activities. The ionic character of these ligands, responsible for the excellent water-solubility, quite often imposes some limitations on the substrate scope, making the catalytic reaction predominantly heterogeneous with non-polar substrates and hence considerably decreasing the catalyst activity and efficiency. Another drawback of water-soluble phosphines containing anionic or cationic substituents such as $-SO_3^-$ or $-NR_3^+$, is their high pH sensitivity.[13] An additional disadvantage of ionic group-bearing phosphines is a high charge accumulation in the coordination sphere of the metal complex that leads to significant Coulombic interligand repulsion and lower stability of the catalyst.[14,15]

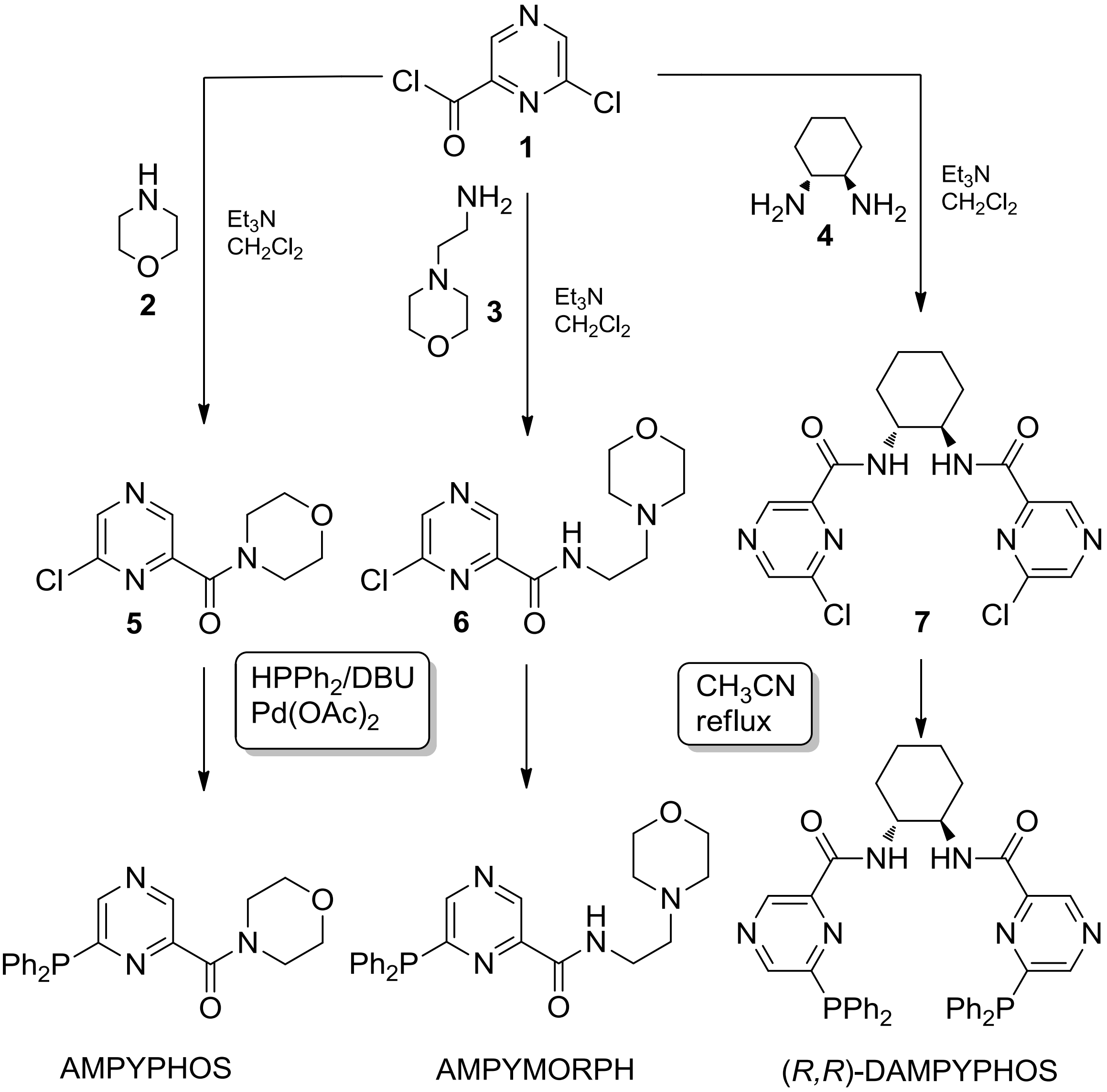
On the other hand, one of the major challenges in aqueous-biphasic catalysis is to bring into interaction the water-soluble catalyst and other reagents with the hydrophobic substrate. For polar molecules, slightly soluble in water, the reaction can occur in the aqueous bulk, however, as the substrate becomes less soluble in water, the rate of the reaction decreases due to the lower concentration of the substrate in the aqueous phase. This problem can be solved by the use of either water-miscible organic cosolvents[16,17] or phase transfer agents.[18,19] These approaches can improve the reaction rates, but may also complicate the phase separation at the end of the reaction. Therefore, the design of ligands, resulting in a catalyst capable of operating in both phases, that needs no cosolvent or surfactant, is very important. Remarkable examples of asymmetric hydrogenation of various acrylic acid derivatives in aqueous medium using carbohydrate-backboned phosphines with about 100% conversions and ee's >99% were reported independently by several groups.[20,21,22,23] However, these ligands are of a limited practical use in asymmetric catalysis because of their high air sensitivity and ability to produce only single enantiomer inherent to the naturally occurring chirality of the carbohydrate backbone. Conversely, to achieve such high enantioselectivities in ketone hydrogenation is much more difficult due to the poor donor ability of the carbonyl group and the lack of additional anchoring sites.[24]

The electron-attracting pyrazine backbone affects the electronic properties of a phosphine-containing ligand, enhancing its π-acceptor properties,[25] as well as impacting the catalytic activity.[26,27] The operational convenience, due to the air stability of such ligands, is another property potentially useful for various asymmetric catalyses.[28] These properties have motivated us to design and prepare *neutral, hydrophilic* pyrazine-containing ligands. This chapter describes a simple and versatile synthesis of three novel hydrophilic non-ionic phosphine ligands with a pyrazine backbone, named AMPYPHOS, AMPYMORPH, and DAMPYPHOS.[29] The successful application of these ligands in the hydride-transfer and aqueous biphasic H_2-hydrogenation of acetophenone, as a model substrate, using 1 M NaOH as an aqueous and substrate ketone as an organic phase *in the absence of a phase transfer agent* is reported.

6.2. Results and Discussion

6.2.1. Ligand Synthesis

In Chapter 4 a facile and high-yielding method for the introduction of phosphorus-containing functional groups onto pyrazine scaffolds was presented. In particular, it was found that phosphinopyrazines are readily accessible via a palladium-catalyzed P-C cross-coupling reaction of various chloropyrazines with secondary phosphines in excellent yields. The novel phosphinopyrazines, AMPYPHOS, AMPYMORPH, and (*R*,*R*)-DAMPYPHOS, were prepared in two steps starting from simple amines, employing this methodology. Thus starting amines **2**, **3**, and **4** were quantitatively acylated with a stoichiometric amount of 6-chloropyrazine-2-carbonyl chloride (**1**) in the presence of 2 equiv. of triethylamine in dichloromethane to give amides **5**, **6**, and **7**, respectively, bearing a 6-chloropyrazine moiety. The resulting amides **5**, **6**, and **7** were subjected to palladium-catalyzed P-C cross-coupling with diphenylphosphine to afford AMPYPHOS, AMPYMORPH, and (*R*,*R*)-DAMPYPHOS, respectively, as oily or waxy air-stable materials, in over 90% yields (Scheme 6.1). The cross-coupling of the chloropyrazines was performed by reaction of the corresponding amide with diphenylphosphine in the presence of DBU and 1 mol % of $Pd(OAc)_2$ in refluxing acetonitrile for 20 h. $Pd(OAc)_2$ was the catalyst of choice, since it was previously found to catalyze the cross-coupling of chloropyrazines with diphenylphosphine under ligandless conditions giving coupled products in high yields (Chapter 5).

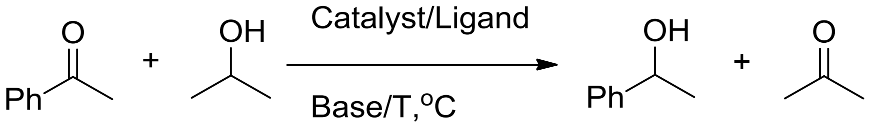


Scheme 6.1. Synthesis of pyrazine-based phosphines: AMPYPHOS, AMPYMORPH, and (*R*,*R*)-DAMPYPHOS.

In the ^{1}H NMR spectra the signal for the pyrazine proton, adjacent to the chlorine, at 8.66 ppm in **5** was shifted to 8.43 ppm in AMPYPHOS. The formation of AMPYMORPH and (*R*,*R*)-DAMPYPHOS was also confirmed by the shift of the characteristic pyrazine proton singlets from 9.22 and 8.69 in **6** and 9.18 and 8.70 in **7** to 9.15 and 8.38 in AMPYMORPH and 8.92 and 8.39 in (*R*,*R*)-DAMPYPHOS, respectively. All the above phosphines revealed distinct signals at -7.42, -8.06, and -8.02 ppm in the ^{31}P NMR spectra for AMPYPHOS, AMPYMORPH, and DAMPYPHOS, respectively. In addition, all the compounds exhibited the respective molecular ion peaks in the electrospray mass spectra.

6.2.2. Catalytic activity

To evaluate the most active catalytic system with $Ru(PPh_3)_3Cl_2$ and $Rh_2(norbornadiene)_2Cl_2$ ($Rh_2nbd_2Cl_2$) as catalyst precursors, using acetophenone as the model substrate, an initial study was performed under transfer hydrogenation conditions in isopropanol in the presence as well as absence of a base with the non-chiral ligands AMPYPHOS and AMPYMORPH (Equation 1). The results are summarized in Table 6.1.



(1)

In the absence of a base none of the catalytic systems revealed any considerable activity (Table 6.1, runs 1-4). On the other hand, the addition of 10 mol% of a base efficiently promoted the catalysis showing an increase of conversion upon increasing base strength. Adding Cs_2CO_3 to the reaction mixture resulted into ~20% conversion (Table 6.1, run 5). The effect of a base was even more pronounced for DBU giving 70% conversion (Table 6.1, run 7), reaching its maximum for *i*-PrONa with 85% and 100% conversions for Ru and Rh catalysts, respectively (Table 6.1, runs 9 and 11). Thus the best system for ketone transfer hydrogenation was found to be $Rh_2nbd_2Cl_2$/AMPYPHOS in the presence of *i*-PrONa. These conditions were used for the asymmetric transfer hydrogenation of acetophenone with $Rh_2nbd_2Cl_2$ in the presence of chiral (*R*,*R*)-DAMPYPHOS (Table 6.1, runs 13 and 16).

Table 6.1. Transfer hydrogenation of acetophenone in isopropanol in the presence of 1 mol % of $Ru(PPh_3)_3Cl_2$ or 0.5% of $Rh_2nbd_2Cl_2$ as a catalyst precursor and 2% or 1% of monodentate or bidentate ligand, respectively, for 15 h.

Run	Catalyst precursor	Ligand	Base	T, °C	Conversion, % (ee, %)
1	$Ru(PPh_3)_3Cl_2$	AMPYPHOS	none	reflux	<2
2	$Ru(PPh_3)_3Cl_2$	AMPYMORPH	none	reflux	<2
3	$Rh_2nbd_2Cl_2$	AMPYPHOS	none	reflux	5
4	$Rh_2nbd_2Cl_2$	AMPYMORPH	none	reflux	<2
5	$Ru(PPh_3)_3Cl_2$	AMPYPHOS	Cs_2CO_3 (10%)	reflux	20
6	$Ru(PPh_3)_3Cl_2$	AMPYMORPH	Cs_2CO_3 (10%)	reflux	15
7	$Ru(PPh_3)_3Cl_2$	AMPYPHOS	DBU (10%)	reflux	70
8	$Ru(PPh_3)_3Cl_2$	AMPYMORPH	DBU (10%)	reflux	57
9	$Ru(PPh_3)_3Cl_2$	AMPYPHOS	*i*-PrONa (10%)	reflux	85
10	$Ru(PPh_3)_3Cl_2$	AMPYMORPH	*i*-PrONa (10%)	reflux	0
11	$Rh_2nbd_2Cl_2$	AMPYPHOS	*i*-PrONa (10%)	reflux	100
12	$Rh_2nbd_2Cl_2$	AMPYMORPH	*i*-PrONa (10%)	reflux	75
13	$Rh_2nbd_2Cl_2$	(*R*,*R*)-DAMPYPHOS	*i*-PrONa (10%)	reflux	100 (70) (*R*)
14	$Rh_2nbd_2Cl_2$	AMPYPHOS	*i*-PrONa (10%)	50	97
15	$Rh_2nbd_2Cl_2$	AMPYMORPH	*i*-PrONa (10%)	50	70
16	$Rh_2nbd_2Cl_2$	(*R*,*R*)-DAMPYPHOS	*i*-PrONa (10%)	50	97 (75) (*R*)

Despite theexcellent catalytic activity at 82 °C, the enantiomeric excess was only 70% (Table 6.1, run 13). Decreasing the reaction temperature to 50 °C only slightly improved the optical yield providing an ee of 75% and a further decrease of the reaction temperature resulted into considerably lower conversions.

Subsequently, the activity of rhodium catalysts with the newly prepared ligands was investigated for the hydrogenation of acetophenone under 10 bar of H_2 at room temperature in a biphasic system consisting of aqueous NaOH (1 M) and the substrate (0.1 M) (Table 6.2). Experiments without any additive or cosolvent only showed moderate conversions of acetophenone to 1-phenylethanol (Table 6.2, runs 1 and 2). Grzybek[30] observed a significant effect of methanol used as a cosolvent in the aqueous biphasic hydrogenation of olefins, therefore it was of interest to study the effect of various alcohols on the conversion as well as on the enantioselectivity in case of our catalytic system. A preliminary experiment with benzyl alcohol as an additive revealed not only an enhancement of the reaction rate, but also an increase in the optical yield of the product 1-phenylethanol (Table 6.2, run 5). Based on these results other alcohols were screened. The addition of EtOH, $PhCH_2OH$, *i*-PrOH, and *t*-BuOH gave rise to considerably higher conversions of 100%,[31] 40%, 100%, and 61%, respectively (Table 6.2, runs 3, 6, 9, and 12). Furthermore, the enantiomeric excess of the product was different, depending on the alcohol used, being maximal for *i*-PrOH (Table 6.2, run 9). Subsequently, the effect of a reduced catalyst load was studied (Table 6.2, runs 6-14). Halving the amount of $Rh_2nbd_2Cl_2$ required the presence of 3 equiv. of $PhCH_2OH$ to accomplish full conversion (Table 6.2, runs 5 and 8).

Table 6.2. Hydrogenation of acetophenone under 10 bar of H_2 at room temperature in an aqueous NaOH (1 M) biphasic system in the presence of $Rh_2nbd_2Cl_2$/AMPYPHOS or (*R*,*R*)-DAMPYPHOS for 15 h.

Run	$Rh_2nbd_2Cl_2$, %	Ligand	additive (equiv.)	Conversion, % (ee, %)
1	1	AMPYPHOS	none	47
2	1	(*R*,*R*)-DAMPYPHOS	none	73 (75) (*R*)
3	1	(*R*,*R*)-DAMPYPHOS	EtOH (1 equiv.)	100 (79) (*R*)
4	1	AMPYPHOS	$PhCH_2OH$ (1 equiv.)	40
5	1	(*R*,*R*)-DAMPYPHOS	$PhCH_2OH$ (1 equiv.)	100 (93) (*R*)
6	0.5	(*R*,*R*)-DAMPYPHOS	$PhCH_2OH$ (1 equiv.)	40 (92) (*R*)
7	0.5	(*R*,*R*)-DAMPYPHOS	$PhCH_2OH$ (2 equiv.)	80 (93) (*R*)
8	0.5	(*R*,*R*)-DAMPYPHOS	$PhCH_2OH$ (3 equiv.)	100 (93) (*R*)
9	0.5	(*R*,*R*)-DAMPYPHOS	*i*-PrOH (1 equiv.)	100 (95) (*R*)
10	0.25	(*R*,*R*)-DAMPYPHOS	*i*-PrOH (2 equiv.)	33 (93) (*R*)
11	0.05	(*R*,*R*)-DAMPYPHOS	*i*-PrOH (2 equiv.)	10 (90) (*R*)
12	0.5	(*R*,*R*)-DAMPYPHOS	*t*-BuOH (1 equiv.)	61 (83) (*R*)
13	0.25	(*R*,*R*)-DAMPYPHOS	*t*-BuOH (2 equiv.)	23 (80) (*R*)
14	0.05	(*R*,*R*)-DAMPYPHOS	*t*-BuOH (2 equiv.)	8 (80) (*R*)

6.2.3. Kinetic Study

To study the hydrogenation in more detail, the reaction was followed over time, using the $Rh_2nbd_2Cl_2$/(*R*,*R*)-DAMPYPHOS catalytic system and water as a solvent with *i*-PrOH as an additive under a constant hydrogen pressure of 10 bar. Figure 6.1 shows a sigmoidal conversion of acetophenone over time, and a drastic reaction rate acceleration after an induction period of about 6 hours. However, when the catalyst was activated in advance under 10 bar of hydrogen for 6 hours, a linear relationship was observed for the formation of 1-phenylethanol; the reaction was now complete in 8 h, compared to 15 h without prior activation.

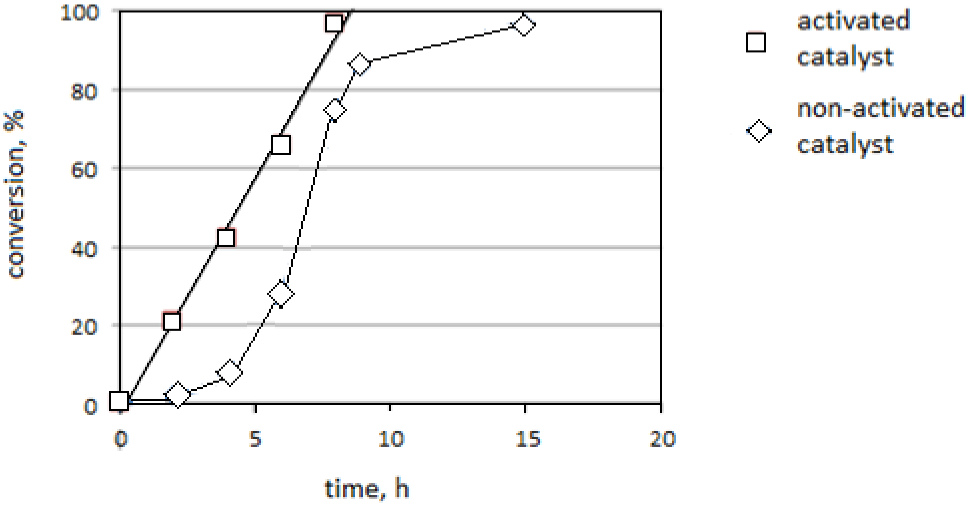
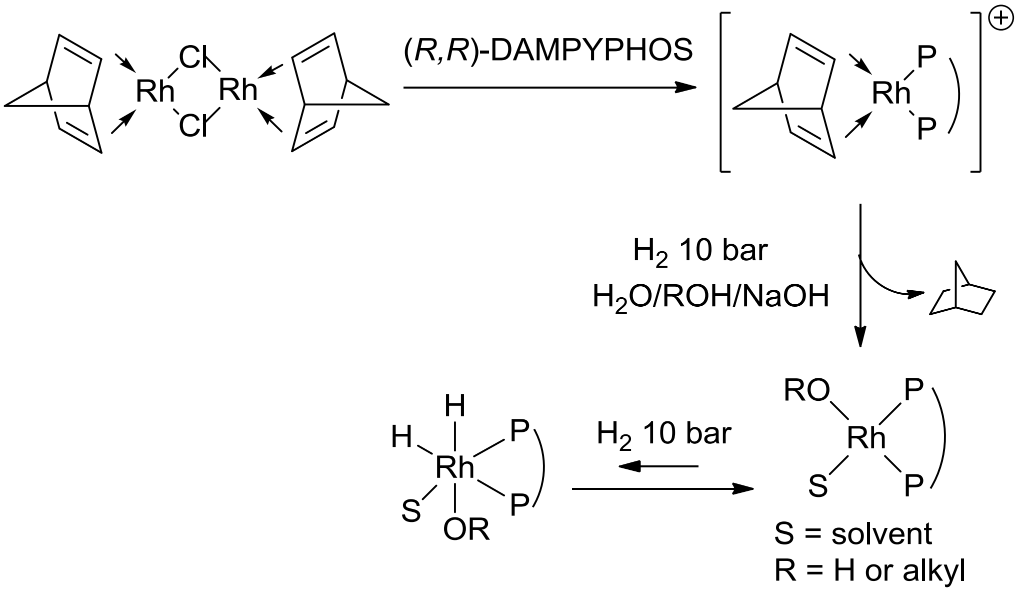


Figure 6.1. Conversion of acetophenone to 1-phenylethanol over time under the catalytic hydrogenation conditions: acetophenone (0.1 M) in aqueous NaOH (1 M) with *i*-PrOH (0.1 M) at 20 °C in the presence of 0.5% of $Rh_2nbd_2Cl_2$/(*R*,*R*)-DAMPYPHOS under 10 bar of H_2 with as well as without catalyst activation.

The catalyst activation can be visualized as shown in Scheme 6.2. Rapid hydrogenation of a diene ligand occurs upon exposure of the catalyst precursor solution to a hydrogen atmosphere. The resulting tetracoordinated rhodium species reveals almost no further hydrogen uptake due to the trans-effect of the bidentate phosphine ligand, which makes the formation of a dihydride Rh(III) complex unfavorable. This effect is also responsible for the oxidative addition of dihydrogen being, most likely, the rate-limiting step.

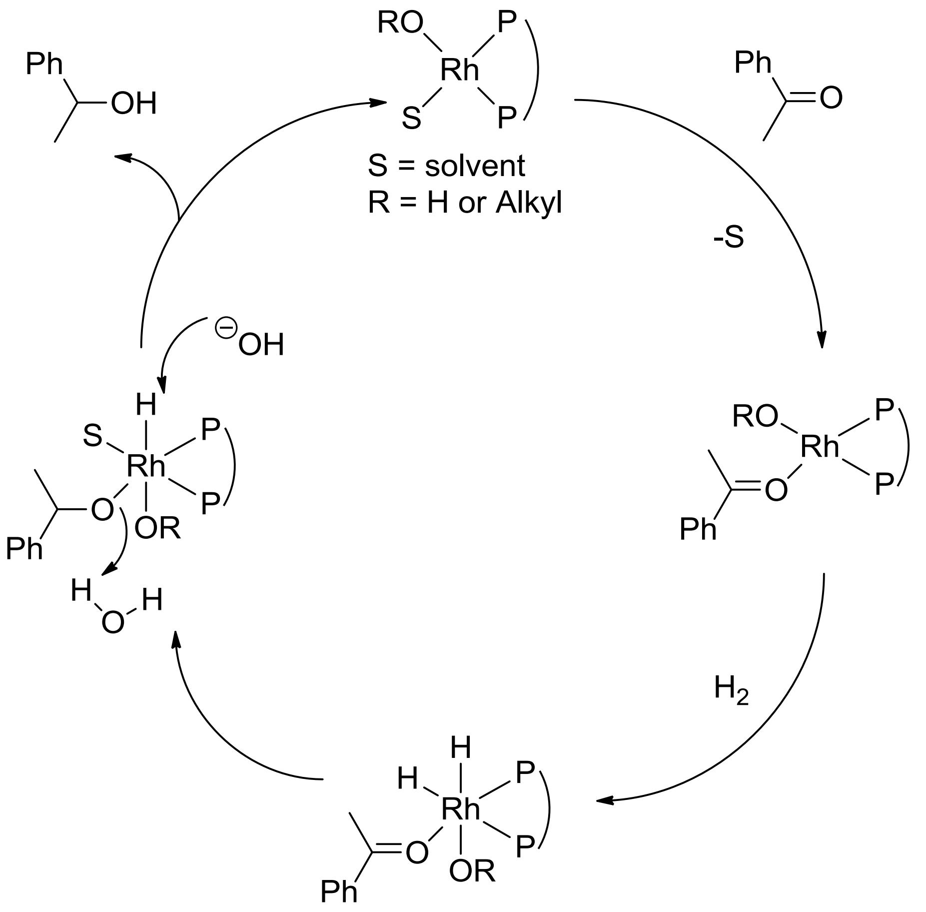


Scheme 6.2. Proposed catalyst activation sequence.

6.2.4. Reaction mechanism and origin of enantioselectivity increase in the presence of an alcohol

When acetophenone was hydrogenated in D_2O/d_1-EtOD/NaOD with H_2 employing $Rh_2nbd_2Cl_2$/(*R*,*R*)-DAMPYPHOS as the catalyst, the reaction product was characterized by ^1H NMR spectroscopy to be a mixture of isotopomers with a high degree of deuteration of the methyl group of 1-phenylethanol, which mostly results from the enolization of the parent acetophenone under basic conditions in the deuterated aqueous medium. However, deuteration at the carbon adjacent to the hydroxyl group was almost negligible. These results prove the absence of proton/deuteron exchange between catalytically active rhodium hydride species and the deuterated (protic) reaction medium, excluding the possibility of the heterolytic cleavage of dihydrogen, which is typical for rhodium-amido[32] and iridium-amidophosphine ambifunctional catalysts.[33] Furthermore, it supports the oxidative addition of dihydrogen to the rhodium metal center as the key step in the catalytic cycle. On the other hand, under comparable conditions, using 10 bar of Ar instead of H_2 gas, no conversion of acetophenone was observed at all after 15 h. This result rules out the possibility of transfer hydrogenation by the alcohol, introduced into the reaction mixture.

Based on these data a mechanism, as summarized in Scheme 6.3, is proposed. Basically, the reaction follows the classical Schrock-Osborn dihydride mechanism[34] involving substrate coordination and the oxidative addition of dihydrogen with the formation of a Rh(III) dihydride complex. Subsequent migratory insertion of a hydride ligand into the C=O bond results into the formation of a Rh(III) monohydride complex with the product alkoxide ligand. This monohydride complex ultimately needs the simultaneous assistance of a base, to abstract the remaining proton from the metal center, and a proton donor, to protonate the product alkoxide, in order to eliminate the product alcohol and to form the initial tetracoordinated Rh(I) complex, closing the catalytic loop.



Scheme 6.3. Proposed mechanism of acetophenone hydrogenation by H_2 catalyzed by $Rh_2nbd_2Cl_2$/(*R*,*R*)-DAMPYPHOS in water.

The amplification of enantioselectivity upon the addition of various alcohols to the reaction mixture can be explained by replacement of the hydroxide ligand by the corresponding alkoxide making the resulting complex more sterically demanding. From several possible coordination modes of acetophenone to the catalytically active tetracoordinate rhodium species only those, that provide the lowest steric interaction of the acetophenone phenyl group with the bulky alkoxide ligand, undergo dihydrogen oxidative addition followed by the preferable formation of the (*R*)-enantiomer of 1-phenylethanol. This is clearly reflected in the enantiomeric excesses of 79%, 93%, and 95%, obtained for EtOH, $PhCH_2OH$ and *i*-PrOH, (Table 6.2, runs 3, 5, and 9), respectively, having an increasing bulkiness in this series of alcohols. The ligand steric bulk finally shields the active site of the catalyst, preventing it from substrate coordination when switching to *tert*-butanol, resulting in lower conversions and an enantiomeric excess close to the values obtained without any additive (Table 6.2, runs 12-14).

6.3. Conclusions

In conclusion, excellent ee's, up to 95%, have been obtained in the rhodium-catalyzed aqueous hydrogenation of acetophenone using a simple and easy-to-make chiral bidentate pyrazinophosphine ligand. The enantioselectivity of the reaction as well as the catalyst activity were found to be significantly improved by adding a small amount of alcohol, indicating the enhancement of the enantiocontrol of the reaction via binding an alcohol molecule by the catalyst. The enantiomeric excess produced by our ligand catalytic system is as high as recently reported for chiral ruthenabicyclic complexes,[35,36] to our knowledge the best catalyst for acetophenone reduction, however, in our case full conversion is achieved at 5 times lower hydrogen pressure and requires no decreased temperatures. The easy preparation, stability towards air oxidation, and amphiphilic nature, that enables application of the described ligands in aqueous organometallic catalysis, will strongly reduce the environmental impact for a large scale catalytic process, thus greatly enhancing perspectives for industrial application.

6.4. Experimental Section

General

All reagents, catalysts, and solvents were obtained from commercial sources and used without further purification. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on a Varian Unity INOVA (300 MHz) spectrometer. Chemical shift values are reported as δ relative to the residual solvent signal for ^{1}H and ^{13}C NMR and H_3PO_4 (85%) as the external reference for ^{31}P NMR. Electrospray ionization (positive mode) mass spectra were recorded on a WATERS LCT mass spectrometer. P-C cross-coupling reactions were performed under nitrogen atmosphere.

General procedure for the acylation of amines

A solution of corresponding amine **2**, **3**, and **4** (10 mmol) and Et_3N (3.0 mL, 20 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a solution of 6-chloropyrazine-2-carbonyl chloride (**1**) (10 mmol) in CH_2Cl_2 (100 mL), freshly prepared from 6-chloropyrazine-2-carboxylic acid (1.4 g, 10 mmol) and oxalyl chloride, at vigorous stirring. The resulting mixture was stirred for 2 h and then all the volatiles were removed in vacuo (except **7**, which was washed with brine and dried over Na_2SO_4). The residue was dissolved in dry EtOAc (100 mL) and filtered through a short plug of silica after which all the volatiles were removed in vacuo affording the pure product.

5: (quantitative). The spectral characteristics of the obtained compound were reported in Chapter 4.

6: (2.6 g, 97%). ^{1}H NMR: δ = 9.22 (s, 1 H, PyzH), 8.69 (s, 1 H, PyzH), 7.98 (bs, 1 H, NH), 3.71-3.65 (m, 4 H, OCH_2CH_2N), 3.52 (q, 2 H, J = 5.6 Hz, $HNCH_2$), 2.55 (t, 2 H, J = 5.6 Hz, CH_2CH_2), 2.49-2.43 (m, 4 H, OCH_2CH_2N). ^{13}C NMR: δ = 163.3, 148.1, 147.6, 144.2, 143.7, 67.0, 56.9, 53.4, 36.0. IR (ν_{max}/cm^{-1}): 2954, 2819, 1666, 1523, 1237, 1390, 1306, 1189, 1167, 1113, 1009, 899, 866, 780, 729, 669. HRMS-TOF (*m/z*): [M + H]$^+$ calcd 271.0962, found 271.0965.

7: (3.6 g, 91%). ^{1}H NMR: δ = 9.18 (s, 2 H, PyzH), 8.70 (s, 2 H, PyzH), 7.85 (bs, 2 H, NH), 4.09-4.00 (m, 2 H, HNC*H$_2$*), 2.22-2.15 (m, 2 H, CH$_2$), 1.63-1.35 (m, 6 H, Alkyl). ^{13}C NMR: δ = 162.1, 148.1, 147.3, 143.7, 141.9, 53.6, 53.4, 32.3, 24.7. IR (ν_{max}/cm^{-1}): 2928, 2859, 1664, 1526, 1443, 1393, 1309, 1165, 1127, 1010, 770, 669. HRMS-TOF (*m/z*): [M + H]$^+$ calcd 395.0790, found 395.0795.

General procedure for palladium-catalyzed P-C cross-coupling

To a solution of chloropyrazines **5**, **6**, and **7** (10 mmol) and Pd(dppf)Cl$_2$ (0.023 g, 1 mol % per reacting chlorine atom) in CH$_3$CN (50 mL) were subsequently added HPPh$_2$ (1.7 mL, 10 mmol per reacting chlorine atom) and DBU (1.5 mL, 10 mmol per reacting chlorine atom). The resulting mixture was refluxed for 20 h and then the solvent was removed in vacuo. The residue was dissolved in dry EtOAc (100 mL) and filtered through a short plug of silica after which all the volatiles were removed in vacuo affording the pure product.

AMPYPHOS: (3.5 g, 93%). ^{1}H NMR: δ = 8.81 (s, 1 H, PyzH), 8.43 (s, 1 H, PyzH), 7.41-7.30 (m, 10 H, ArH), 3.72-3.60 (m, 4 H, CH$_2$O), 3.31 and 3.25 (t, 2 H, *J* = 5.1 Hz, CH$_2$N). ^{13}C NMR: δ = 162.7, 149.0, 148.5, 147.7, 144.1, 132.1, 132.0, 128.9, 128.8, 128.6, 66.7, 47.5. ^{31}P NMR: δ = -7.42. IR (ν_{max}/cm^{-1}): 1636, 1541, 1437, 721, 669, 650. HRMS-TOF (*m/z*): [M + H]$^+$ calcd 378.1371, found 378.1379.

AMPYMORPH: (4.0 g, 95%). ^{1}H NMR: δ = 9.15 (s, 1 H, PyzH), 8.38 (s, 1 H, PyzH), 7.98 (bs, 1 H, NH), 7.38-7.30 (m, 10 H, ArH), 3.57-3.42 (m, 6 H), 2.61-2.35 (m, 6 H). ^{13}C NMR: δ = 163.0, 145.3, 144.3, 142.7, 142.2, 134.3, 134.1, 129.8, 129.0, 128.9, 66.6, 56.7, 53.2, 35.7. ^{31}P NMR: δ = -8.06. IR (ν_{max}/cm^{-1}): 1670, 1540, 1521, 1436, 720, 669, 650. HRMS-TOF (*m/z*): $[M + H]^+$ calcd 421.1793, found 421.1797.

(*R,R*)-DAMPYPHOS: (6.2 g, 90%). ^{1}H NMR: δ = 8.92 (s, 2 H, PyzH), 8.39 (s, 2 H, PyzH), 7.80-7.70 (m, 2 H, NH), 7.41-7.30 (m, 20 H, ArH), 3.82-3.72 (m, 2 H, C*H*NH), 1.74-1.68 (m, 2 H, AlkH), 1.74-1.68 (m, 2 H, AlkH), 1.35-1.26 (m, 4 H, AlkH). ^{13}C NMR: δ = 163.0, 145.7, 144.6, 144.0, 141.8, 134.3, 134.1, 128.9, 128.8, 53.2, 32.2, 24.6. ^{31}P NMR: δ = -8.02. IR (ν_{max}/cm^{-1}): 2931, 2857, 1669, 1521, 1435, 1406, 907, 846, 727, 692, 645. HRMS-TOF (*m/z*): $[M + 2H]^{2+}$ calcd 348.1266, found 348.1272.

General procedure for the transfer hydrogenation of acetophenone

A catalyst precursor (1 mol % of $Ru(PPh_3)_3Cl_2$ or 0.5% of $Rh_2nbd_2Cl_2$) and 2 mol % or 1 mol % of monodentate or bidentate ligand, respectively, were premixed in *i*-PrOH for 30 min. Thereafter acetophenone (0.12 mL, 1 mmol) and a base (10 mol %) were added and the volume of the solution was adjusted to 10 mL with *i*-PrOH. The resulting mixture was stirred for 15 h at the desired temperature after which all the volatiles were removed in vacuo and the residue was partitioned between H_2O (5 mL) and CH_2Cl_2 (5 mL). The organic phase was collected and the solvent was removed under reduced pressure. The residue was analyzed by NMR spectroscopy. Conversions and product compositions were determined on the basis of the integrations of the $PhC(O)CH_3$ and $PhCH(OH)CH_3$ signals. Enantiomeric excesses were calculated from the ratio of the integrals of the corresponding enantiomers with the chiral shift reagent europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] obtained from Sigma-Aldrich. The configuration of the product 1-phenylethanol was estimated by ^{1}H NMR spectroscopy relatively to (*S*)-1-phenylethanol of 98% enantiomeric purity available from Sigma-Aldrich.

General procedure for the hydrogenation of acetophenone with H_2 in water

A 15 mL glass vial was charged with acetophenone (0.12 mL, 1 mmol), $Rh_2nbd_2Cl_2$ (0.05 to 1 mol %) and a corresponding ligand (4 equiv. of monodentate or 2 equiv. of bidentate phosphine in respect to $Rh_2nbd_2Cl_2$). The resulting mixture was stirred till complete dissolution, after which the corresponding alcohol was added (1 to 3 equiv. in respect to acetophenone) and the volume was adjusted to 10 mL with aqueous 1 M NaOH. The vial was placed into a stainless steel autoclave. The autoclave was sealed, pressurized with H_2 to 10 bar and maintained with stirring at 25 °C for 15 h. The pressure was released and the reaction mixture was extracted with CH_2Cl_2 (5 mL). Volatiles were distilled off from the extract and the mixture of products was analyzed by ^{1}H NMR spectroscopy as described above.

6.5. References and Notes

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Chapter 7

Highly Active and Robust Rhodium(I) Catalyst for the Polymerization of Arylacetylenes in Polar and Aqueous Media under Air Atmosphere

A catalytic system consisting of $Rh_2nbd_2Cl_2$ and a hydrophilic, neutral phosphinopyrazine ligand was developed for the polymerization of phenylacetylene (PA) and other terminal arylacetylenes in alcohol and water in air at room temperature. The catalyst proved to be highly stable and robust without loss of the catalytic activity upon repeated use. The influence of an external base, the effect of solvent and monomer/catalyst molar ratio were also studied. In general, the addition of base increased the molecular weight of the polymer, however, weakly coordinating bases (such as Et_3N) gave a unimodal molecular weight distribution, whereas strongly coordinating hydroxides/alkoxides gave bimodal polymers. Highly crystalline red-brown PPA obtained in water with the above catalyst revealed a high molecular weight (58500 Da) with a bimodal molecular weight distribution. The polymers were characterized by ^1H NMR spectroscopy as highly stereoregular cis*−transoidal with >99% of* cis*-content.*

7.1. Introduction

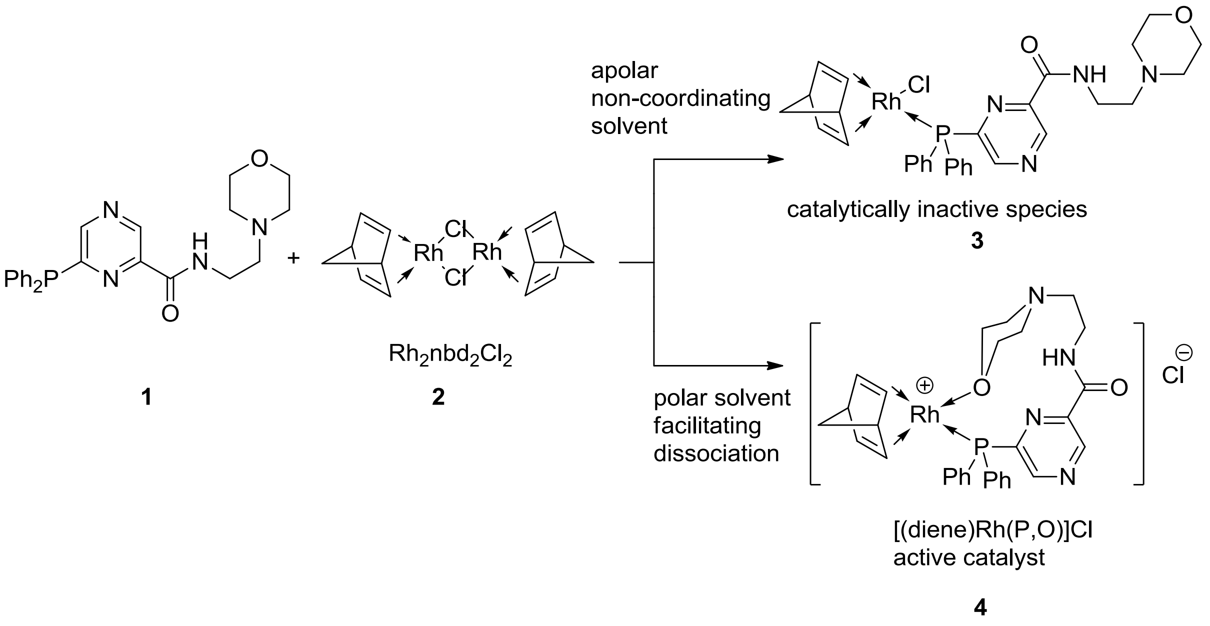
Polyacetylenes[1] represent an important class of highly conjugated organic polymers with unique properties such as electrical conductivity,[2] non-linear optical[3] and magnetic susceptibilities,[4] and electro- and photoluminescence,[5] that are not exhibited by other conventional organic polymers. Within this class of materials monosubstituted polyacetylenes have been studied extensively due to their higher degree of conjugation and stereoregularity compared to disubstituted analogues. A variety of early transition metal catalysts such as Ziegler-Natta catalysts[6] and group VB-VIB metal halides[7,8] was examined, and found to polymerize mono- and disubstituted acetylenes, resulting in high molecular weight polymers. However, in the past decade much attention focused towards the development of late transition metal catalysts, that display high tolerance towards air and moisture. Within this row of elements, Rh catalysts have drawn more attention because of their high activity and the relatively wide range of applicable monomers that can produce functional polymer materials. Classical Rh catalysts, derived from the revolutionary work of Furlani[9] and Noyori,[10] generally contain a π-acidic diene ligand which defines the catalyst activity. Masuda *et al.* [11] have shown that the increase of the π-acidity of the diene ligand leads to higher catalyst activity and turnover frequency. Recently, a few reports on cationic rhodium complexes with hemilabile ligands incorporating non-labile phosphine and labile OR, NR_2, and SR ligating groups have appeared.[12,13] Cationic rhodium complexes with aminophosphine ligands were found to be efficient catalyst precursors for the polymerization of terminal arylacetylenes, giving highly stereoregular polymers of high molecular weight and narrow molecular weight distribution.

Recently, the rhodium-catalyzed aqueous polymerization of phenylacetylenes has drawn a lot of attention. Being the most ecologically benign solvent for chemical reactions and transition metal-catalyzed processes, water offers many other advantages such as absence of safety risks, ease of product separation and catalyst recovery from the reaction mixture. The hydrophilicity of transition metal complexes is traditionally achieved by incorporation of water-soluble ligands. Various groups reported on the aqueous polymerization of arylacetylenes with water-soluble Rh-catalysts incorporating *p*-toluenesulfonate,[14] sulfonated triarylphosphines,[15,16] and cationic bipyridyl ligands.[17]

In Chapter 6, the preparation of a series of hydrophilic phosphinopyrazines was described, which were successfully used for Rh-catalyzed aqueous hydrogenation. In this chapter the hemilabile hydrophilic, neutral phosphinopyrazine ligand **1** is employed (see Scheme 7.1 below) for the polymerization of terminal arylacetylenes in water as well as in other solvents under open air atmosphere conditions. The pyrazine backbone of the ligand increases the π-acidity of the phosphino group, thus increasing the Lewis acidity of the Rh center together with a norbornadiene (NBD) ligand via π-backbonding. The morpholine ring acts as an intramolecular base deprotonating the arylacetylene coordinated to the catalytic center, which may give rise to faster polymerization initiation. In addition, the presence of morpholine in close proximity of the active Rh center may prevent its protonation followed by the reductive elimination of a growing polymer, postulated as the chain termination step.[13]

7.2. Results and Discussion

Typically, the generation of cationic rhodium species in apolar solvents requires the use of a halide scavenger such as $AgBF_4$.[12] Thus, in apolar solvents in the absence of a halide scavenger hydrophilic phosphinopyrazine (**1**) binds to the metal as a monodentate phosphine ligand and forms catalytically inactive neutral rhodium species **3** (Scheme 7.1). However, in polar solvents, that are capable of coordination to the metal center or solvation of a halide anion, the dissociation of a halide ligand is rather facile and the desired cationic rhodium species can be formed in situ. The dissociation degree, however, is strongly dependent on the nature of the polar solvent. The free coordination site formed upon the dissociation of a chloride ligand is “protected” by the labile donor group of the ligand or by a solvent molecule, which expels the chloride ligand into the outer coordination sphere and stabilizes the cationic rhodium complex **4** (Scheme 7.1). In other words performing the polymerization in polar solvent helps to avoid the use of expensive silver salts in order to generate a highly active cationic rhodium species.



Scheme 7.1. Formation of the catalytically active and inactive Rh species.

Performing the polymerizations of phenylacetylene with the $Rh_2nbd_2Cl_2$/**1** catalytic system, starting from 1 mol% catalyst load, in various solvents revealed a significant influence of the solvent properties on the resulting polymer yield, molecular weight, stereoregularity, and polydispersity. Almost no polymerization occurred in toluene in the presence of 10 mol % of Et_3N or pyridine, and only 10% of yellow non-stereoregular unimodal polyphenylacetylene (PPA) was obtained in the absence of a base in course of the overnight reaction (Table 7.1, runs 1-3). Carrying out the reaction in THF resulted into a much higher catalyst activity, accomplishing full monomer consumption in 1 h. The PPA obtained in THF in the presence of Et_3N had a higher molecular weight, M_w of 5.62 x 10^4, and a higher polydispersity, PDI of 1.35, compared to the polymer obtained in the absence of base (M_w = 1.18 x 10^4, PDI = 1.07), Both polymers, however, displayed a unimodal molecular weight distribution and a high degree of stereoregularity, being 92% of *cis*-content (Table 7.1, runs 4 and 6). Using neat Et_3N as the reaction medium afforded almost the same result as in the case of the THF/Et_3N system, giving highly stereoregular PPA with M_w = 6.02 x 10^4, PDI = 1.41 and 95% of *cis*-content.

Exploring the possibility of polymerization in protic solvents, a series of experiments was performed in various alcohols and water. The polymerization in *t*-BuOH in the presence of 10 mol% of *t*-BuOK was very slow and afforded only 17% yield of PPA after overnight reaction. The resulting PPA revealed a very low stereoregularity and a bimodal molecular weight distribution with M_w = 8.23 x 10^4/PDI = 1.51 for the first GPC peak and M_w = 0.49 x 10^4/PDI = 2.56 for the second one (Table 7.1, run 8). Switching to *i*-PrOH led to quantitative conversions of the monomer into PPA. The resulting polymer displayed a very high degree of stereoregularity, being >99% of *cis*-content, relatively low PDI, but somewhat lower molecular weight of the main fraction compared to the PPA obtained in *t*-BuOH (Table 7.1, runs 8 and 9).

Again the PPA obtained in the presence of *i*-PrONa revealed a bimodal molecular weight distribution. To further increase the polarity of the solvent, the polymerizations were performed in water (Table 7.1, runs 12 and 13). Interestingly, the experiments in water revealed no influence of the base, affording highly stereoregular polymers (95-97% of *cis*-

content) of a high molecular weight, with almost the same M_w value and a bimodal distribution. It is important to note that polymerizations in Et_3N as a solvent, *i*-PrOH, and water were instantaneous and quite exothermic, so that the resulting polymer was filtered off in 5 min after addition of phenylacetylene to the catalyst solution. These results indicate the strong dependence of the catalyst activity on the solvent polarity. For example, in the series *i*-PrOH, *t*-BuOH, and toluene the relative polarity of the solvent steadily decreases, being 0.546, 0.389, and 0.099, respectively.[18] Lowering the polarity of a protic solvent diminishes the dissociation of the chloride ligand, hence lowering the concentration of the catalytically active cationic rhodium species.[19] Consequently, the dissociation in a non-polar, poorly coordinating solvent such as toluene is almost negligible, which makes polymerization almost impossible. Apparently, a different result was obtained in methanol. In addition to a low yield of <5% and low stereoregularity the resulting polymer showed a surprisingly low molecular weight. A plausible explanation for this outcome could be that the high acidity of methanol, the pK_a of which is even lower than that of water,[20] enables the chain termination step via the direct protonation of the rhodium center.

Table 7.1. Polymerization of phenylacetylene.

Run	Solvent	Cat. Load, %	Base (10%)	M_w x 10^{-4}/PDI[a]	Distribution/ stereoregularity	Yield, %
1	Toluene	1	None	0.99/1.13	unimodal/non-regular	10
2	Toluene	1	Pyridine	-	-	0
3	Toluene	1	Et_3N	-	-	0
4	THF	1	None	1.18/1.07	unimodal/*cis* - 92%	97

5	THF/H_2O (1:1)	1	None	1.04/1.29	unimodal/*cis* - 87%	99
6	THF	1	Et_3N	5.62/1.35	unimodal/*cis* - 92%	100
7	Et_3N	1	Neat	6.02/1.41	unimodal/*cis* - 95%	100
8	*t*-BuOH	1	*t*-BuOK	8.23/1.51 0.49/2.56	bimodal/non-regular	17
9	*i*-PrOH	1	None	0.30/1.91	unimodal/*cis* >99%	100
10	*i*-PrOH	1	*i*-PrONa	0.50/2.39 0.29/1.78	bimodal/*cis* >99%	100
11	MeOH	1	None	-	-	5 (lower PA oligomers)
12	H_2O	1	None	5.12/1.39 1.07/1.65	bimodal/*cis* -97%	99
13	H_2O	1	NaOH	5.85/1.48 0.66/2.29	bimodal/*cis* -95%	100
14	*i*-PrOH	0.1	None	5.88/1.74	unimodal/*cis* >99%	100
15	*i*-PrOH	0.1	*i*-PrONa	9.30/1.87 0.73/1.53	bimodal/*cis* >99%	100
16	*i*-PrOH	0.03	none	10.32/1.08	unimodal/*cis* -97%	75
17	CH_3CN	1	none	0.78/1.12	unimodal/*cis* -93%	98
18	CH_3CN	1[b]	none	0.83/1.14	unimodal/*cis* -91%	95
19	CH_3CN	1[b]	none	1.13/1.09	unimodal/*cis* -92%	97

[a] Molecular weights were measured in $CHCl_3$, which is reported to decrease the molecular weight of PPA with time, 24 h after the preparation of the PPA solutions.[21,22] For polymers with bimodal distributions M_w and PDI are given for both GPC peaks.

[b] Initial catalyst load.

Another interesting phenomenon is that the polymer morphology is strongly impacted by the solvent properties.[23] Reactions in aprotic solvents (CH_3CN, THF, Et_3N) afforded amorphous bright-yellow PPA, whilst polymerizations in *i*-PrOH resulted in the appearance of a small fraction of red PPA. Increasing the polarity of a protic solvent further and performing polymerizations in water and a 1:1 water/THF mixture yielded brown and dark red polymers with a considerable amount of a bright red PPA, insoluble in organic solvents. The soluble brown or dark red PPA was characterized as a *cis*-transoidal crystalline polymer with a π-conjugated columnar pseudohexagonal structure, while an insoluble bright red polymer was assigned a *cis*-cisoidal conformation, responsible for a more dense packing in crystallites and insolubility of the polymer in most of the organic solvents, as also found by Mawatari *et al.*[23] and Tabata *et al.*[24] Thus the presence of a polar protic solvent induces coagulation and results into self-assembly of the *in situ* formed PPA chains into highly ordered columnar hexagonal polymer structures with high yields.

7.2.1. Base Effect

Tabata *et al.*[25] and Furlani *et al.*[9] have found that basic additives such as Et_3N and NaOH accelerate Rh-catalyzed phenylacetylene polymerizations. Noyori *c.s.* [26] reported the effect of the addition of DMAP as the external base to the reaction mixture to decrease the polydispersity, but at the same time also decreasing the molecular weight of the resulting polymer. The role of Et_3N and NaOH can be easily explained as the scavenging of HCl, generated upon the reaction of the chloride-containing Rh precatalyst with phenylacetylene, preventing the chain termination reaction by the direct protonation of the Rh-active center. The role of DMAP is more complicated, since it is responsible not only for the proton scavenging, but also suppresses the formation of Rh-dinuclear species, that are of much lower activity. However, the presence of a base had a totally different outcome in our case. Although both bases Et_3N and *i*-PrONa resulted in polymers with higher molecular weights, than those obtained in the absence of a base, there is a distinct difference. Polymerization in the THF/Et_3N system resulted in a higher molecular weight of the obtained PPA compared to the polymerization in neat THF, while a unimodal GPC profile of the polymer was retained (Table 7.1, runs 4 and 6). In contrast to that, PPA obtained in the presence of i-PrONa in i-PrOH revealed a distinct bimodal molecular weight distribution (Table 7.1, runs 14 and 15) (see Figure 7.1).

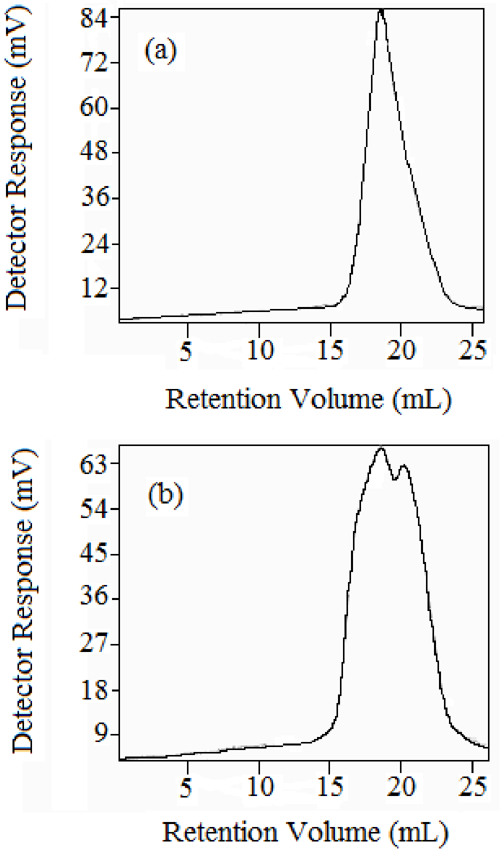


Figure 7.1. GPC traces of PPAs obtained in the absence (unimodal) (a) as well as in the presence (bimodal) of *i*-PrONa in *i*-PrOH (b) (Table 7.1, runs 14 and 15).

Notably, the molecular weight of the first GPC peak is significantly larger than that of the second one, which is indicative for the reductive coupling of two active chains. On the other hand, considering the excellent ability of hydroxide as well as alkoxide to act as a bridging ligand, it can be assumed that the presence of an anionic base with multiple lone electron pairs can facilitate the formation of bridged dimeric rhodium species in which a coupling reaction of two active polymer chains is highly probable due to the close proximity of two rhodium centers. The same outcome with the bimodal molecular weight distribution was obtained in the *t*-BuOH/*t*-BuOK system (Table 7.1, run 8), however, the bulkiness of *t*-butoxide prevented a good stereoregularity of the obtained polyphenylacetylene as evidenced by ^{1}H NMR spectroscopy[27] (Figure 7.2a).

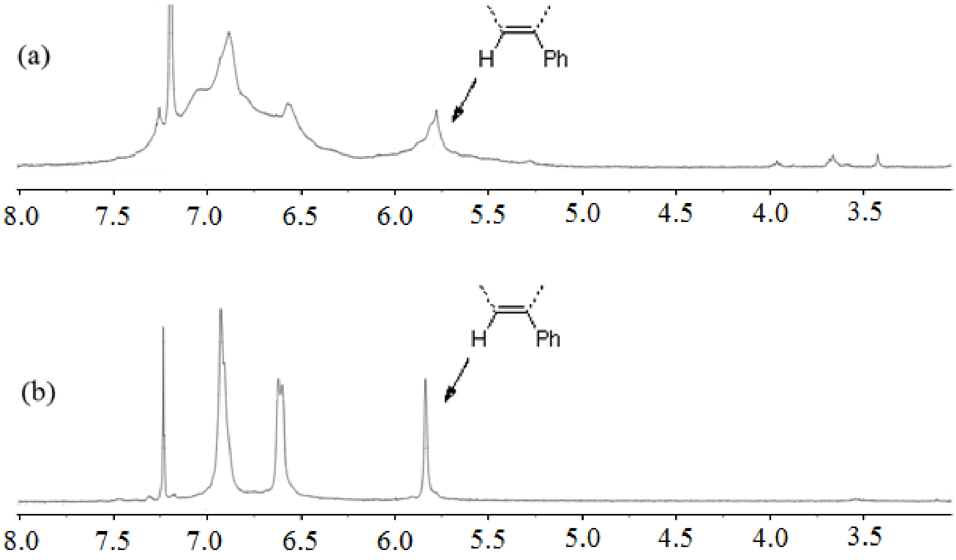


Figure 7.2. ^{1}H NMR spectrum in $CDCl_3$ at 298 K of (a) PPA obtained from *t*-BuOH (Table 7.1, run 8), (b) PPA obtained from *i*-PrOH (Table 7.1, run 10).

The effect of the bridging ligand was even more severe in case of water used as a solvent. Performing polymerization in aqueous medium resulted in a bimodal molecular weight distribution. Either a base (NaOH) was introduced in the reaction mixture or not, the molecular weight of both samples remained almost the same (Table 1, runs 12 and 13). A similar effect was described by Jimenez *et al.*[12] for a related Rh catalyst. The presence of water considerably improved the catalyst activity, but had an adverse effect on the PDI of the resulting PPA.

7.2.2. Catalyst Load Effect

The effect of the catalyst loading on the polymerization of phenylacetylene was studied in *i*-PrOH. In the range of catalyst/monomer ratios from 1% to 0.1% the polymerization was still instantaneous giving a quantitative conversion of the monomer, so that no decrease in the reaction rate could be detected. However, decreasing the catalyst/substrate ratio to 0.03%, keeping the reaction time and conditions the same, resulted in a 25% decrease in polymer yield compared to the latter two, indicating a small decline in the reaction rate. At the same time, decreasing the catalyst load subsequently from 1% to 0.1% and 0.03% led to a considerable increase of the molecular weight of the resulting polyphenylacetylene from 0.30 x 10^4 to 5.88 x 10^4 and 10.32 x 10^4, respectively (Table 7.1, runs 9, 14, and 16).

On the other hand, performing the polymerization in acetonitrile with a starting catalyst/monomer ratio of 1% and subsequent reusing of the filtrate after polymer separation revealed no loss of the catalytical activity of the CH_3CN solution which was used three times in a row. Only in case of the third use of the catalyst solution a slight increase in the molecular weight of the obtained polymer was noticed, thus indicating a possible decrease of the catalyst concentration by trapping it inside the polymer bulk.

7.2.3. Polymerization of other arylacetylenes

The polymerization of (4-methoxyphenyl)acetylene (MeOPA) in *i*-PrOH and H_2O also proceeded instantaneously at room temperature resulting into the formation of a red-brown precipitate of poly(4-methoxyphenyl)acetylene (MeOPPA). However, within the same reaction time full conversions were achieved with higher catalyst loadings (Table 7.2, runs 1, 2) compared to the polymerization of phenylacetylene (Table 7.1, runs 14-16), the degree of polymerization (M_n) of PPA and MeOPPA was comparable in all cases.

Table 7.2. Polymerization and copolymerization of 4-methoxyphenylacetylene with phenylacetylene in the presence of 1% of the catalyst.

Run	Solvent/ monomer(s)	Cat. load, %	Base (10%)	M_w x 10^{-4}/ PDI	Distribution/ stereoregularity	Yield, %
1	*i*-PrOH/ MeOPA	1	*i*-PrONa	11.20/2.52 0.56/2.08	bimodal/*cis* >99%	100
2	*i*-PrOH/ MeOPA	0.1	*i*-PrONa	9.15/2.15 0.64/1.95	bimodal/*cis* >99%	70
3	H_2O/ MeOPA	1	None	0.6/1.27	unimodal/*cis* >99%	95
4	CH_3CN/PA/ MeOPA	1	None	1.23/1.16	Unimodal (block-copolymer)	100

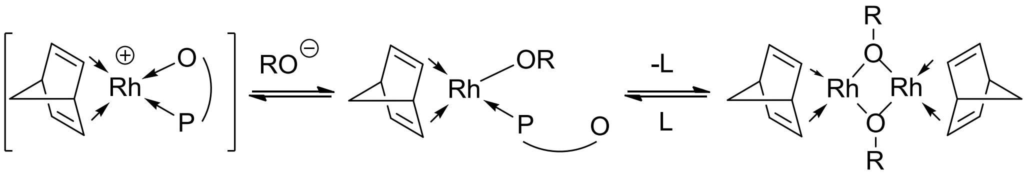
Switching from *i*-PrOH to H_2O resulted into a dramatic decrease of the M_w of the resulting MeOPPA (Table 7.2, run 3). This result can be explained by the presence of the strongly electron-donating methoxy group in the aromatic ring of the monomer, which makes the terminal acetylenic carbon atom more basic and hence more susceptible towards hydrolysis in aqueous medium during the growth of the active chain.

The stepwise addition of stoichiometric amounts of PA and MeOPA in CH_3CN resulted into an AB block copolymer with a 1:1 ratio of the monomer units as determined by comparing the ^{1}H NMR integrals of the vinylic protons at 5.84 and 5.76 ppm for the PA and MeOPA units, respectively (Table 7.2, run 4).

7.2.4. NMR Study of the Polymerization Reaction

An NMR study revealed that a mixture of 1 equiv of $Rh_2nbd_2Cl_2$ and 2 equiv of the phosphinopyrazine ligand in CD_3CN leads to the quantitative formation of tetracoordinated Rh complex **4** (Scheme 7.1). The *P*,*O*-binding mode of the ligand is supported by a low-field shift of the pyrazine protons from 9.14 and 8.50 ppm to 9.25 and 9.22 ppm, and of the CH_2O-protons of the morpholine ring from 3.49 to 3.80 ppm, respectively, while the rest of the proton signals remained unchanged. In addition, preliminary conformational analysis revealed the sterical constraint of the *P*,*N*-binding mode of the ligand due to the lone pair of pyrazine nitrogen and shortness of the ethylene linker. This steric strain prevents ligand from adopting the conformation suitable for the *P*,*N*-ligation. The labile oxygen donor group of the morpholine ring of the ligand is capable of a reversible coordination to the metal center, thus preventing catalyst inactivation via blocking of the free coordination site with ligands/anions that bind stronger than arylacetylenes. In the ^{31}P NMR spectrum the signal at -8.59 ppm, characteristic for the free ligand, disappeared showing a doublet at 29.1 ppm ($J_{P\text{-}Rh}$ = 177.1 Hz) instead, thus indicating P-Rh coupling.

The addition of *i*-PrONa to a CD_3CN solution of the catalyst resulted in the complete dissociation of the labile oxygen-bound morpholine moiety from the rhodium center and a significant upfield shift of the pyrazine protons, thus indicating the binding of the isopropoxide. At the same time ^{31}P NMR spectroscopy revealed a small peak of the free ligand at -8.59 ppm. Based on this data a possible equilibrium, induced by the presence of an alkoxide or hydroxide base, can be proposed (Scheme 7.2).



Scheme 7.2. Proposed equilibrium, induced by the presence of an alkoxide or hydroxide base.

Overall, depending on the presence or absence of a hydroxide or alkoxide base, the formation of two different catalytically active forms of the initial Rh complex is possible: with a coordinated or non-coordinated labile part of the ligand.[28,29,30]

The addition of 1 equiv of PA to a CD_3CN solution of the catalyst revealed no change in the pyrazine or morpholine proton signals of the complexed ligand. However, an upfield shift of the aromatic proton multiplets of the Ph_2P group by approximately 0.2 ppm and the complete absence of the acetylenic proton signal of free PA as well as a change of the $J_{\text{P-Rh}}$ value from 177.1 to 162.9 Hz indicated the binding of PA by the catalyst. Interestingly, no protonation of the morpholino-nitrogen as well as formation of Rh-hydrido spieces was observed in the ^{1}H NMR spectra. However, Rh complexes with DAMPYPHOS and AMPYPHOS ligands, that have no pendant labile group (Chart 7.1), proved to be completely inactive in the polymerization of PA.

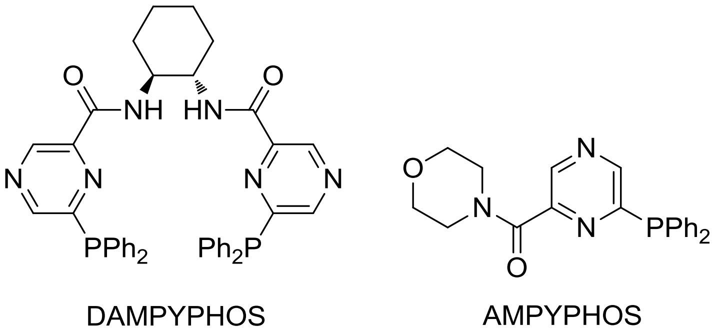


Chart 7.1. Pyrazinophosphines without pendant amino arm.

Addition of the second equivalent of phenylacetylene resulted into a fast formation of the polymer precipitate in the NMR tube, while the ^{1}H NMR spectrum revealed the recovery of the initial rhodium-phosphinopyrazine complex, thus indicating a high polymerization rate defined by the catalyst activity.

Based on these results, the presence of a pendant amino group appears to be a prerequisite for the polymerization. However, its role still remains unclear, since no species with a protonated morpholine moiety could be detected upon addition of PA.

7.3. Conclusions

In conclusion, a hemilabile, hydrophilic, neutral phosphinopyrazine ligand was successfully applied for the Rh(I)-catalyzed polymerization of terminal arylacetylenes without an external base in a variety of protic and aprotic polar solvents. The highest polymerization rates and yields were observed for alcohols and water as a solvent. The outstanding stability and robustness of the catalyst allows repetitive polymerizations in oxygen atmosphere without any loss of activity. In general, the aqueous, alcohol and acetonitrile polymerization systems are superior in terms of faster reaction rates, ease of polymer separation and catalyst recycling. To the best of our knowledge, polymerization of phenylacetylene with our catalyst system resulted into PPA with the highest molecular weight of 58500 Da, compared to 31200 Da reported by Tang *et al.*,[14] and a stereoregularity in the highest yield ever reported for the aqueous polymerization of arylacetylenes. Moreover, the presented catalytic system yielded the polymer in quantitative yield in the shortest reaction time of less than 5 min compared to 30 min and 1 h reported by Wang and Tsai[17] and Tang *et al.*,[14] respectively. Although the detailed mechanism for the polymerization remains unknown, the conditions and parameters required to control the molecular weight distribution and the polymerization rate have been thoroughly investigated. Overall, our catalytic system is very suitable for the polymerization of terminal arylacetylenes in water, and may be useful for the development of photoluminescent or conductive materials under oxygen atmosphere.

7.4. Experimental

General

All reagents, catalysts, and solvents were obtained from commercial sources and used without further purification. ^{1}H NMR, and ^{31}P NMR spectra were recorded on a Varian Unity INOVA (300 MHz) spectrometer. Chemical shift values are reported as δ relative to the residual solvent signal for ^{1}H and H_3PO_4 (85%) as the external reference for ^{31}P NMR. The molecular weights and polydispersity indices of the obtained polymers were measured in $CHCl_3$ by GPC, using microstyragel columns with pore sizes of 10^5, 10^4, 10^3, and 10^6 Å (Waters) and a detection system consisting of a differential refractometer (Waters model 410), a differential viscometer (Viscotek model H502) and a UV absorbance detector (Waters 486). Molecular weights were determined relative to polystyrene standards.

General procedure for catalyst preparation.

Solutions of the catalyst were prepared by stirring 1 equiv. of $Rh_2nbd_2Cl_2$ and 2 equiv. of the ligand in 1 mL of the desired solvent for 30 min except H_2O, for which premixing of the catalyst precursor and the ligand was done in 0.3 mL of *i*-PrOH, finally adjusting the volume of the solution to 10 mL with H_2O.

General procedure for polymerization of terminal arylacetylenes.

The polymerization reactions were carried out in open tubes (15 mL) under an air atmosphere. In a typical experiment phenylacetylene (0.11 mL, 1 mmol) was added to a solution of the catalyst of a certain concentration with or without 10 mol% of a base in 10 mL of the desired solvent or solvent mixture at 25^{o}C. After a few minutes of vigorous stirring the resultant polymer was filtered, washed with acetone, and dried in vacuo to a constant weight, except the polymerizations in THF and CH_3CN for which the reaction was carried out for 1 hour. In case of THF solvent, the polymer was precipitated in methanol and worked up as above.

7.5. References and Notes

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[27] Several methods have been proposed to determine stereoregularity in PPA: one of the most accepted is based on ^{1}H NMR analysis through the equation: *cis*-% = $[A_{5.82}/(A_{total}/6)] \times 100$ ($A_{5.82}$ is the area of the vinyl proton in the *cis*-isomer and A_{total} is the total area of the polymer spectrum).

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Summary

The research presented in this thesis concerns the design of ligands for a wide range of applications, from nuclear waste treatment to catalysis. The strategies employed to design actinide-selective extractants, for instance, comprise the fine tuning of the ligand electronic properties as well as use of the multivalency concept. The design of novel phosphines for rhodium catalysts involved, in addition to the above mentioned, tuning of the ligand solubility in the desired solvent. The pyrazine core was chosen as the base for a ligand scaffold construction because of its unique electronic properties, which in their turn are responsible for it's, to a certain extent, unusual chemistry.

Chapter 1 illustrates a broad range of applications of polydentate heterocyclic ligands and shows the position of pyrazine-based ligands within this family of compounds.

Chapter 2 gives a brief overview on the recent progress in the field of transition metal-catalyzed functionalization of pyrazines. The uniqueness of pyrazine, due to the increased electron deficiency of the aromatic system, is exemplified by increased reactivity in numerous cross-coupling reactions compared to conventional aromatics.

Chapter 3 concerns a study on the reactivity of activated methylene compounds in Pd/C-catalyzed Michael addition reactions to activated styrenes and Knoevenagel condensation reactions with aromatic aldehydes. The application of the Pd/C-catalyzed reactions towards a one-pot multicomponent synthesis of highly substituted 4*H*-pyranes is presented.

Chapter 4 deals with the development of a novel methodology for the palladium-catalyzed cross-coupling of chloro- and dichloropyrazines with phosphorus pronucleophiles to give phosphino-, phosphoryl-, and phosphonopyrazines. This methodology was successfully applied for the synthesis of lipophilic and hydrophilic pyrazine-based extractants for trivalent cations from model nuclear waste solutions. Hydrophilic ligands of this series exhibited a high selectivity for Am^{3+} over Eu^{3+}.

Chapter 5 describes an extention of the methodology presented in Chapter 4 on calix[4]arene-based systems. Novel, supramolecular, multivalent calix[4]arene-based extractants, employing a divergent synthesis strategy, based on a stepwise build-up of the ligating site on the platform, are presented. The extraction behavior of the ligands was studied on Am/Eu mixtures mimicking nuclear waste. The influence of a synergist, as well as the grouping effect of the calix[4]arene platform, were investigated. Phosphorylpyrazine-functionalized calix[4]arenes displayed a great acid resistivity, preserving the extraction ability up to 3 M HNO_3, and a high affinity for americium.

Chapter 6 describes a simple two-step procedure for the synthesis of pyrazine-based hydrophilic phosphines. These ligands revealed a high activity in the ruthenium- and rhodium-catalyzed reduction of acetophenone under hydride transfer and dihydrogen conditions. The chiral (*R*,*R*)-DAMPYPHOS ligand and $Rh_2(norbornadiene)_2Cl_2$ as the catalyst precursor gave exceptionally high conversions and enantiomeric excesses in the presence of small amounts of isopropanol. The chiral induction enchancement, compared to hydrogenations in the absence of alcohol, is attributed to alcohol coordination to the active center of the catalyst.

Chapter 7 represents the development of a novel, highly active catalytic system consisting of $Rh_2(norbornadiene)_2Cl_2$ and a hydrophilic, neutral phosphinopyrazine ligand for the polymerization of phenylacetylene and 4-methoxyphenylacetylene in alcohol and water. The high stability and robustness of the catalyst allowed its use in the open air atmosphere without loss of the catalytic activity in recycle runs. The effects of an external base, solvent, and amount of the catalyst were investigated. The addition of a base resulted in an increase of the molecular weight of the polymer. However, poorly coordinating or hindered organic bases gave a unimodal molecular weight distribution, while bases capable of acting as a bridging ligand afforded bimodal polymers. Polymers obtained with the above catalyst revealed a high molecular weight and a high stereoregularity, being >99% of *cis*-content.

In conclusion, the newly developed methodology for the palladium-catalyzed P-C cross-coupling of chloropyrazines allowed the synthesis of a family of pyrazine-based ligands with specifically tuned donor properties as well as solubility. Hydrophilic pyrazine-based extractants revealed a high selectivity for americium over europium and showed a great potential for use in the “innovative selective actinide extraction process (i-SANEX)”, directed towards lanthanide/actinide separation (Chapter 4). The same ligand motif being incorporated onto a supramolecular calix[4]arene platform resulted into a series of multivalent ligands with an outstanding acid resistivity and even higher affinity for americium, than that of monovalent ligands (Chapter 5). The synthesis of novel phosphinopyrazines gave rise to novel, highly active and robust catalytic systems for ketone reduction and polymerization of terminal arylacetylenes in ecologically benign solvents (Chapters 6 and 7).

Finally, the above strategies, initially used to design and synthesize novel selective extractants for nuclear waste treatment, proved to be universal and effective in the development of ligands for multiple purposes, and uncovered new prospects in the systematic design of novel ligands with improved properties, which are of high demand in industry.

Samenvatting

Het in dit proefschrift beschreven onderzoek omvat het ontwerp van liganden voor een brede schakering aan toepassingen variërend van de verwerking van kernafval tot katalyse. Als basis voor deze liganden is gekozen voor een pyrazinering vanwege de unieke electronische en chemische eigenschappen.

De synthese van dit type liganden, met zowel specifiek afgestemde donoreigenschappen als oplosbaarheid, is gebaseerd op een nieuw ontwikkelde methodologie voor de palladium-gekatalyseerde P-C-‘crosskoppeling’ van chloorpyrazines. Op pyrazine-gebaseerde hydrofiele extractiemiddelen bleken een hogere selectiviteit voor americium te hebben dan voor europium en bieden perspectief voor toepassing in het op lanthanide/actinide-scheiding gerichte “innovatieve selectieve actinide extractieproces (i-SANEX)”. Het bijeenbrengen van meerdere eenheden van dit ligandmotief op het supramoleculaire calix[4]areen-platform heeft geresulteerd 0 voor het systematisch ontwerp van nieuwe liganden met verbeterde eigenschappen, waar in verschillende industrietakken een grote vraag naar is. Meer details zijn te vinden in de Engelse versie van de samenvatting.

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Enschede

About the Author

Nicolai I. Nikishkin was born on May 31, 1980, in Minsk, USSR. He received his M.Sc. degree (*cum laude*) in 2002 from Belarusian State University, where he studied chemistry. He continued his study at Michigan Technological University and later at LG Chem working on the design and synthesis of novel catalysts for terminal olefin polymerization.

In September 2008, he joined the Molecular Nanofabrication group of Prof. Jurriaan Huskens group in MESA+ Institute for Nanotechnology as a PhD-candidate with Dr. Willem Verboom as a supervisor. His research work was focused on the synthesis of novel pyrazine-based ligands for nuclear waste processing and catalysis. The results of his research work are described in this thesis.