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Enantioselective liquid-liquid extractions

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Enantioselective liquid-liquid extractions

On the synthesis and application of chiral phosphoric acids

Erik Bert Pinxterhuis

On the cover:
two chiral snails, one with a left handed shell, the other carrying a right handed one. Generally, depending on the species, the right handed house is far more abundant.

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Enantioselective liquid-liquid extractions

On the synthesis and application of chiral phosphoric acids

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. E. Sterken
and in accordance with
the decision by the College of Deans

This thesis will be defended in public on

Friday 28 September 2018 at 16.15 hours

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Chapter 1

Resolution by enantioselective liquid liquid extraction

Introduction

Even though the concept of chiral molecules has been known for over a century, one of the challenges in both industrial as well as academic research revolves around obtaining chiral compounds in an enantiopure form.[1,2] The availability of enantiopure compounds, however, is of major importance for many different industries such as agrochemical,[3] flavor,[4] fragrances and pharmaceutical industries[5,6,7] and therefore has a high impact on society as a whole. The importance of chirality is especially underlined in the case of pharmaceutical compounds, where unintended side effects and unnecessary environmental hazards are highly undesired.[8,9,10] Currently however, when it comes to obtaining the variety and scale of chiral compounds requested by the chemical market, challenges are present for the chemical community to deliver.[11]

The very first example of chiral molecules was observed by the famous chemist Louis Pasteur in 1848, after which he defined the concept of chirality.[12,13] He observed that crystals and solutions of naturally occurring tartaric acid rotated the plane of polarization of light passing through, while synthetic tartaric acid had no such effect.[14,15] Moreover, he was the first to successfully hand-pick two different forms of crystals, after spontaneous resolution in the crystallization of racemic ammonium sodium tartrate.[16]

Whereas in the case of Pasteur, hand-picking of different crystal forms resulted in resolution of the tartrate allowing him to obtain the enantiopure compound, this technique is not only highly labor intensive, but also very limited due to infrequent occurrence of chiral crystals for almost all chiral compounds.[17,18]

Chiral products directly obtained from nature or derivatives of such compounds stem from natural sources.[19,20,21,22,23] One of the most viable ways to obtain chiral compounds from natural sources is via fermentation processes or agriculture[24,25], something resulting in a relatively cheap production process.[26,27] Well-known examples of molecules belonging to this class of compounds are amino acids[28], various small acids[29,30] and penicillin[31,32]. However, most chiral compounds cannot be obtained directly from nature, requiring the conversion of non-chiral or pro-chiral molecules into their desired chiral counterparts.[33] This can be done both in an enantioselective and racemic fashion, logically giving two more strategies.[34,35] In the case of enantioselective synthesis towards chiral molecules, the application of asymmetric synthesis[36,37,38] is commonly employed, using a variety of chiral reagents and catalysts[39,40] or enzymes.[41,42,43] Although by itself a very powerful technique to

obtain chiral compounds, being a widely explored field in the chemical community, the high cost price of catalysts[44] and the limited development time due to time-to-market pressure[45] can be seen as a practical limitation. Moreover, the application of heavy metal based catalysts can be unwanted in light of sustainability and environmentally friendliness and in drug development.[46,47,48]

A practical alternative to the two previously mentioned strategies relies on the racemic synthesis and subsequent separation of the enantiomers.[32,33] Generally this leads to in an easier and more facile synthesis resulting in a more cost efficient synthesis, a shorter development time and thus potential reduction of the time-to-market. An obvious requirement for being successful and efficient is resolution of the enantiomers, preferably using a broadly applicable technology that is already in existence or easily developed.[49] Currently the separation of enantiomers is performed on industrial scale using mainly two types of techniques, crystallization[50,51] and chromatography[52,53,54]. Of these two, crystallization is used most frequently, in several forms including co-crystallization[55] and seed-crystallization[56]. Having obvious drawbacks as expensive and cumbersome solid material handling and a maximum yield of 50% (unless racemization can be applied) leaves possibilities for the introduction of other more advantageous techniques.[57] Especially in the case of compounds that are unsuitable for crystallization, chromatography based enantioseparation techniques are applied, such as simulated moving bed chromatography[49,58,59]. Especially on large scale application, high capital investments are required for the employment of this technique.[50,51] More successful is the use of chromatography based separation on smaller and laboratory scale, where the high capital investments are negated by the overall cost of drug development or total compound development costs.[60] Here we see the application and scale up of highly diverse laboratory techniques such as gas and liquid chromatography[61,62] and capillary electrophoresis[63], as well as chiral separation involving membrane based technologies[64,69]. In the latter cases, chiral hosts are embedded and immobilized inside (liquid) membranes, allowing for a reduction of the amount of host needed. Limited transport rates and time-output ratios are seen as major limitations to membrane based technology.[66,67]

To overcome several of these drawbacks, while offering a new approach to solve the challenges around resolution of enantiomers, enantioselective liquid liquid extractions[54,68] (ELLE) were first introduced in the late sixties by Bauer *et al.*[69]. This approach relies on the transport of a single enantiomer from a racemate between two immiscible liquid phases. By employing an enantiopure host or selector that is

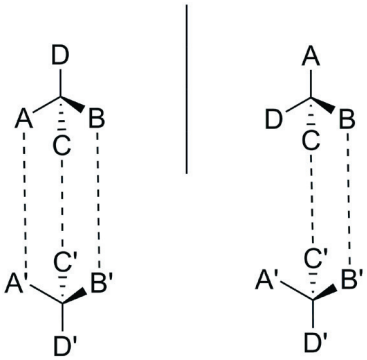
solely soluble in one of the two immiscible phases, the formation of diastereomeric complexes is used to discriminate between the two enantiomers of the racemate.[54,70] The high importance of guest-host complexation immediately becomes apparent. Due to the potentially relatively large contact area, in comparison to for example membrane based technologies[63], the transport of material can be driven to astonishing speeds. Being derived from the mature and in industry omnipresent liquid-liquid extractions[71,72], a lot is known when it comes to scale up and transfer of batch to continuous processes on large scale. Being a highly attractive alternative to the previously mentioned chromatography and crystallization strategies, to the best of our knowledge, so far no industrial scale implementation of ELLE has been achieved.

Operating on the interfaces of several fields and chemical communities including but not limited to catalysis, enantiomeric recognition, supramolecular chemistry, synthesis and chemical engineering, ELLE can be seen as a bridging field between academia and industry.[73] Ever since the first report of enantioselective counter current extraction by Bauer *et al*.[65] the research topic has been inseparable from the field of guest-host chemistry. Highly understandable, seeing ELLE is built on the principles of the application of diastereomeric complexes in novel extraction systems to separate enantiomers. In this chapter, a historical overview of the development of hosts will be given based upon their proposed operating mechanism. First however, a brief insight into the underlying principles and explanation of parameters used in the field are given.

Underlying stereochemical principles of ELLE

As described briefly in the introduction of this chapter, ELLE can been seen as a field on the edge of knowledge in both the engineering as well as the chemical communities. Combining the concepts of solvent extraction and enantiomeric recognition, the method relies, in an ideal scenario, on the transport of a single enantiomer from a racemate between two immiscible liquid phases. By employing an enantiopure host or selector that is solely soluble in one of the two immiscible phases, the formation of diastereomeric complexes is used to discriminate between the two enantiomers of the racemate.[54,66] As with any complexation driven chemistry, chiral recognition is essential in the application of ELLE. After all, without chiral recognition, no enantioselective process can possibly be sustained. In almost all cases currently present in literature[74] the diastereomeric complexes are formed resulting from supramolecular interactions between the enantiopure host and the members of the racemic guest. Relying on, often supported by DFT calculations[75], relatively low strength interactions such as ion pairing, hydrogen bonding, π-π interactions

and Van der Waals interactions, enantiodiscrimination is obtained abiding by the 3-point interaction rule[76] as described by Davankov[77] and Booth.[78] In this simplified model it is argued that not all of the interactions have to be of attractive nature, as long as at least one is an attractive interaction with strong enough force. These revised interpretations of the three point rule of interactions have therefore redefined the initial statement from Stedman.[79,80] Nevertheless the basic principles behind the 3-point interaction rule for chiral recognition are unchanged and displayed in Scheme 1. Herein it is clearly visible that one enantiomer is capable of undergoing 3 interactions, while the other enantiomer only allows for 2 interactions. This difference in number of interactions leads to a difference in complexation energy and therefore complex stability, creating the preference of the host for one specific guest.



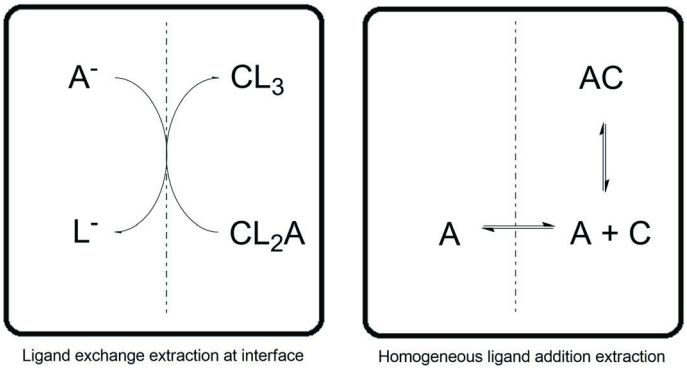
Scheme 1: 3-point interaction model for chiral recognition.[73,74]

Extraction and phase transfer

Next to enantiomeric recognition, ELLE highly relies on the concept of solvent extraction.[65] The phase transfer of one of the enantiomers is of crucial importance to the efficiency of ELLE. Being derived from the well-established field of liquid-liquid extraction (LLE), the transfer of desired molecules between at least two immiscible phases has been investigated significantly[67,68]. From small scale, as separatory funnels and micro reactors, to industrial scale continuous countercurrent systems, LLE is performed in many different systems and shapes. In the case of ELLE, LLE is expanded with several more criteria. A typical ELLE system has a host that is confined to one phase, generally found in the organic phase of the system, which has an extremely low solubility in the other phase.[54] Moreover, the racemic substrate predominantly has to reside in the aqueous phase, however, the diastereomeric complexes formed with the host should be lipophilic enough to completely reside in the organic phase, allowing for host-mediated phase transfer of the substrate.

Finally, enantiodiscrimination between the enantiomers of the racemic guest should occur, a topic which we discussed earlier.

In literature two main phase transfer mechanisms are proposed (Scheme 2), one of which relies on ligand exchange extraction at the interface, while the other relies on homogeneous ligand addition extraction.[81] The main difference between the two proposed models is the place in which complexation occurs. Even though both complexations do not happen in the bulk of the phases, rather close to the interface, a crucial difference is found in the behavior of the guest.[82] In the case of ligand exchange extraction, a process currently most attributed to situations in which both guest and host are confined to their respective liquid phases, complexation only occurs at the interface. This type of mechanism is frequently observed in the field of metal-ion extractions[4]. In the second type of mechanism, the guest is slightly soluble in the other phase. Therefore, racemic phase transfer is an undesired side-effect.[4] The subsequent complexation in the host phase allows for the formation of diastereomers and therefore ELLE.



Scheme 2: Proposed mechanisms for interfacial ligand extraction and homogeneous ligand addition, in which A, L and C represent substrate, ligand and host respectively.

Definition of parameters

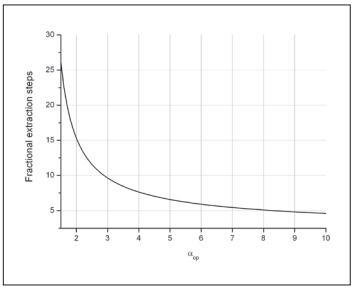
Since the field of ELLE relies on the concepts of both solvent extraction and enantiomeric recognition, the outcome of experiments are represented by parameters from both fields. Where in the field of solvent extraction the efficiency of the process can be expressed by distribution ratio of the extractant over both phases and the yield obtained after isolation[67,68], in all approaches involving asymmetric interactions the term enantiomeric excess is dominant[22,27]. ELLE however combines both concepts, therefore the efficiency of this process is expressed as its operational selectivity

(α_{op}) which represents the ratio of the distributions of the enantiomers between the two phases as shown in Equation 1.a (Scheme 3).[54] The distribution is defined as the ratio between the concentration of one enantiomer in the organic phase and the concentration of the same enantiomer in the aqueous phase (Equation 1.b, Scheme 3). It is important to note that for full resolution (ee >99%) complete selectivity is not required. After all, multistage extraction processes have been proven, in simulation as well as empirically, capable of reaching complete enantioseparation from much lower selectivity's.[83] The relationship between the operational selectivity and the minimal number of fractional extraction steps is given by the Fenske equation (Equation 1.c, Scheme 3) and is displayed graphically in Scheme 3 for ee = 99%.

a) $\alpha_{op} = \frac{D_R}{D_S}$ b) $D_i = \frac{[i]_{org}}{[i]_{aq}} (i = R, S)$

c) $N_{min} = \frac{\ln\left(\frac{x_R/(1-x_R)}{x_S/(1-x_S)}\right)}{\ln \alpha_{op}}$ (Eq 1)

d)



Scheme 3: a) Equation for the calculation of α_{op} b) Equation for the calculation of the distribution of the enantiomers over the different phases in the system. c) Fenske equation d) The relationship between the operational selectivity and the minimal number of fractional extraction steps is given by the Fenske equation (Equation 1.c) and is displayed graphically for >99% ee. Adapted from Schuur et al. (Org. Biomol. Chem. 2011, 9, 36-51)[57]

Host classes

In this overview, a differentiation between various categories of hosts will be made upon their proposed mechanism of action. As described previously in this chapter, two main extraction and phase transfer mechanisms are proposed, allowing for a diffentiation between several groups of hosts. In the first part, a historical overview of the single host systems will be given which is anticipated to operate according to the homogeneous ligand exchange extraction model. This model is, according

to literature, observed mostly for non-metalic single host ELLE systems.[84,85,86] The second category will consist out of single hosts suspected of following the ligand exchange extraction model, as is typically observed for metal based selector systems and anion exchange extractions.[87] The last section shall contain hosts relying on the interactions between multiple hosts and a guest, in some cases using a combination of chiral host molecules contained in the same phase,[88] while in other cases using a host-guest system in both phases.[89]

Non-metallic single host selector systems

The field of enantioselective liquid liquid extractions is relatively old, as the first host-guests systems have been reported as far back as the sixties of last century by Bauer *et al*.[65] This group reported the enantioenrichment of a chiral ferrocene derivative using cyclohexane-diethyltartrate as host in a countercurrent system with 80 units, after which an ee of 12% was obtained.

Ever since then, a dominant role can be observed for crown ether based hosts, as discovered by Pederson.[90,91,92] These crown ethers were modified using chiral moieties by Lehn[93] and Cram,[94] and applied as chiral hosts in enantioselective recognition and ELLE. Especially the introduction of two different chiral 1,1'-bi-2-naphthol (BINOL) scaffolds led to the development of one of the earliest ELLE systems for the extraction of ammonium salts of amino acids and amino acid esters (Figure 1, host 1).[95,96] Moreover, with an intrinsic selectivity of 31 for host 2, an excellent and efficient system, leading the field for over 3 decades in highest selectivity observed. It took until 2016 to be able to surpass this efficiency, by the SPINOL derived chiral phosphoric acids (Chapter 3)[97]. It is therefore not surprising that the three before mentioned scientists shared the Nobel prize in 1987 for their pioneering work and "development of molecules with structure-specific interactions of high enantioselectivity."[98]

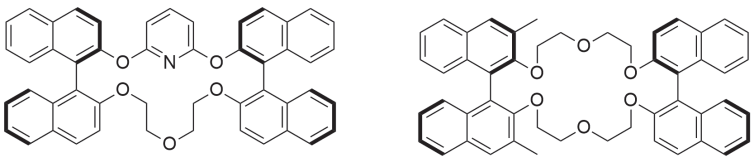


Figure 1: Crown ether based hosts, developed by Cram et al. [95,96]

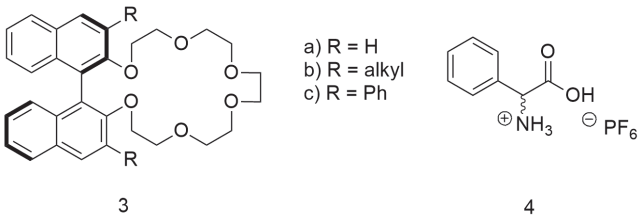
Cram's dilocular (bearing 2 chiral moieties) hosts consist of an asymmetric crown ether as center core surrounded by two different BINOL scaffolds. By further modification, the importance of the pyridine moiety was investigated.[90] Extensive crystallization studies gave insight into the complexation and supported the assumption that

these hosts operate according to the homogeneous ligand extraction model. Using chloroform as organic solvent, it was assumed that the primary chiral amine salts with various counter ions (F^-, Br^-, Cl^- or PF_6^-) were capable of slight solubility in the organic phase to allow complexation. Using ^{1}H-NMR studies, the importance of the formation of two identical and chiral cavities by the naphthalene 'walls' contributed highly to the pioneering success of this host.

The later introduction of two methyl substituents at the 3,3'-position of one of the BINOL backbones furnished a highly efficient host capable of enantioselective extraction of chiral ammonium salts of amino acids and amino acid esters.[99] Extension of the chiral barriers of the naphthalene rings enforced, according to the authors, a more rigid conformation, providing better binding to the guest resulting in a higher intrinsic selectivity. Distributions of up to 0.5 were observed using chloroform as solvent at 0 °C. Intrinsic selectivities of up to 19.2 for amino acids[91], up to 12 for primary amine salts,[100] and up to 31 for amino ester salts were reported.[101]

The close connection of the fields of ELLE and chiral recognition becomes once more apparent, as simultaneously the group of Stoddart[102] and Lehn[103] worked on the introduction of different chiral scaffolds into multiheteromacrocyclic structures as crown ethers. Whereas Stoddart *et al*. incorporated saccharides[104], Lehn incorporated tartaric acid moieties.[105] In both cases chiral recognition for the same chiral ammonium salts was observed as for the previously mentioned hosts developed by Cram.[90] These systems were, however, never used in ELLE.

In the years following the dilocular crown ether hosts, the elimination of one of the chiral moieties was established by extending the reach of the 3,3'-substituents on the BINOL scaffold (Figure 2). The nature of these 3,3'-substituents proved vital to the chiral differentiation between the enantiomers of the guest. In the case of R = H, only slight recognition is described, while the introduction of a short alkyl chains provides reasonable intrinsic selectivities. When R = Ph is employed, the highest selectivities are reported ranging from 3.9 to 19.5 for the ammonium salts of amino acids and amino acid esters.[99] Propositions are made that additional attractive π-π or Van der Waals interactions between the aromatic R substituent and ammonium salt contribute to better binding. Special attention was given to the extraction of phenylglycine, by optimizing solvent combinations and temperature. An increase to a selectivity of 23.4 was realized by employing a mixture of acetonitrile and chloroform.



3 4

Figure 2: Crown ether and BINOL derived hosts, developed by Cram, and its respective guest phenylglycine 4. R= directing group.

Based upon literature discussing the chiral interaction between small molecules,[106,107,108,109,110] De Mendoza *et al*.[111] reported in 1992 a novel host based upon structural design. Having four potential points of interaction with the designated guest molecules phenyl alanine and tryptophan, enantioselective extraction was envisioned and achieved under neutral conditions. Addressing the long standing challenge of enantioselectively extracting compounds in a netto uncharged form.[112] Based upon a crown ether, guanidinium and naphthalene ester, the host can be obtained in four synthetical steps and has optimal interaction with amino acids in their zwitterionic form (Figure 3). The specialized design allows for non-selfcomplementary binding sides and prevents internal collapse. Using DCM for extracting experiments, distributions of 0.7 and up to 30% ee are observed, prompting the hypothesis on a 1:1 complexation structure. Competition experiments showed that amino acids without aromatic moiety have lower affinity to the receptor.

Application[113] of this host into a U-tube extractor[114] allowed for expansion of the number of tested guests and hosts. Inside this W- (and later on U-) shaped reactor vessel, the processes of extraction and back extraction to the host containing organic phase could be combined. By employing both a feeding and receiving phase, the capability of a host to release the enantioenriched guest can be established. Moreover, employing a U-tube experiment is a good procedure to demonstrate that the host can transport the desired enantiomer in a catalytic fashion with multiple turnovers. Modification of the host by changes to or omission of the naphthalene ester allowed for optimization of the ee observed to 79% ee for tryptophan. Moreover, changing the ester functionalities for amides was found to give more extraction, albeit at a lower ee. Subsequent structural and molecular dynamic studies explained the high enantioselectivity when omitting the naphthalene interaction point, as these fully support a two-point interaction model between guest and host.[109,115] Application of a host-guest system in a U-tube extractor not only allows for direct optimization

of the parameters involved in extraction,[54] but also shows the ability of the host to quantitatively release the guest and indicates its applicability to large scale processes.

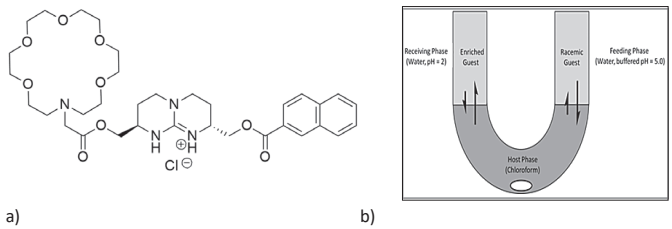


Figure 3: a) Guanidinium based hosts, developed by De Mendoza.[111] b) The general model of a U-tube extraction vessel.

The use of crown ether based hosts continued by publications by Bradshaw *et al*.[116] Their derivatization of the crown ether was based on the addition of alkyl chains of various sizes and branching, and the inclusion of a pyridine ring creating a chiral cavity.[117] The obtained hosts were capable of extraction of [α-(1-naphthyl)ethyl] ammonium picrate salts with operational selectivities between 2.2 and 3. They hereby clearly state that the three point rule of chiral recognition has been satisfied by the inclusion of the pyridine ring,[102] allowing for π-π interaction between guest and host and creating chiral selection. Similar observations were made earlier in crown ether chiral extractions.[118, 119] The other two binding points are hydrogen bond based.[120,121] The choice of a picric acid based counter ion is justified by their solubility in both organic and aqueous phases,[122] allowing the guest to conform towards the homogenous ligand addition extraction mechanism.

One year later, the group of Nishimura reported the chiral recognition of amino acids[123] by the transport thereof using calix[4]arene derived esters (Figure 4).[124] These inclusion type hosts[125] were shown to form a 1:1 complex with amino acids and amino acid esters in a DCM/water system. It was observed that amino acids (esters) bearing an aromatic group showed significant increased binding properties. Ee's were reported ranging from 11 to 73%. Application of these findings were performed by Goto *et al*. who enhanced the efficiency of an enzymatic hydrolytic resolution by selectively extracting the unreacted amino acid ester, whereas the amino acid was not extracted.[126] The sensitivity of these systems was explored by Yilmaz, who reported that derivations of the calix[4]arene led to a loss of enantioselectivity, [127] even for ammonium picrate salts. The extraction of organic molecules and organic cations has since then been a hot topic, however few cases report enantioselectivity.[128,129] Application of calix[4]arene bearing amino alcohols in U-tube extractors was reported by Sirit *et al*.[130,131] Operational selectivities of up to 3.3 were obtained, as well

as good transport rates. Both transport rate and ee decreased after a period of 90 min. Moreover, a relatively difficult synthesis route decreased the industrial viability.

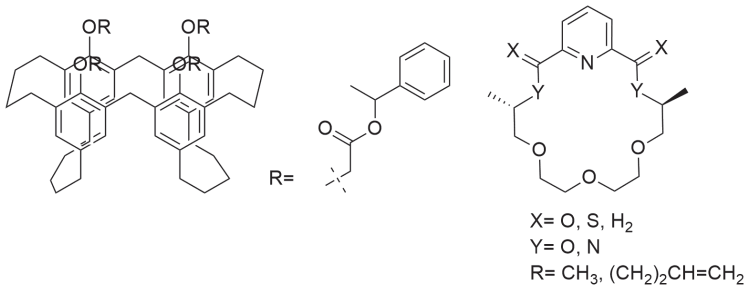


Figure 4: Calix[4]arene based hosts, developed by Nishimura.

In 2005 the group of Gil reported another crown ether based host system (Figure 5) upon the same principle as the work of Bradshaw (Figure 4),[132] however, eliminating the need for an included pyridine ring. The introduction of long alkyl chains overcame the challenge of the solubility of the host in aqueous media and the pH sensitivity involved (Figure 5). Successful chiral extraction was obtained for two guests, *sec*-butylammonium picrate and α-methylbenzylammonium picrate, using acetonitrile as organic solvent. Host derivatization was obtained by modification of the 'ends' of the lipophilic chains by the introduction of aromatic moieties. In line with the results obtained by Bradshaw,[112] the re-introduction of aromatic groups into the host (albeit in a different position) increased the obtained ee and amount extracted. Moreover the steric hindrance involved in the aromatic groups showed to be important towards the extraction, indicating that the extended aryl functionalities bend over to interact in the vicinity of the crown ether.

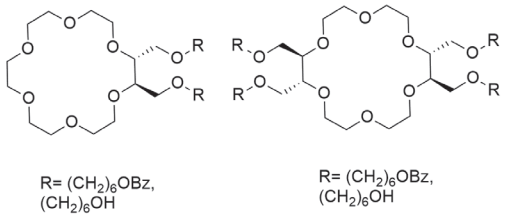


Figure 5: Lipophilic crown ether based hosts, developed by Gil and Bradshaw.

The relatively easy access to cinchona alkaloids quinine/quinidine and chinchonine/cinchonidine from natural sources allowed for their implementation into the medical domain[133], and later in the field of enantiomeric recognition.[134,135,136,137] Their application in the extraction of enantiomers from a racemic mixtures was first reported by Tsurubou in 1988[138] and subsequently in 1991.[139] In combination with

acid derivatives of camphor or acetyl substituted amino acids as guests, a maximum operational selectivity of 1.21 was observed. The host in its neutral form, however, was found to be soluble in both the aqueous and organic phase. As a result, complexation may take place in both phases,[140] resulting in a lower observed selectivity.

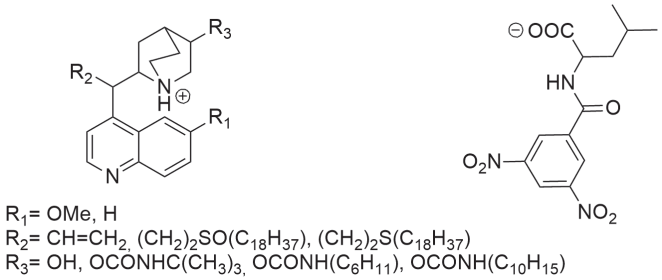


Figure 6: Modified cinchona alkaloid based hosts, and their complementary DNB-protected amino acid guest.

Further derivatization of cinchona alkaloids by protection of the alcohol group and introduction of a long alkyl chain to ensure solubility in organic solvents allowed for the successful extraction of dinitrobenzyl substituted amino acids.[141,142] The reported selectivities are much higher than previously observed by Tsurubou[126], which is supported by various studies regarding conformational spaces.[143,144,145] Studies regarding enantioselective interactions for (derivatives of) cinchona alkaloids showed that the difference in extraction efficiency is most likely due to the effect of steric hindrance around the coordination site. (Figure 7)[146,147] Extensive research towards the parameters involved in extraction, i.e. solvent, pH, host/guest ratio, substrate structure, was performed, yielding optimal extraction conditions giving an ee of >95% and 70% complexation of DNB protected leucine in a single extraction/back extraction cycle. The DNB group was proven to be vital to efficient extraction, as lack of it led to a reduction of ee obtained to maximum 20%. This importance is contributed to a π-π interaction between the DNB protecting group and the aromatic moiety of the cinchona alkaloid. [148,149] Using NMR, NOE, X-ray, and molecular modelling studies, the mechanism of the stereoselective recognition and the enantiomeric interactions involved were revealed.

Application of the cinchona alkaloids in centrifal of centrifugal contactor separators was achieved by De Vries *et al*.[79,150] Using the advantages of highly efficient mixing, the very short contact times allow for rapid resolution.[151,152] Optimization of solvent, pH, substrate and resident time, as well as the optimization of the host structure allowed for continuous separation with ee's up to 67% and excellent transport over the phases. Full resolution with an ee >99% was obtained using a series of centrifal

of centrifugal contactor separators,[153] indicating their capability of fully substituting the U-tube devices.[110] This allowed for a throughput of 1,9 L/min, or 17.7 kg guest/ week using only 60 grams of host. The largest commercially available CCS (2009) was calculated to perform resolution on multi ton scale, up to 10 tons/week. This was the first time any ELLE process was performed in a continuous countercurrent mode, giving the opportunity to obtain full resolution of the racemate into the corresponding single enantiomers. Continuous recycling of the host up to 50 times without loss of enantioselectivity in the process was achieved. Modelling studies showed that the homogeneous ligand exchange mechanism applies to the extraction of DNB-substituted amino acids, even in CCS equipment.[154] Moreover, they showed that equilibrium modeling is capable of describing an ELLE system in continuous operation mode.[141] In light of a 'greener' and more environmentally benign version of this ELLE, very recently, the previously preferred dichloroethane as solvent was replaced by octanol.[155] Moreover, for the first time, an enantioselective liquid liquid extraction process was performed in a micro reactor using slug flow, potentially enabling for a faster time to market and scale-up process, as well as precise control over the parameters involved and the possibility of direct, in-line analysis.[156]

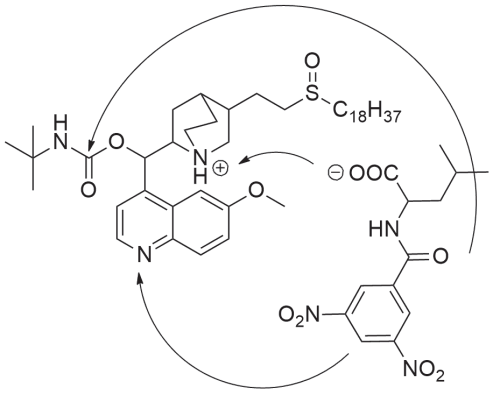


Figure 7: Modified cinchona alkaloid based hosts, and the proposed interactions with the complementary DNB-protected amino acid guest.

Even though the work on cinchona alkaloids derivatives as hosts in ELLE is still ongoing, the realm of the crown ether still dominated during the early years of existence of cinchona alkaloid research. Another example of a crown ether based chiral selector was reported in 1997 by the group of Naemura. [157] The design of their host was based upon a chiral phenolic crown ether having first alkyl (adamantyl, methyl, t-butyl) and later aryl (phenyl or naphthyl) chiral barriers.145,[158],[159] Moreover, extending the incorporated phenol with a p-(2,4-dinitrophenylazo)-functionality was proposed to enhance the chiral barrier to the extent of efficient chiral interaction,

however, not to introduce large amounts of repulsive interactions and/or sterics.[160] This specific functionalization also increased the acidity of the phenol by the electron withdrawing properties of the nitro groups. The advantage of the use of a phenol incorporated crown ether was found to be the extraction of chiral amines and amino alcohols under neutral conditions, where the involvement of the hydrogen bond between the phenol and the guest is of vital importance. Optimization of extraction procedure and parameters was performed by De Haan *et al*. in 2006.[77] They identified the requirement for the stereogenic center to be located next to the amine in the guest compound to allow enantiodiscrimination by the host. Using butanol/hexane as organic solvent and optimized aqueous pH of ~9.7, intrinsic selectivities between 1.5 and 3.2 are observed, with exception of phenylglycinol, yielding an intrinsic selectivity of 12. Currently research is performed towards the possibility of using light to switch the cis/trans behavior of the azo-phenolic moiety and the influence thereof on the extraction behavior (Figure 8).

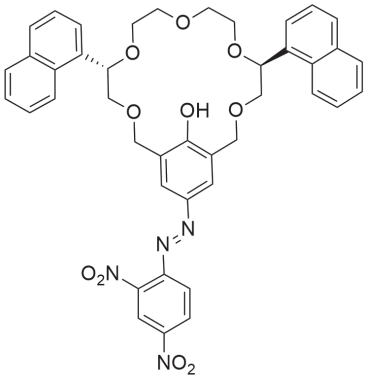


Figure 8: Azaphenolic crown ether hosts.

Reintroduction[107] of the guanidinium moiety as base for a host was performed by Davis *et al.* in 1999,[161] in combination with a modified cholic acid moiety, previously used by the group.[162,163] The host was found to be efficient for the enantioselective extraction of N-acetyl protected amino acids (Figure 9).[164] Modification of the cholic acid moiety was established via the protection of both alcohol groups via a phenyl substituted carbamate. Up to 10:1 diastereomeric ratio (for N-acetyl-alanine) and distributions of up to 1.0 (for N-t-Boc-valine) are reported, where it becomes apparent that the N-acetyl-functionality enhances the ee observed. When omitted, a loss of diastereomeric ratio to a maximum 2:1 was reported. Using NMR and NOE experiments, host-guest structures are proposed, in which interactions were observed between the carbamate protecting groups of the host and the amine functionality of the guest. A collaboration between the groups of Davis, De

Mendoza and De Vries allowed for application of this guanidinium based host into both U-tube and hollow fiber extraction equipment.[165] Enantioselective transport and release via ion exchange was obtained in the U-tube extractor and the host showed several turnovers. The transported guest in the receiving phase had an ee of around 64%, showing a slight decrease in ee over time. (something common for U-tube extraction devices)[110,54,166] Being highly dependent on the relative surface area between the phases, implementation in hollow cellulose fibers potentially allowed for investigation in an industrially relevant setting.[153] Using 1-octanol in hexane, up to 31% ee and 70 turnovers were observed. Transport was found to be highly sensitive towards pH, as small changes in receiving or source phase resulted in loss of ee or lack of transportation. The rate of transport in the membranes was too slow for large-scale application.

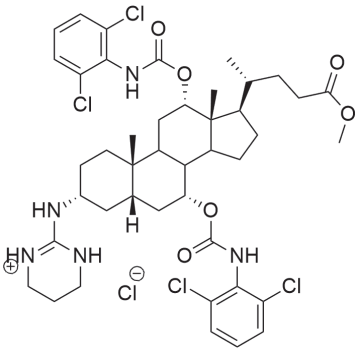


Figure 9: Steroidal guanidinium host.

Spada *et al*.[167] reported in the same year a new class of hosts relying on deoxyguanosine derivatives for the formation of G-quadruplex aggregates by self-assembly[168,169] to form an inclusion host (Figure 10).[170] The presence of K^+ ions is vital to the formation of these supramolecular structures, prompting the employment of the potassium salts of DNP-protected amino acids as guests. Using long alkyl chains for solubility reasons, short and long oligomeric structures are observed, with slight difference in enantiomeric discrimination. It is expected that the outside of the assembled structures is lipophilic, while the inside with the hydrogen bonds between the different participating deoxyguanosine moieties is hydrophilic. Extraction experiments are reported with ee values up to 29% (for DNP-protected tryptophane) and selectivities between 1.1 and 3.0. Highly reversible binding between the chiral guest and intermolecular complexation of these aggregates is observed, making the system sensitive to different counter ions.

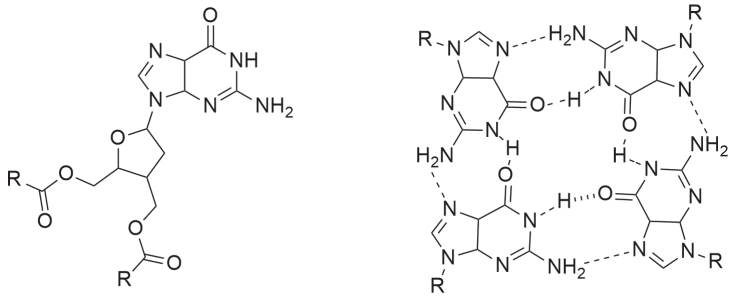


Figure 10: Deoxyguanosine derivative used to form the self-assembled G-quadruplex aggregates (right). R = p-(n-$C_{12}H_{25}O$)C_6H_4

A special version of the non-metal based host designs was reported by Lacour and coworkers,[171] as indeed their host does not contain a metal, however the employed guests are chiral bipyridine ruthenium (II) complexes (Figure 11). Finding many applications in the fields of organometallics[172,173], photochemistry[174], materials[175] and biochemistry[176,177] the choice for this specific class of guest is highly understandable. The separation of the racemic metal complexes, however, proved challenging,[178,179] making the application of such separation via ELLE highly desirable.[83] The chiral recognition between chiral TRISPHAT anions[180] and bipyridine ruthenium (II) complexes could be established.[181,182] The mechanism relies on the difference of solubility between the individual host and guest (and their respective counter ions) and the diastereomeric complexes. Since the host-guest complex is soluble in the organic phase, movement of the diastereomeric host-guest complex from the aqueous into the organic phase is observed after complexation. Thus there is a reverse homogeneous ligand exchange mechanism operating.[183] Full extraction is observed on vigorous stirring in only 10 min, using chloroform as organic solvent, where diastereomeric ratios of up to 49:1 are observed using ^{1}H-NMR experiments.

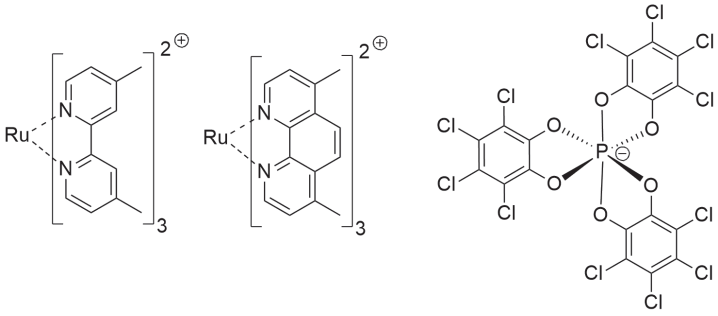


Figure 11: Ruthenium(II) complexes and TRISPHAT salts, as used by Lacour.

In 2008 the group of Kim[184] reported two highly promising hosts for the extraction of amino alcohols containing an aromatic moiety. Surprisingly, this is the first host-guest system that relies on covalent binding upon 'complexation'.[185] Using a BINOL derived scaffold with an salicyl aldehyde functionality allows for nucleophilic attack of an unprotonated primary amine under slightly acidic or basic conditions (Figure 12) to form the corresponding imine. The systems remains dynamic since water is always present in the biphasic system, and strong pH-shifts encourage release of the amine and allow for back extraction.[186] In comparison to non-covalent binding, covalent imine formation is slower, however much stronger. Energy minimization studies by DFT calculations indicate the importance of the urea/guanidinium moiety in hydrogen bonding and enantiomeric recognition. Using the host employing a urea functionality, moderate intrinsic selectivities are described (α = 3-5)[184], while the implementation of the guanidinium functionality yielded high intrinsic selectivities for a range of amino alcohols. The best intrinsic selectivities were obtained for 2-amino-1-propanol and 2-amino-1-butanol. Subsequent modification of the aldehyde to a ketone yielded a slightly higher de, up to 52%, but a much higher yield up to 96%.[187] 1H-NMR studies were preformed to calculate the separate binding strengths of the enantiomers and indicates the importance of using an apolar solvent. The use of polar DMSO resulted in a complete loss of stereoselectivity. Finally acid hydrolysis with a pH <1 was used to release the guest from the complex. Full complexation was obtained, applying chloroform as a solvent, in just under 1 h at 40°C, however higher enantioselective discrimination is reported at 0°C. Modeling studies indicate the reduced strength of the hydrogen bonds involved in recognition at elevated temperatures, and even release of the guest at temperatures above 50°C. To ensure the presence of the guest in both phases (and abide by the homogenous ligand exchange model81) aliquat 338 was used as both a phase transfer catalyst and counter ion to the amino alcohol guest. The imine complex, however, was found to be freely soluble in organic solvents, but not in aqueous media, despite its ionic character.[175]

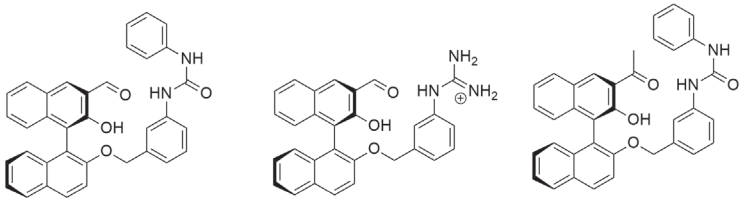


Figure 12: BINOL derived, aldehyde and ketone based covalently binding hosts.

In 2011 our group reported the use of BINOL derived chiral phosphoric acids as hosts for the extraction of various primary chiral amines (Figure 13).[188] Using 4 different hosts (with different sustituents at the 3,3'-positions on the BINOL scaffold) operational selectivities of up to 2.0 are described. The importance of the aromatic substitution on the 3,3'-positions (highlighted in blue, figure 13) was immediate apparent as lack of substituents leads to a complete loss of enantiodiscrimination. Optimization of extraction parameters such as solvent, pH and temperature were reported. It was found that the highest extraction values could be obtained using tetrachloromethane with ee values of up to 24%. Host-substrate complexation data were obtained *via* a combination of NMR, UV-vis and CD spectroscopic techniques. Finally, reversibility of the host-guest binding was proven by employment of 1 of the hosts in a U-tube extractor, indicating the host to be capable of multiple turnovers, dynamic binding and release of the guest upon strong pH changes. Subsequent introduction into CCS extractors (as previously described)[142] allowed to demonstrate the ability of BINOL derived chiral phosphoric acid based hosts to allow for scale up to an industrially viable process.[189] Using a series of 6 consecutive CCS extractors, 70% ee was obtained. Modeling studies were used to indicate the optimal extraction parameters for the employed centrifugal contactor-separators.[190]

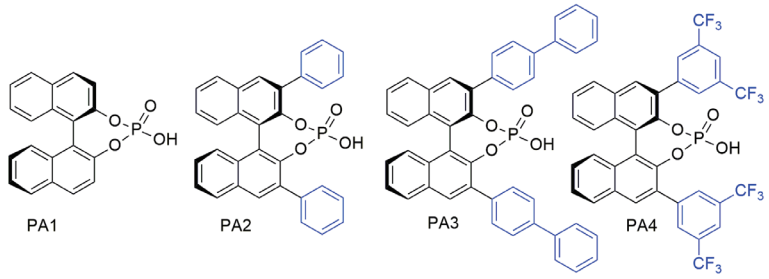


Figure 13: Chiral BINOL derived phosphoric acids for the extraction of chiral amines.

The three classes of cyclodextrin (α,β,γ-) have been known to perform well as inclusion hosts[191] and they have found application in chiral capillary electrophoresis[192,193,194] and chiral HPLC[195,196,197,198,199]. They often show a generally high solubility in aqueous media[200] meaning that extraction of a racemate from an organic solvent is possible. This allows for the extraction of relatively apolar substrates such as ibuprofen.[201] Operational selectivities of up to 1.3 were obtained, and modelling studies were used to indicate the optimal range for extraction parameters as pH and concentration. Similar operational selectivities were obtained by the group of Tang, for the extraction of 2-chloromandelic acid[202], α-cyclohexyl-mandelic acid[203] and equol ((3*S*)-3-(4-hydroxyphenyl)-7-chromanol) (Figure 14).[204] In each

case modelling studies were applied to indicate the optimal extraction conditions. Modelling also showed that multiple extractions can be applied to increase the ee to >95%. This was confirmed for the above mentioned substrates, where the group of Tang applied their system in the previously described CCS systems.[205] In this paper it was also shown how important the correct pH regime is towards the distribution observed during extraction. Moreover, the introduction of phenylsuccinic acid[206] and ketoconazole[207] as guest using the same host type in CCS systems has been reported. The latter compound is widely used as antifungal drug. Even though it is marketed as racemate, recent studies reported that the two enantiomers have a different pharmacological activity.[208] Kockmann *et al*. reported[209] the first application of ELLE in liquid-liquid extraction columns, successfully extracting phenylsuccinic acid using the same system as used by Tang.[202]

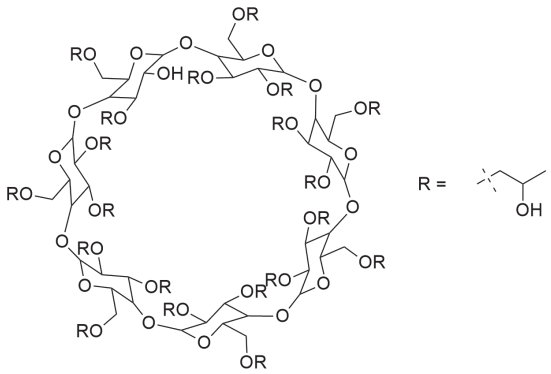


Figure 14: cyclodextrin derived inclusion hosts, as used by Tang.

Recently, an efficient enantioselective extraction with an operational selectivity of 3.1 was reported for the extraction of 4-chloro-mandelic acid by *N*-2-chloro-benzyloxycarbonylvaline using DCM/water mixtures.[210] Optimization of the extraction parameters indicated high distribution values at a low pH of <3, however pH values of >3.5 were required for high operational selectivities. Although only one guest (4-chloro-mandelic acid) was investigated, host variation with different amino acids resulted in loss of selectivity (α_{op} <1.1). Variable Temperature experiments indicated efficient extraction can be found between 10-25°C.

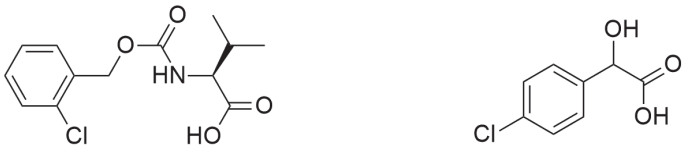


Figure 15: 2-Chloro-N-carbobenzoyloxy-valine and 4-chloro-mandelic acid.

Metal based selector systems

The second category of selectors consists of single hosts suspected of following the ligand exchange extraction model, as is typically observed for metal-based selector systems.[83] Herein, as described in the introduction of this chapter, the contact between free guest and free host is only present at the interface of the two immiscible layers involved in enantioselective liquid liquid extraction. The metal complex generally resides in the organic phase, by the employment of hydrophobic enantiopure ligands. The ligands are designed in such a way that the diastereomeric host-guest complex is solely soluble in the organic phase, allowing for extraction of the guest from the aqueous into the organic phase.

This principle was first applied by the group of Gil-Av in 1979 for the resolution of amino acids based on ligand exchange chromatography.[211] The use of a chiral mobile phase employing a copper(II)proline complex as addition to the eluent separated racemic mixtures of amino acids on a cation-exchange column without the need of prior derivatization of the amino acids. With separation factors up to 1.3, not only the resolution of racemic mixtures of amino acids were presented, but also full resolution of mixtures of several racemic amino acids. Temperature is an important parameter, as in some cases better resolution was observed at higher temperatures. In the case of serine however, some racemization was observed at high temperatures (above 90°C). Application of pressure allowed for more efficient resolution,[212] a technique still used in chiral HPLC today.[213,214]

Even though the concept of chiral separation on chiral stationary phases had been known[215,216], Gübitz and coworkers were the first to employ Cu(II)proline based complexes as chiral stationary phase for the resolution of amino acid (Figure 16)s.[217] α-Amino acids can complex in a bidentate fashion allowing fulfillment of the 3 point rule of chirality.[218,102] The thereby formed dynamic diastereomeric complexes have different physical properties, allowing one enantiomer to be released preferably then the most stable diastereomeric complex, thereby changing the retention time and creating resolution.[219] The retention time was also found to be dependent on the hydrophobicity of the amino acid. The absence of the hydroxy group in the side group of the proline resulted in a significantly lowered selectivity, leading to the assumption that this hydroxyl functionality is involved in the binding of the Cu(II) ions. Moreover, this hydroxyl functionality contributes to the hydrophilicity of the material.[220] The use of other metal ions, such as cobalt (II), nickel (II) and zinc (II) did not result in sufficient resolution. High temperatures (50-80°C) were required for

obtaining resolution. A large variety of amino acids could be separated on analytical scale using this technique.

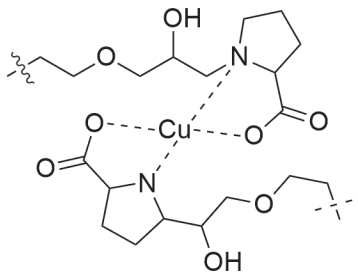


Figure 16: Cu(II)- amino acid based complex as applied by Gübitz.

The application of this type of host in enantioselective liquid liquid extraction, however, was first performed by Takeuchi *et al*. in 1984.[221] N-alkylation with long alkyl chains of L-proline resulted in a highly suitable ligand for Cu(II) and ELLE of neutral amino acids. The long alkyl chain was introduced for solubility purposes, as this confines the host in the organic phase. Using n-butanol and water as solvents, several amino acids could be extracted successfully. Enantioselecitivity observed in ligand exchange was higher when 4-hydroxy proline derivatives were used, coated on ODS silica gel, yielding intrinsic selectivities of up to 4.5. When covalently bound to normal silica or organic polymers, however, lower enantioselectivity was observed. High concentrations of guest were applied, to ensure sufficient availability of the desired enantiomer. Variation of concentration of cupric-ions were used to determine complexation constants of the amino acid enantiomers with respect to the pure enantiomers. Several years later, Pickering and Chaudhuri proposed the interfacial complexation mechanism as main model for this system based on Cu(II)-L-proline based hosts.[222,223] This was supported by Pursell and coworkers, who found a good correlation between the interfacial ion exchange model and experimentally obtained data.[224]

The Cu(II)(*N*-(2-hydroxydodecyl)-L-hydroxyproline complex was studied as a host by de Haan *et al*.[77] as extractant for a series of chiral amines. Varying the position of the hydroxyl functionality form the 4 to the 5 position in comparison with Takeuchi, yielded a highly pH dependent extraction system. At low pH values, only physical partitioning, extraction without host involvement, is observed, while at high pH values moderate selectivities up to 1.3 are observed. The polarity of solvent and solvent compositions were found to have a large influence on the extent of the extraction and the selectivities obtained. When using high percentages of hexane to decrease

the polarity of the organic layer, operational selectivities could be boosted to 1.7. A limitation was noted, as they were unable to separate 2-aminopentane enantiomers, indicating the requirement for a second functional group for enantioselective recognition.[77]

Europium in combination with chiral camphor based ligands form complexes reported to "induce enantiomeric shifts of NMR signals" in aqueous media by the formation of a rapid equilibrium.[225,226] The application of bidentate ligands was found to induce a much larger shift. Of high importance is the presence of water molecules, as they occupy a number of coordination sites around the europium ion. Displacement of these water molecules by the zwitterionic amino acids leads to the formation of diastereomeric complexes, proposed to be responsible for the shift difference.

Based upon this form of chiral recognition, the group of Tsukube turned towards the application of chiral tris(β-diketonates) lanthanide(III) complexes as host for the ELLE of unprotected amino acids in 1996.[227] Using DCM as solvent, the application of amino acids in their zwitterionic form allowed for a 1:1 complexation to the host. Apart from the previously described europium system, three other lanthanide complexes were examined based on praseodymium (Pr), erbium (Er) and ytterbium (Yr) for a small range of amino acids (4 examples). In each case europium tris(β-diketonates) were found to yield the highest extraction, however ytterbium tris(β-diketonates) complexes were found to yield the highest ee during extraction (up to 49%, $\alpha_{op} = 2,2$). Information on the basic receptor/carrier behavior was obtained using FAB-MS, which revealed that the lanthanide complexes were anionic species.[228,229] Ion-pair interactions between the metal-ion and the ammonium salt of the amino acids, in combination with hydrogen bonding with the β-diketonate ligands are anticipated to induce two-point binding, creating the diastereomeric complexes involved. Moreover, ligand differentiation was found to increase the obtained ee for europium tris(β-diketonates) up to 49% ee, however, at a considerable loss of amount extracted guest.

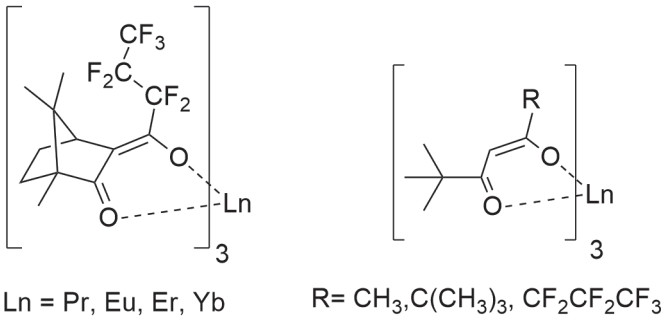


Figure 17: Chiral tris(β-diketonates) lanthanide(III) complexes as applied by Tsukube.

Host design based on metalloporphyrins was described by Inoue *et al*.[230] Since chiral strapped porphyrin complexes with C2h or C4h symmetry, bearing an iron or manganese core were found to efficiently catalyze asymmetric oxidations of olefins and sulfides[231],[232] preferential chiral interactions were envisioned for chiral extraction as well. Using covalent blocking of the unstrapped face of the porphyrin allowed for the formation of a cavity in which electrostatic, hydrogen bonding and Van der Waals interactions are strategically incorporated. NMR and IR studies were used to confirm these type of interactions. As opposed to most previously reported hosts who target the cationic,[91,92,] neutral[107] or zwitterionic form[112] of amino acids, the design aims to achieve high enantioselectivity by binding the anionic carboxylate of the amino acid. Using chloroform and water as solvents, and 10 h of stirring at room temperature, diastereomeric ratios of up to 96/4 could be obtained for several N-protected amino acids. The nature of the protecting group (-Cbz, -Boc, -acetyl, -(3,5-dinitrobenzyl)) does not seem to have a large influence on the obtained enantioselective extraction. Unfortunately, the release of the guest was not reported.

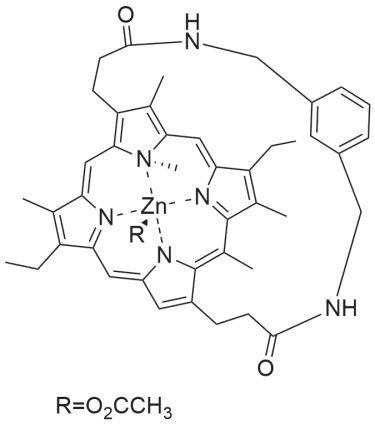


Figure 18: Strapped N-alkylporphyrin zinc hosts.

Salen-type ligands, well known in asymmetric catalysis for their use in highly enantioselective catalytic processes, such as epoxidation[233], epoxide opening[234] and kinetic resolution[235], were first applied in ELLE as their respective cobalt (III) complexes in 2006 by the groups of Gennari and de Vries (Figure 19).[236] The chiral recognition properties of this type of complexes was proven by Fuji,[237] pointing De Vries in the direction of N-benzyl protected amino acids. Ligand structure optimization allowed for exceptionally high ee values up to 96% with a range of N-benzyl protected amino acids. Moreover, the extracted yield is almost quantitatively, indicating highly efficient binding. Hypotheses were proposed that suggested the enantioselective recognition is due to bidentate complexation with the cobalt(III)-cation, and steric repulsion between the amino acid side group and the Salen-type ligand. The best obtained results were reported for N-Bn-alanine (equivalent extracted: 0.99, ee 93%), but extraction method optimization led the other amino acids to closely follow these values. Major drawback for this guest-host system towards their industrial application lies in the inefficient back extraction of the N-protected amino acid. Guest release was effected via reductive back extraction using 10 equiv. of sodium dithionite, after which the obtained Co(II)-complex needs to be air-oxidized before it can be re-used. Studies towards the iterative liquid-liquid extraction and resolution was conducted by Reeve *et al*.[238], indicating full resolution of both enantiomers in just 6 iterative steps. Moreover, they found a more efficient reductive back extraction method, employing 1 equiv. of L-ascorbic acid in methanol. [239] The implementation of different N-protected-amino acids as guest in this extraction system was investigated by the same group, yielding less efficient extraction results.[240]

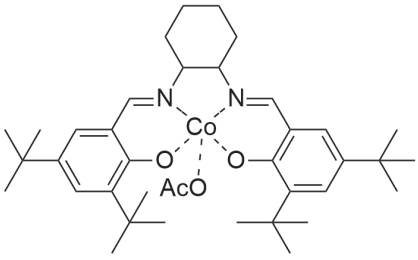


Figure 19: Chiral cobalt(III)salen type complexes for the extraction of N-benzyl-amino acids.

In recent years, the application of palladium based host systems was developed by a collaboration of the groups of Feringa, De Vries and Minnaard[241] Using [$PdCl_2$((S)-BINAP)] as host, the extraction of amino acids at neutral pH could be established with operational selectivities of up to 2.8 (Figure 20). Various extraction parameters, as pH, solvent combinations, and substrate scope were investigated,

before application in a U-tube extractor device. At least 4 turnovers were achieved in 10 h, with ee values reported of up to 30% ee for the extraction of tryptophan. In the subsequent paper[242] more extensive counter ion, solvent combinations and substrate scope were presented. Using chlorinated solvents, the importance of the electron density of the aromatic moiety of the amino acid was investigated, allowing for an increase of observed operational selectivity to 6.8. The application of an N-protecting group was found to reduce the selectivity to about 1.3 under the same conditions. The group observed high preference of the host complex for α-amino acids over β-amino acids and reported a single step separation/enantio-extraction combination, with ratios of up to 50:1 preference towards the α-amino acid.[243] The group of Schuur later on reported successful application of this host to a new type of substrate, DL-α-methylphenylglycine amide, with operational selectivities of up to 7.4.[244] This host system was used by the group of Tang for further substrate scope analysis, and modeling studies,[245,246] including kinetic studies[247,248]. Their efforts in modeling were rewarded when they found it was possible to obtain similar values using the more environmentally benign copper PF6 precursor.[249] Nickel based precursors were found to be less selective. Continuation of modeling and application of copper BINAP complexes as host resulted in the efficient extraction of a range of substrates[250,251,252,253,] with reasonable operational selectivities (2.0-6.0). Modelling of the extraction parameters such as pH, temperature and concentration was performed to predict the optimal extraction regime for multistage extraction. This indicated that 18 sequential equilibrium stages were required for full resolution.

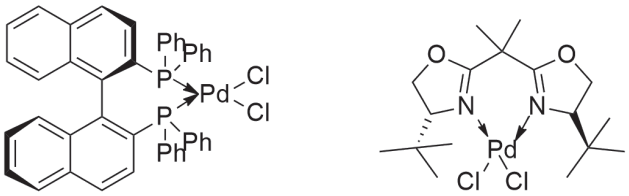


Figure 20: [PdCl2((S)-BINAP)] complex and bisoxazoline based palladium complex hosts.

The first introduction of palladium complexes comprising N-type ligands was reported by Verkuijl *et al.* in 2010 (Figure 20).[254] Their introduction of two commercially available bisoxazoline (BOX) complexes allowed the extraction of zwitterionic amino acids at pH values between 6 and 7. The observed operational selectivities ranged from 1.1 to 2.0. Optimization of several parameters such as pH of the aqueous phase, counter ion and solvent combination was performed, as well as UV/vis titration experiments to obtain the binding constants.

Dual Host selector systems

While the previous two categories could be relatively simply allocated by the type of host (non-metal/ metal based) and therefore to the expected type of extraction mechanism, several hosts won't allow this type of allocation. The application of multiple hosts, either residing in a single phase, or residing in all phases of the extraction, has been used several times in the history of ELLE. One could argue that the application of multiple hosts simply leads to the occurrence of parallel binding events, however evidence for this is currently lacking. Moreover, in some systems, the application of a single host does not yield enantiodiscrimination.[255] This currently smallest category has grown significantly over the last few years.

Starting in 2006, the group of Luo reported a system based upon multiple hosts residing predominantly in a single phase.[147] Based upon the very well-known phosphoric acid D2EHPA (Figure 21) and dialkyl tartaric acid enantioselective extraction of tryptophan was obtained. Both host were separately known for their supramolecular interactions, in the case of D2EHPA with various metals[256,257,258] and amino acids[259], and in the case of tartaric acids with ephedrine and various alcohols[260,261,262]. When the independent distribution and enantioselectivity of both hosts were determined in the presence of a racemic tryptophan guest, it was found that without the simultaneous presence of both hosts, no enantioselectivity could be observed. The system was also found to be solvent dependent. For instance, when octanol was used, enantioselectivity was lost. The authors propose the host is a complex formed by D2EHPA and the tartaric acid derivative with an optimal operational selectivity of up to 5.3 for tryptophan.[263] Ee values of up to 57% were achieved in the aqueous phase, however diastereomeric salt formation was observed (indicating partial classical resolution). The relatively low distribution values were highly increased by the addition of trioctyl methyl ammonium chloride (Aliquat 336) as anionic carrier.[264]

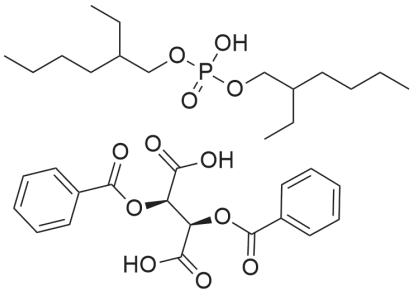


Figure 21: D2EHPA (above) and the tartaric acid derivative as used by Luo.

Using the same synergetic system of D2EHPA and tartaric acid derivative, the group of Ren described the extraction of salbutamol.[265] DFT calculations were applied to indicate the importance of hydrogen bonding towards enantiomeric extraction. After investigation of flow rate, pH and concentration dependence, separation factors of up to 2.0 could be observed. This time however, the enantioenriched salbutamol could be obtained indicating the possibility towards industrial scale-up of the system. At higher pH values, higher distribution ratios were confirmed.

Another system dependent on a combination of hosts comprises of cyclodextrins in combination with tartaric acid derivatives. As previously mentioned, the history of cyclodextrins as a chiral host lies in chiral capillary electrophoresis[104] and HPLC[107] and these compounds often show a high solubility in aqueous media. In this case however, either host resides in a different layer during the extraction experiments. Their application to ELLE was introduced by Huang and coworkers in combination with previously mentioned alkyl tartrate derivatives for the resolution of mandelic acid.[266] Operational selectivity of up to 2.1 was observed using decanol as solvent under highly acidic conditions (pH = 2.3). Relatively high distributions ranging from 7 to 14 are reported. Using a different tartrate derivative, the group of Tang confirmed the usefulness of this system.[267] While the cyclodextrin is observed to preferentially interact with (S)-mandelic acid in the aqueous phase, the tartrate is selective towards (R)-mandelic acid in the organic phase. Additionally, the concentrations, pH and solvent type were investigated, yielding an operational selectivity of up to 1.5. Corderí *et al.* showed that the presence of the tartrate derivative is not strictly required, but at a loss of operational selectivity to a maximum of 1.33 for mandelic acid. In this case, the presence of n-octanol and highly optimized conditions are required.[268] Replacement of the organic phase with ionic liquids yielded similar results.[269] In the subsequent years, Tang reported the enantioselective extraction of several substrates.[270,271,272] These included some pharmaceutically interesting compounds

such as flurbiprofen[273] and oxybutynin.[274] Substitution of the tartrate derivative by alkylated versions of acetic acid yielded a system capable of resolution of tropic acid (3-hydroxy-2-phenylpropionic acid) enantiomers using CCS. Operational selectivities of up to 1.6 were obtained with these systems.[275]

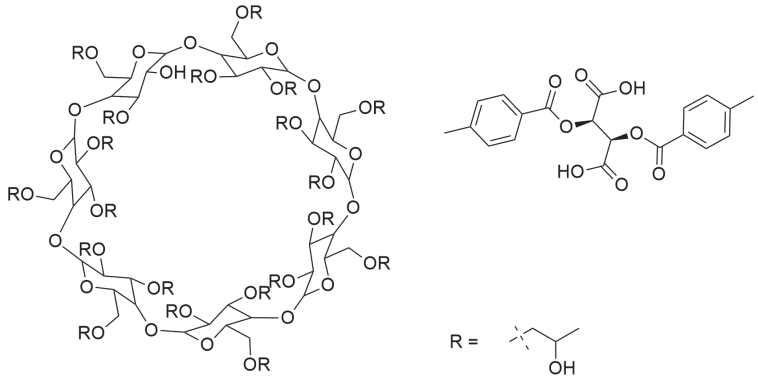


Figure 22: Cyclodextrin derived hosts and the tartaric adic derivative as used by Huang.

During the preparation of this chapter, an eloquent concise review on the recent history of ELLE was published by the group of Schuur.[276]

Concluding remarks

Enantioselective Liquid Liquid Extraction has drawn the constant attention of many chemists over the years, including Nobel laureates Cram, Lehn and Feringa, due to its complexity; requiring multidisciplinary knowledge to comprehend and investigate. Spanning over several decades, a variety of host-guest systems has been developed, all abiding to the difficult challenges set in multiphase, dynamic, supramolecular chemistry. Recently, much renewed interest was shown in the topic, and many publications over the past few years testify to this. With many innovations pertaining to engineering, hosts-guest systems and scope, the innovations in the field progress steadily. These innovations, spanning from fundamental synthetic chemistry to applied engineering, challenge many assumptions traditionally made by chemists. Moreover, it pushes the boundaries of many commonly accepted ideas in terms of molecular recognition and the generation of chiral compounds. Showing capable of meeting industrial requirements towards obtaining chiral fine chemicals at reduced costs, ELLE is a flourishing modern day field in chemistry.

Of course several bottlenecks are present still in enantioselective liquid-liquid extractions. Most systems only work well at relatively high dilution, making the method uneconomic. Especially the long lasting challenge of high selectivity at large scale, with a high turnover number and high turnover frequency is far from achieved. As is the challenge of providing full resolution of non-charged low functional racemates. Research towards the relatively poor understanding of the supra molecular interactions and underlying principles of ELLE could give highly useful clues towards solving these questions, allowing ELLE to become a highly desirable, low cost, continuous industrial process.

Outline of the thesis

The content of the research described in this thesis revolves around two high impact topics in the chemical community: enantioselective liquid liquid extractions and metal based catalysis. The previous sections address an overview of (part of) the currently available literature on enantioselective liquid liquid extraction divided in an explanation of the field and the underlying principles, as well as a differentiation of host-guest systems as used in ELLE in three categories based upon mode of action. Under scribing the pioneering work of Cram et al. and the subsequent major steps that have reported, room for further improvement on the especially highly efficient selectors and understanding of the underlying principles still remains. The first chapters in this thesis seek to apply chiral phosphoric acid towards the enantioselective extraction of chiral amines in an efficient and economically viable way.

Herein focusses chapter 2 on the further optimization of BINOL-derived chiral phosphoric acids in ELLE of chiral amines, while trying to find answers to the role and importance of 3,3'-aryl substituents. Moreover, the relatively low solubility of this type of selector in organic solvents is addressed, by the introduction of alkyl derivatives on the 6,6'-positions of the BINOL backbone.

In chapter 3, chiral phosphoric acids containing a SPINOL derived backbone are designed and synthesized. Their subsequent application in ELLE of chiral amines is further described, as well as the highly successful extraction of amino alcohols.

Chapter 4 describes the introduction several different chiral phosphoric acids in the chiral extraction of amines. First, the introduction of VAPOL- and VANOL-derived phosphoric acids are described, followed by the introduction of H8-BINOL and TADDOL derived chiral phosphoric acids as selectors.

In chapter 5, a faster, greener, highly concentrated and additional solved free alternative to the previously described palladium catalyzed lithium mediated carbon-carbon cross coupling is described. Moreover, the advantages (as high reaction speed and low catalyst loading) are shown using an extensive starting material scope and a direct comparison with established procedures.
Chapter 6 explores a one pot procedure for a highly efficient palladium catalyzed (cross)-coupling of hetero aryls, while maintaining a low E-factor and low waste generation.

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Chapter 2

Application of BINOL-derived chiral phosphoric acids in enantioselective liquid liquid extractions

Introduction

The current extensive application of 1,1′-bis-2-naphthol (BINOL) derived chiral phosphoric acids[1] in asymmetric catalysis was brought about by the pioneering work of Akiyama[2] and Terada[3] in 2004. Both groups initially reported these chiral acids for the catalytic enantioselective Mannich reaction. In the search for replacement of the, until then employed chiral urea-type Brønsted acids, the much milder (less acidic) BINOL derived phosphoric acid was introduced[4,5]. They reported being able to obtain high enantioselectivities up to 95% ee in combination with 99% conversion to the product with low catalyst loadings (2 mol%) and showed the remarkable potential of this type of catalysts. Their pioneering work paved the way for the extensive application of these catalysts[1,6,7,8]. The combination of the relatively rigid axial chirality of binaphthols, generally substituted with highly sterically demanding aryl groups at the 3,3′-positions, and the bidentate nature of the phosphorous moiety proved key towards this highly active catalytic system.[9,10] Indeed, the presence of a H-bond accepting phosphoryl oxygen moiety allows an additional point of interactions, which allows the fulfilment of the requirements of chiral recognition according to the three point rule of chiral interactions[11,12,13,14,15].

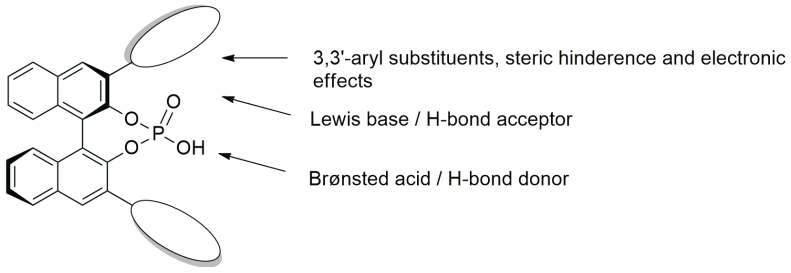


Figure 1: BINOL-derived chiral phosphoric acids and their host design

The essential role of the 3,3′-substitution became instantly evident when omission resulted in a drop off enantiomeric excess to just 12% ee in the case of the previously described Mannich reactions.2 At that time no real reasoning behind the selectivity of these chiral phosphoric acids was provided. Several years later, DFT-calculations were reported indicating their key role[16,17,18.] Moreover, it was shown that next to the 3,3′-aryl substituents, both the Brønsted acid and Lewis base groups are most likely also involved in the mechanism of the Mannich reaction.[19,20,21] The next example of the direct employment of BINOL derived phosphoric acids was in the application for an asymmetric Fiedel-Crafts alkylation in 2004 by Terada[22]. The vital role of the 3,3′-substituents comes from their ability to allows for enantiodiscrimination through the formation of a highly catalytically active and selective cavity around the phosphoric acid moiety[23,24].

From chapter 1 it is apparent that the field of enantioselective liquid liquid extractions is mainly dominated by BINOL based host-guest systems[25,26], especially before 2006. Here, similar observations were reported 25 years earlier towards the importance of 3,3'-substitution of binaphthols by Cram and coworkers.[25] From the early dilocular hosts, relying on a crown ether bearing 2 different chiral BINOL moieties,[27] (Figure 2, left) Cram and coworkers later reported systems with only one chiral BINOL moiety on the crown ether.[28](Figure 2, right) The application of BINOL derivatives for chiral extractions was reported throughout the field of ELLE.[29]

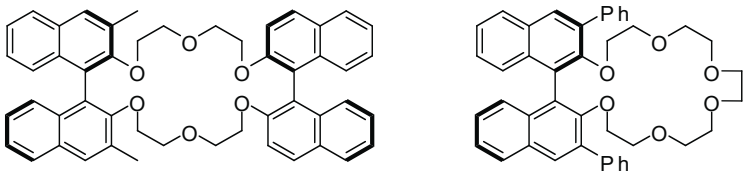


Figure 2: On the left, the dilocular cown ether host, on the right the upgraded system involving the 3,3'-substituents.

Separately, the use of racemic phosphoric acids in ELLE as hosts was also reported. As described more elaborately in Chapter 1, in 2006 Luo and coworkers reported the application of di-(2-ethylhexyl)phosphoric acid (D2EHPA) for the extraction of tryptophan. Enantioselective extraction, however, could only be observed in the presence of a tartaric acid derived additive as co-host[30].

The combination of these two concepts, BINOL derived chiral backbones and phosphoric acid moieties, was therefore a small but highly important step towards another class of hosts[31] reported by the groups of Feringa and De Vries. They also reported on the importance of the presence of aryl substituents on the BINOL backbone, in this case as a requirement for enantioselective extraction. Only in the cases where 3,3'-aryl substituents were present on the binaphthyl backbone, enantiomeric extraction of chiral amines was observed. Our group reported that the most efficient host was bearing bis(3,5-bis(trifluoromethyl)phenyl) – functionalities **(PA4)**, followed by the phenyl- **(PA2)** and bis(2,6-di([1,1'-biphenyl]-4-yl) substitutiens **(PA3)**. Even though a number of analytical data were presented, no explanation as to the efficiency of these particular 3,3'-substituents is given in this paper, nor in the more application based paper subsequently published by Schuur *et al.*[32] regarding the same guest-host system.

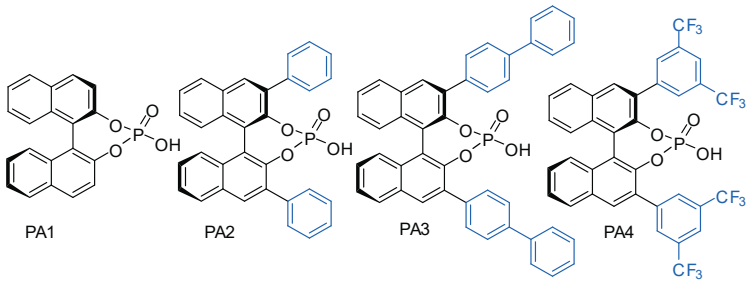


Figure 3: Chiral BINOL- derived phosphoric acids PA1 to PA4.[31]

This poorly understood, however, surprisingly dominant importance of the 3,3'-groups has therefore drawn the attention of groups in asymmetric catalysis[5,33], including those of Jacobsen[34,35] and Rueping[36]. On several occasions, generally throughout small molecule catalysis, these BINOL-derived chiral phosphoric acids are proposed to catalyze a mechanism involving strict ion pairs. This is similar to their predecessors; chiral urea-type Brønsted acids. Another similarity can be found in the importance of aromatic functionalities, where for both catalyst types these are key to efficient enantioselective catalysis. In the case of chiral urea-type Brønsted acids the quadrupole moment[37] of the aryl substituent is reported to play a major role in organizing the enantiodetermining transition states.[38,39] Eyring analysis and enthalpy/entropy compensation studies[40] indicate a cation-π interaction[41,42,43,44,45] between the quadrupole moment of the aryl substituent and the ionic substrate, to be the principle determinant of enantioselectivity.[46] Similarly, for BINOL-derived phosphoric acids, the 3,3'-aryl substituents are proposed to be involved in a cation-π interaction with the substrate. The question remains, if in the case of BINOL derived phosphoric acids, this interaction is also the principle determinant for enantioselectivity.

In some examples in catalysis in general, inversal of quadrupole moment of the 3,3'-substituents by the introduction of various fluorine atoms, has led to completely different reactivity and even opposite asymmetric induction[47,48,49]. Another example of this phenomenon was reported by Terada last year[50].

To be able to investigate the importance of these two variables a library of BINOL-derived chiral phosphoric acids was synthesized. Herein, only the 3,3'-substituents are varied, while keeping all other parameters involved in ELLE as similar as possible. By testing the performance of the obtained series of chiral phosphoric acids against a wide range of racemic amines and amino alcohols under equilibrium conditions, we hope to be able to shed some light

on the chemical principles behind the importance of the 3,3'-substituents in BINOL derived chiral phosphoric acids in diastereoselective binding events.

On the synthesis

Hosts suitable for enantioselective liquid liquid extraction have to meet a number of conditions and criteria to be generally applicable to a certain class of substrates.[31,51] Among these are requirements regarding their relative solubility and the possibility to form diastereomeric complexes with the guest. Ideally, when placed in the presence of two immiscible phases, the host should be confined to a single phase with a very low physical partitioning[52]. Moreover, it should possess sufficient functionalities allow a three point chiral interaction.[11-15] The thereby obtained diastereomeric complexes ideally are dynamic enough to support an efficient extraction and chiral induction, while still being able to release the guest later on.

All hosts present in the current study are obtained via previously described synthesis routes, or slight modifications thereof[53]. In most cases, the synthetic route proceeds as follows: (Figure 4) Starting from cheap commercially readily available (R)-BINOL **S1**, protection of the alcohol groups is realized using ether based protecting groups. Subsequent selective halogenation of the 3- and 3'-position, is followed by a Suzuki reaction for the introduction of the aryl groups **S4**. Deprotection of the phenol groups is achieved *via* acidic workup or via a separate deprotection step. Subsequent phosphorylation with $POCl_3$ and hydrolysis produces the desired BINOL derived phosphoric acids. Exceptions on this general procedure are **PA7, PA11** (obtained from commercial sources) and **PA8** (after a modified procedure of Jiao *et al.*).[54]

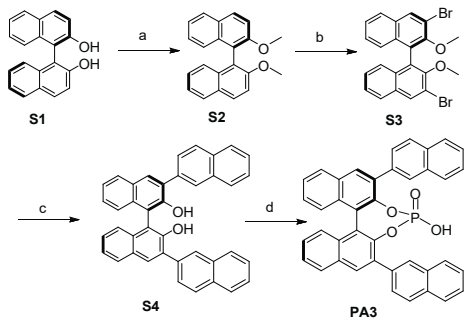


Figure 4: Synthesis route for 3,3'-BINOL-derived chiral phosphoric acid PA3. Reaction conditions: a) Me_2SO_4, K_2CO_3, acetone, r.t, o.n., 94% b) t-Buli, THF, -78 °C 2h, then $C_2Cl_4Br_2$, r.t. 1h, 96% c) Na_2CO_3, $Pd(PPh_3)_4$, Ar-BOH_2, then BBr_3, DCM, r.t., o.n., 86% d) $POCl_3$, pyridine, reflux then, H_2O reflux, 32%

The selective introduction of halogen atoms on the 3,3′-position is performed *via* selective lithiation.[55,56,57,58,59] The selectivity of said lithiation depends highly on the neighboring ether groups. Without these, lithiation of the 6- and 6′-position is expected, as these are more reactive. Moreover, even though Suzuki reactions in the presence of free phenols are known[60], higher yields are observed when these phenols are protected (Figure 4). Already in the pioneering work of Akiyama published in 2004, a methoxy moiety was employed[2]. The coordinating effect of the oxygen present in this group allows for, under the right conditions, selective lithiation at α-positions[61]. An even more coordinating effect can be found for a methoxymethyl acetal (MOM) ether, while maintaining its stability towards the high reactivity of lithium reagents, resulting in a reduction of reaction time required towards full conversion for the lithiation.[62] Another advantage lies in their susceptibility towards acidic conditions; a MOM group is relatively easily removable[63]. Even though it is possible to very quickly lithiate the α-position next to a MOM-group under additional solvent free conditions[64,65] (chapter 5, 6), the use of ethereal solvents is more conventional. Over a period of 6 h at -78°C full conversion is achieved using *n*-BuLi and TMEDA in THF, whereas in the case of *t*-BuLi 2 h suffices, without the use of additives. Subsequent *in situ* lithium-halogen exchange was applied for the introduction of bromine or iodine functionalities by the use of Br_2 or I_2, respectively. However, both result in a substantial amounts of monohalogenated product (around 29% for Br_2 and 14% for I_2) even though super stoichiometric amounts of reagents are added in several batches. In case of Br_2, the formation of unwanted byproducts was overcome by the use of alternative brominating agents such as dibromo-tetrachloroethane, resulting in full conversion and 96% isolated yield. In some isolated cases, the mono-halogenated version can be useful for further application[66].

After successful α-halogenation at the 3- and 3′-position of BINOL, in most reported cases a Suzuki reaction was employed for the introduction of a variety of aryl groups[67]. Whereas in early cases the boronic acid moiety was placed on the BINOL backbone[2] while employing a halogen on the aryl-substituent, later on this sequence was inverted. This was done, as especially in the cases where the aryl-substituent is electron poor, increased yield was observed, since electron poor boronic acids are prone to hydrodeborylation.

Deprotection of the –MOM or -methoxy protecting groups was achieved, either by quenching the Suzuki reaction using 1M aq. HCl or via a deprotection step employing BBr_3[68]. Phosphorylation of the BINOL core and the conversion to the phosphoric acid proved to be challenging with low initial yields. We hypothesized that the presence

of an ionic residue in the cavity, such as residual silica or cations from previous purification, coordinating to the free phenols of the starting material, drastically lowers their nucleophilicity by the formation of supramolecular structures such as dimers. Although HRMS and NMR experiments could neither rule out, nor confirm this hypothesis, the issues were solved by vigorously washing the diol with high concentrations (2-6M) of aq. HCl. In cases involving high sterical hindrance **(PA6, PA9, PA10)** the use of dioxane in combination with triethylamine was used during phosphorylation, rather than pyridine, resulting in a faster and higher yielding reaction.

Purification after each step of the sequence is of high importance, as the combination of several steps into a one-pot procedure always led to a loss of conversion towards the desired product. Characterization of the previously described intermediates was generally performed using NMR, unless otherwise stated. For the previously described desired phosphoric acid hosts, NMR in combination with mass spectrometry was used. For new compounds, a combination of NMR spectra, exact mass and specific rotation was obtained. Even today, optimization of the synthesis of 3,3'-substituted BINOLs is a hot topic of research[69,70] (chapter 5, 6).

The application in enantioselective liquid-liquid extractions

While BINOL-derived phosphoric acids have been shown to give acceptable levels of ELLE for amines,2,3 little is known of their use for other guest families. In addition only a minor range of guest structures were tested and much structure activity relationship studies are still required before their activity is understood. We therefore tested a wide range of PAs (**PA5-13**, figure 5) as hosts in the enantioselective extraction of a variety of racemic chiral amino acids, amino alcohols and amines, using already studied **PA1-4** as comparison.[31]

Apart from stronger and weaker quadrupole moments, also cases with different sterical hindrance (i.e **PA6** vs **PA9**) were investigated. The use of heteroatoms **(PA7, PA8)** could potentially allow for additional interactions, such as additional H-bonds.

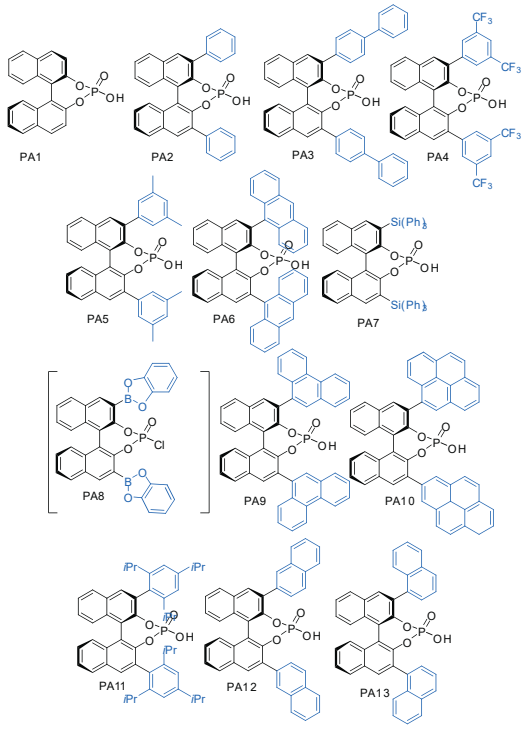


Figure 5: Chiral BINOL derived phosphoric acids. PA1 – PA13 A variety of 3,3'-aryl substituents were introduced. PA7 and PA11 were obtained from commercial sources, PA8 was isolated without purification and characterization.

To our surprise, both **PA8** and **PA10** were unsuitable for application in ELLE. In the case of **PA8**, hydrolysis of the boronic ester was observed in the last synthetic step, during the phosphorylation and subsequent hydrolysis. The corresponding phosphoryl chloride was submitted to the biphasic standard ELLE conditions, hoping for successful hydrolysis to the phosphoric acid *in situ*. Here also however unwanted hydrolysis was observed, cleaving the bond between the BINOL backbone and the benzo[d][1,3,2]dioxaborole group. In the case of **PA10**, rotation around the bond between the BINOL backbone and the aryl substituent was obstructed to such an extent, that even a sample heated to 100˚C in DMSO inside a NMR spectrometer, no bond rotation could be observed. It is therefore reasonable to assume the formation of atropoisomers at room temperature, as can be observed in the 1H-NMR spectrum (figure 6). Due to the R-configuration in the BINOL backbone, the protons present in both MOM-groups are chemically inequivalent, yielding two distinctive doublets. In combination with the newly introduced 1-pyrene groups, 4 distinctive sets of double doublets are now observed. Attempts towards separation of the atropoisomers using chiral HPLC were made, however separation was not obtained. Even though such a

molecule could have highly interesting properties as an asymmetric catalyst, it loses its potential applicability towards a successful and industrially viable ELLE process. The behavior of **PA10** surprised us, as similar molecular structures as -phenanthrene **(PA9)** were not liable to the formation of rotamers at room temperature. Currently, we have no explanation as to this peculiar behavior of **PA10.**

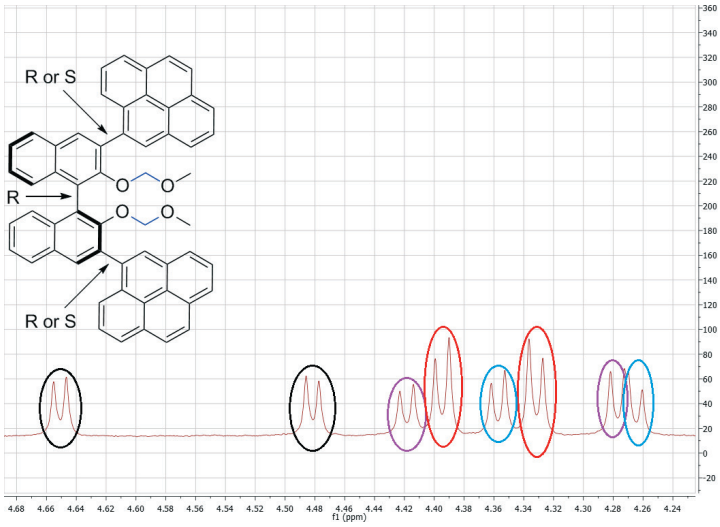


Figure 6: Part of the 1H-NMR spectrum (from 4.68-4.24 ppm) of an intermediate towards the synthesis of PA10, in which each color represents a set of chemically inequivalent MOM CH_2-signals (indicated in blue), indicating the presence of four different atropoisomers.

The other 11 chiral phosphoric acids were found to be stable under the standard ELLE conditions.

The substrate scope of chiral amines and amino acids was kept the same throughout this chapter as much as possible to allow for direct comparison between all hosts as far as the chiral phosphoric acids are concerned. The substrate scope as depicted in figure 7 contains a variety of racemic chiral amino acids, amino alcohols and chiral amines. In a typical non-catalytic ELLE experiment two immiscible phases are stirred together for 16h at 6˚C. The organic layer (DCM) contains a 1mM concentration of host, while the aquous phase contains a 2 mM concentration buffered at pH 5.0 using a phosphate buffer with 0.1 M buffer strength. The physical partitioning for all given examples was determined to be 0 at pH 5.0 at 6˚C, indicating that all extraction under these conditions is host induced.

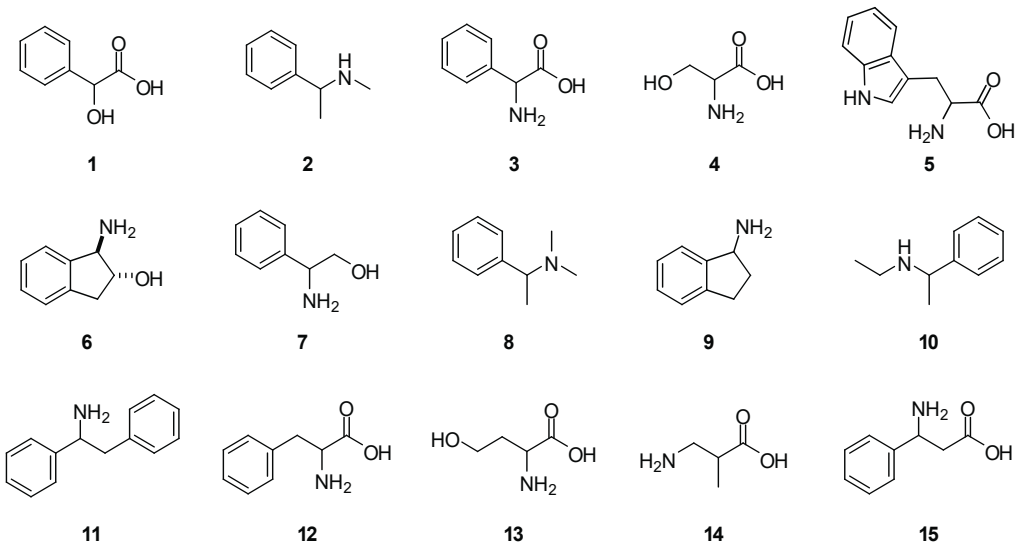


Figure 7: ELLE screening of chiral substrate classes with PA5-PA13. Conditions: 2 mM guest solution (H_2O, pH 5 phosphate buffer) vs 1 mM host solution ($CHCl_3$), 6 °C. Determination of the ee, distribution and α_{op} via reverse phase HPLC of aqueous phase aliquots using a crownpack (+) column.

A host induced distribution, in effect a reactive liquid liquid extraction, (LLE) was observed for all tested racemic mixtures in combination with host **PA5-7**, **PA9**, **PA11-13**, with varying efficiency; distributions ranging from 0.1 to 0.9 were observed. No LLE was observed with compounds **1** and **8**. In the cases of the amino alcohols **6** and **7** asymmetric induction, and therefore successful ELLE, was observed in combination with **PA5-7**, **PA9** and **PA11** (Table 1, Entry 1 and 2). Since these are both amino alcohols, the additional interactions between the hydroxy group of the amino alcohol and the Lewis basic free electron pairs of the phosphoric acid are therefore highly likely to contribute towards diastereomeric interactions and enantioselective extraction. The lack of enantioselectivity obtained for the amino acids supports this. At pH 5.0 it is expected that any amino acid tested is present in its corresponding zwitterionic form, lacking the ability to form a hydrogen bond interaction, like the amino alcohols, with the chiral phosphate.

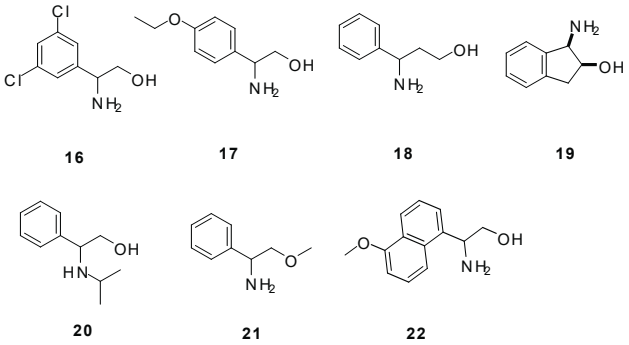
Not all 14 chiral PA hosts presented in Figure 5 were capable of successful ELLE. Those without 3,3'-aryl substituents (**PA1**) only achieved racemic extraction, something already noted in previously reported experiments[11]. Similarly, use of **PA12** and **PA13** also resulted in racemic extraction of compounds **6** and **7** under standard ELLE conditions, with a distribution around 0.6. The initial investigation

showed the preference of **PA5** and **PA6** for the more rigid 1,2-amino alcohol **6**, with an observed ee of 10% and 12%, respectively (Table, entry 1), while **PA7**, **PA11** and **PA9** gave the highest ee for 1,2-amino alcohol **7**. Whereas **PA5**, **PA6** and **PA11** have a strict preference for one of the two amino alcohols, **PA7** and **PA9** have affinity for both **6** and **7**. We were pleased to observe that the operational selectivity (α_{op}) for our new guest-host systems are notably higher (Table 1) then previously reported. (α_{op} = 1,7 for a combination of **PA4** and **15**).

Entry	Guest	PA5		PA6		PA7		PA9		PA11	
		ee%	α_{op}	ee%	α_{op}	ee%	α_{op}	ee%	α_{op}	ee%	α_{op}
1	**6**	10	1.8	12	2.6	9	1.9	15	2.0	--	1
2	**7**	--	1	--	1	19	1.7	25	2.3	13	2.3

Table 1: Outcome of single extraction experiments for PA5-PA7, PA9 and PA11 for guests 6 and 7.

With these highly promising results in hand, an investigation towards the scope of enantioselectively extractable amino alcohols and the importance of functional groups involved, was started. Therefore several readily available (commercially, or in one synthetic step) amino alcohols were selected for their specific properties. Unfortunately, 1,2-amino alcohol 22 did not dissolve in water under standard ELLE conditions (6˚C, pH = 5,0) rendering it useless for ELLE.



Entry	Guest	PA7		PA11		PA6		PA9	
		ee%	α_{op}	ee%	α_{op}	ee%	α_{op}	ee%	α_{op}
1	**16**	31	3.6	31	4.2	--	1	17	2.0
2	**17**	38	2.4	22	2.1	25	1.9	--	1
3	**18**	22	2.1	10	1.7	10	1.7	14	1.6
4	**19**	8	1.3	18	2.6	6	1.6	19	2.1
5	**20**	--	1	--	1	--	1	--	1
6	**21**	--	1	--	1	--	1	--	1

Table 2: Outcome of single extraction experiments for PA6-PA7, PA9 and PA11 for guests 16 to 22

Chiral phosphoric acids **PA7** and **PA11** extracted guest **16** with 31% ee and an extremely good 3.6 and 4.2 α_{op}, respectively, while **PA9** extracted **16** with 17% ee and a good α_{op} of 2.0 (Table 2, Entry 1). This sets a new record for the ELLE of 1,2-amino alcohols by BINOL derived phosphoric acids. Even higher ee was observed for **PA7** and guest **17** under standard ELLE conditions, yielding an impressive 38% ee. Due to a relative lower distribution, the α_{op} was calculated to be 2.4. **PA11** and **PA6** allowed for 22% and 25% ee, respectively (Table 2, Entry 2). Generally lower ee's and α_{op} were observed for guest **18** (Table 2, Entry 3), indicating the importance of the close proximity of the alcohol and amine functionality. All four tested phosphoric acids had good interactions with guest **17**, ranging between 22 and 10% ee and an α_{op} of 2.1 to 1.6. In the case of guest **19** (Table 2, Entry 4), the cis-diastereomer of guest **6**, small differences were observed. Whereas similar ee's are observed for **PA7**, **PA11** highly prefers cis-**19** over the trans-**6**. **PA6** however, prefers the trans-**6**. **PA9** yields similar ee's and α_{op}, indicating the delicacy of the ELLE process. As expected, for guest **20** and **21** no enantioselectivity was observed, indicating the importance of both the alcohol, as well as the primary amine functional group in chiral recognition (Table 2, Entries 5 and 6).

Application towards ELLE from a racemic reaction mixture

Previously in this chapter, we established both the selectivity of BINOL-derived chiral phosphoric acids towards amino alcohols, and the low affinity for (especially enantioselective interaction) both α and β amino acids. Combining these data, we envisioned that the direct application of ELLE onto the reaction mixture in which amino alcohols are made (by reduction from amino acids) could allow for simultaneous induction of ee and purification/extraction of the amino alcohol from the mixture, leaving behind any residuals and starting materials in the aqueous phase. To test this, several model reaction mixtures were made, containing a variety of derivatives (portraying the possible by-products in the reaction mixture) of 1,2-amino alcohol **7. PA7** and **PA9** were employed as model phosphoric acids, having established that these two chiral phosphoric acids yielded the highest ee for guest **7** in batch extraction reactions (table 1, entry 2).

Entry	Guest	PA7		PA9	
		ee%	α_{op}	ee%	α_{op}
1	**7**	19	1.7	25	2.3
2	**7+3**	23	2.7	30	2.6
3	**7+3+15**	23	2.7	30	2.6
4	**7+1**	17	2.8	22	2.8

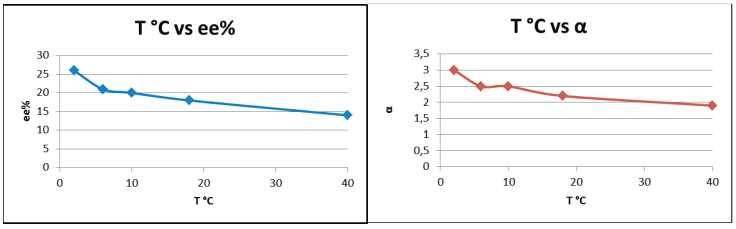
Table 3: Single extraction experiments for mixtures of guests and PA7 and PA9. Herein, entry 1 is a copy of results from Table 1 entry 2 for clarification purposes. All mixtures were prepared in 1:1 or 1:1:1 molar ratio.

When a model reaction mixture composed of amino alcohol **7** and its corresponding α-amino acid **3** was submitted to ELLE under standard conditions with **PA7** and **PA9**, successful enantioselective extraction of only amino alcohol **7** is observed. α-Amino acid **3** is in both cases (**PA7** and **PA9**) most predominantly left behind in the aqueous phase with a respective distribution of <0.1. Moreover, not only selective guest selection is observed in guest mixtures, but also an increase of ee (from 19 to 23% and from 25 to 34%, respectively) is observed, as well as a large increase in α_{op} (Table 3, entry 2). The large increase of α_{op} can be attributed to a change in distribution observed for guest **7**, while the distribution of guest **3** remained low (<0.1). We propose that the increase in distribution of guest **7** is due to a process similar to 'salting out' where the presence of more ionic species in the aqueous phase

force the least soluble compound to reside, to a larger extent, in the organic phase. The introduction of β-amino alcohol **15** to the mixture of guests **7** and **3** did not result in significant changes for the extraction of compound **7**, indicating insignificant influence of byproducts in the reaction mixture on the direct ELLE of **7** (table 3, entry 3). Similar results were observed for a model reaction mixture of **7** and α-hydroxy acid **1**, where similar ee's but increased α_{op} was observed (table 3, entry 4).

Study and optimization of the ELLE of amino alcohols by BINOL derived phosphoric acids

With the interesting results of the initial testing of BINOL derived phosphoric acids in ELLE in hand, optimization of several of the important parameters involved was performed. We started with the investigation of the temperature dependence of ELLE. To the best of our knowledge, BINOL derived chiral phosphoric acids hosts have only been investigated at room temperature and 6 °C,11 where no significant changes were observed. Knowing the importance of temperature changes in enantioselective catalysis, a proper investigation of the temperature dependence of ELLE systems is required. A physical cut off point was found at temperatures close to 0 °C: As the aqueous phase comes close to its freezing point this drastically lowers the solubility of all components. The resulting diffusion is not controlled and therefore racemic. Using **PA9** and guest **7** as model, batch experiments were performed under standard ELLE conditions with variation in temperature.

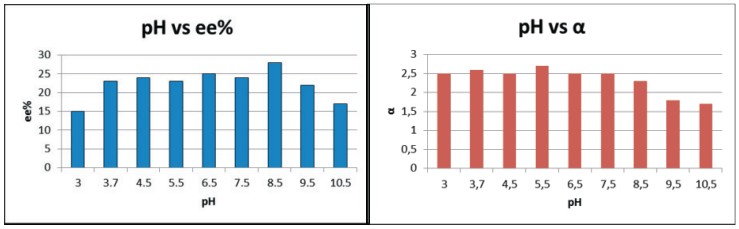


Scheme 1. *Temperature screening for the ELLE of 7 with PA9. Conditions: 2 mM guest solution (H_2O, pH 5 phosphate buffer) vs 1 mM host solution, 16h. Determination of the ee, distribution and α_{op} via reverse phase HPLC of aqueous phase aliquots.*

Despite the indeed relatively small differences observed between ELLE experiments performed at 6 °C and room temperature, more significant differences are found at lower temperatures. An increase in both ee and α_{op} are noted when the temperature at which the extraction was performed was set to 2 °C (Scheme 1). A gradual decrease in ee and α_{op} is observed with an increase in extraction temperature; something in line with expectations for any enantiomeric process.[71]

Influence of pH

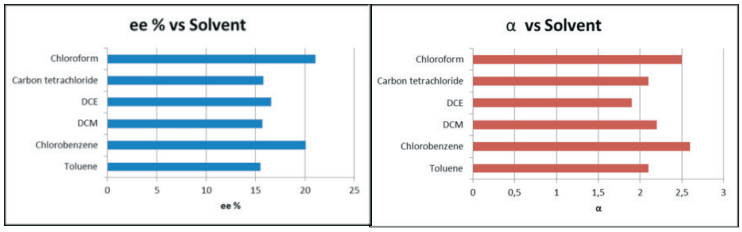
Next to temperature dependence, pH dependence of the enantioselective extractions were investigated. Experiments concerning the pH optimization using **PA9** yielded results in line with previously obtained experiments using **PA4**.[11] Over a large pH range, relatively little difference is observed in both ee and α_{op}, in comparison to SPINOL and VAPOL derived chiral phosphoric acid hosts (discussed later in chapter 3 and 4). This is shown graphically in Scheme 2.



Scheme 2. *pH screening for the ELLE of* ***7*** *with* ***PA9****. Conditions: 2 mM guest solution (H_2O, phosphate buffer) vs 1 mM host solution ($CHCl_3$), 6 °C., 16h.*

Influence of organic solvent

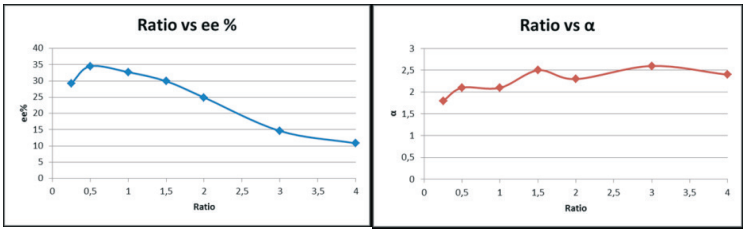
After the optimization of temperature and pH, a solvent screening was performed to determine the optimal solvent for **PA9** in combination with guest **7** under standard ELLE conditions. The graphs shown in Scheme 3 clearly indicate that the best organic solvents to use are chloroform and chlorobenzene, as in these cases a relative higher ee of up to 21% is observed. We limited our search to chlorinated solvents, as it has been established in literature[26] that chlorinated solvents perform well in enantioselective extraction experiments. This is moreover visible by the employment of toluene, yielding a slightly lower ee of 16% and a lower α_{op} of 2.1. In the other cases, as DCE and DCM, a similar ee of 16% and 17% ee is observed, respectively.



Scheme 3*. Solvent screening for the ELLE of 7 with PA9.*
Conditions: 2 mM guest solution (H_2O, pH 5 phosphate buffer) vs 1 mM host solution, 6 °C.

Influence of guest host ratios

Finally, the importance of the ratio between host and guest was investigated. A study on the relationship between the stoichiometry between host and substrate has shown small variations in α_{op}, however much more significant differences in ee are observed (Scheme 4). In these batch experiments under standard ELLE conditions, the host is at constant concentration (2.0 mM), whereas the guest concentration is varied to come to the corresponding ratio. From a ratio of 0.5 to a ratio of 4 a gradual decrease in ee is observed (aqueous phase). A relatively steady α_{op} is observed over the stoichiometric ratio range, similar to the previously reported case.[11]



Scheme 1. *Results of the screening at different concentrations of guest* **7** *in the ELLE with* ***PA9.***
Conditions: X mM guest solution (H_2O, pH 5 phosphate buffer) vs 1 mM host solution, 6 °C.

With the optimal conditions for batch extraction in hand, we investigated the scalability of the process. The ability to recover the guest from the host dynamically is of vital importance, next to a good distribution and operational selectivity. To investigate this, a U-tube extractor was employed, based on a modified design by Cram.[72] (Figure 8) By employing both a feeding and receiving phase, the capability of a host to release the enantioenriched guest can be established. Moreover, employing a U-tube experiment is a good procedure to demonstrate that the host can transport the desired enantiomer in a catalytic fashion with multiple turnovers. A blank reaction without host present showed that no background leaching of the guest is observed over a period of 48 h under standard conditions (6 ˚C, pH=5.0). This clearly indicates that all observed extraction would be due to transport by the host. A 20 mM solution of guest was used as feeding phase, a 0.5 mM solution of host was used in combination with an equivolumetric amount of receiving phase at pH= 1.5. After 15 min, 37% ee was observed, gradually decreasing over time to 20% ee after 5 h. During the 5 h run time, multiple turnovers were established, where the first was reached in little under 1 h. The slow erosion of ee is attributed to an increase in transport of the second enantiomer as a result of depletion of the feeding phase of the one enantiomer. Overall, these results clearly indicate the process was catalytic

and can be scaled up in this fashion. We have previously established that, using highly similar operational selectivities, large scale racemate separation can efficiently be performed using counter current flow in combination with centrifugal mixing separation devices.[73] When placed in series, each reactor enhances the ee according to the Fenske equation (Chapter 1, Scheme 3).

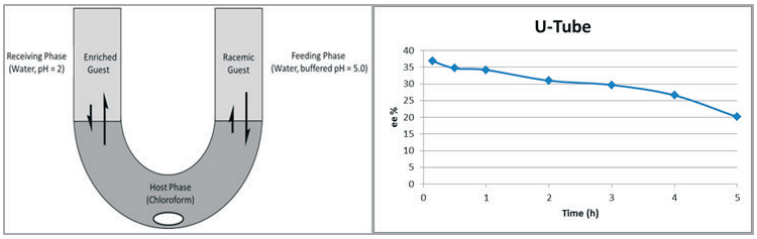


Figure 8. a) U-Tube model reactor. Conditions: Host phase: PA9 in chloroform (0.5 mM,10 ml). Feeding phase: 7 in H_2O (20.0 mM pH 5 phosphate buffer). Receiving phase: aq. HCl (5 ml, pH 2), 6°C b) Obtained ee in the receiving phase plotted version the experimental running time.

The modification of the 6,6'-position of BINOL derived chiral phosphoric acids

A large number of BINOL derived chiral phosphoric acids have been synthesized since their first appearance in the literature in 20041; many of these were used as organocatalysts. Several of these have already received a place in this chapter, however almost all have derivatizations at the 3 and 3'-positions, directly influencing the cavity around the phosphoric acid moiety. A second, currently existing challenge is the low to moderate solubility of PAs in organic solvents, generally not exceeding 2.0 mM in chlorinated solvents. This has severe consequences for the productivity of a large-scale ELLE process. Based on prior experiences, we envisioned that the polarity of the BINOL derived chiral phosphoric acids is important in determining the selectivity of an ELLE process. We wondered if a lower polarity of the host could result in a potential increase in operational selectivity. In addition, the introduction of alkyl chains on the 6- and 6'-position could potentially increase the solubility of PAs in organic solvents, allowing for a higher host concentration and therefore faster transport and higher volume-to-time ratio in a U-tube extractor (Figure 9). Even though BINOL derived chiral phosphoric acids are abundantly present in literature[74], those with alkyl functionalities at the 6,6'-position are scarcely represented. C8-Trip, the derivative of PA11 with octyl chains at the 6,6'-position received far most attention, as it is commercially available.

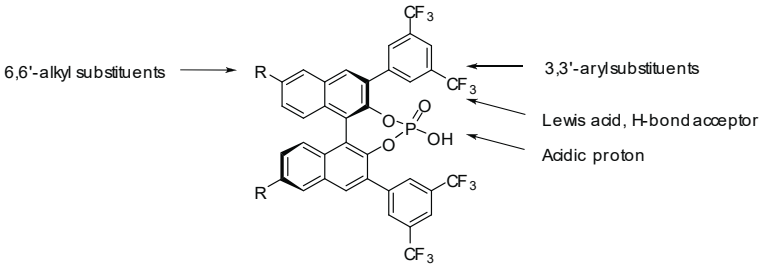


Figure 9: 6,6′-alkyl BINOL-derived chiral phosphoric acids and their host design

For this particular research, different alkyl chains were introduced at the 6- and 6′-positions of BINOL derived chiral phosphoric acids. To ensure as little difference between the selected hosts, other than those proposed, we have chosen to make derivatives of only **PA4**. We therefore selected 5 different alkyl substituents, varying in length and branching.

On the synthesis

The synthesis of a typical 6,6′-distubstituted-3,3′-diaryl BINOL derived chiral phosphoric acid is longer, but similar to the synthesis of 3,3′- BINOL derivatives. We envisioned the introduction of an electron poor aryl group on the 3,3′-position *via* a Suzuki reaction. For the introduction of the alkyl groups, we envisioned the use of a Kumada coupling. Since the 6,6′-position on the BINOL are known to be most reactive, we decided to introduce the alkyl substituents first (Figure 10).

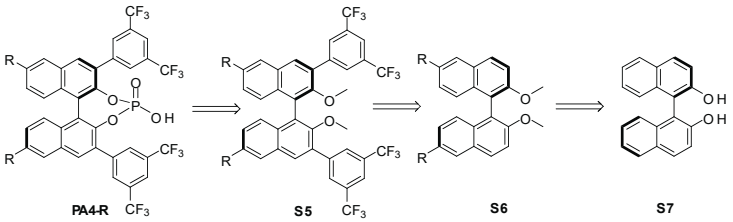


Figure 10: Retro synthesis of 6,6′-diakly-3,3′-biaryl BINOL-derived chiral phosphoric acids and their synthesis design

Starting from commercially and readily available R-BINOL **S7**, a selective bromination at the 6,6′-position is performed using Br_2 at low temperatures *via* electrophilic aromatic substitution. Keeping the temperature at -76 ˚C is crucial to obtaining the desired selectivity and yield to give **S8**. This reaction was scaled up to 25 grams without loss of selectivity or axial chirality or selectivity. Subsequent protection of the alcohol groups and Kumada coupling are used to introduce the different alkyl

chains, yielding **S6**. This palladium catalyzed cross coupling, developed in 1972, is well-known for furnishing sp^2-sp^3 carbon-carbon bonds.[75]

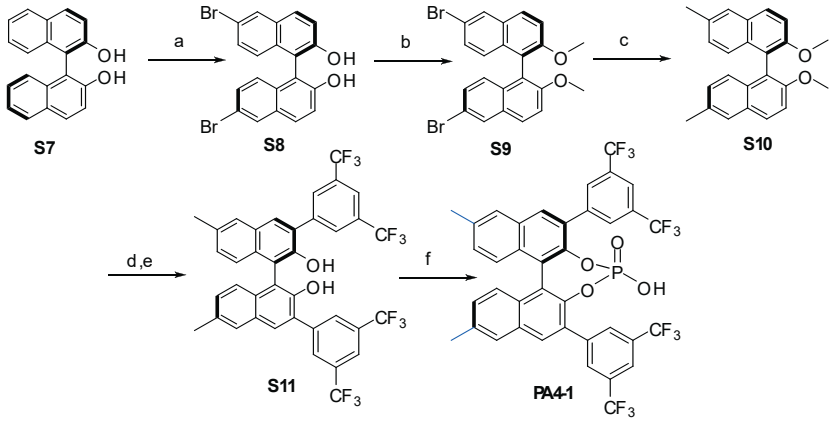


Figure 11: Synthesis route for 6,6′- 3,3′-BINOL-derived chiral phosphoric acid PA4-1. Reaction conditions: a) Br_2, DCM, 4h, -78 °C 96%. b) Me_2SO_4, K_2CO_3, acetone, r.t, o.n. 70%, c) MeMgBr, $PdCl_2(dppf)$ THF, reflux, 2h, 36% d) Br2, DCM, 0 °C, 1h, e) Na_2CO_3, $Pd(PPh_3)4$, Ar-BOH_2, then $Bf_3.SMe_2$, DCM, r.t., o.n., 41% f) $POCl_3$, pyridine, reflux then, H_2O, reflux, 55%

To our great surprise, the well-established selective ortho-lithiation we employed for introduction of halogens on the 3,3′-positions did not occur under standard conditions. (Figure 11) Clearly the presence of alkyl chains on the 6,6′-position hamper an efficient lithiation on the 3,3′-positions. The use of the stronger *sec*- or *tert*-BuLi and the addition of TMEDA did not result in a conversion over 50%. Even switching the methoxy protecting group for a more coordinating MOM protecting group did not result in an efficient lithiation. Quenching with D_2O indicated that the low conversion to the desired halogenated product was due to low conversion in the lithiation step, rather than due to the quenching with Br_2, $C_2Cl_4Br_2$ or I_2. We therefore changed our approach by taking advantage of the absence of the reactive 6,6′-position and applied a direct bromination as described by the group of Evans.[76] The new approach allowed for good yields of up to 96% of the 3,3-dibrominated-6,6′-dialkylbinol intermediate. A note on the use of acid sensitive protecting groups should be placed, as we found that the MOM protecting group is not quite stable under the reaction conditions. Another palladium catalyzed carbon-carbon bond forming reaction (Suzuki reaction) was then used to introduce the aryl groups on the 3,3′-positions, in a highly similar fashion as to **PA4**. Using K_2CO_3 as a base, in combination with $Pd(PPh_3)_4$ gave the corresponding 3,3′-substituted products (Figure 9). When initial deprotection of the methoxy protecting groups was performed using BBr_3, an exchange of a certain amount of fluorine atoms from the $–CF_3$ moieties by

a –Br was observed. The application of mass spectrometry experiments confirmed this. We therefore modified the existing procedure by exchanging BBr_3 for $BF_3{\cdot}SMe_2$ to solve the previously observed issues. Once more it became apparent that washing product **S11** under strongly acidic conditions, was key to obtaining good yields during phosphorylation. This method resulted in the desired **PA4-1** in reasonable yield of 55%. Similar synthesis routes were applied to the formation of **PA4-2** to **PA4-5**. (Figure 12)

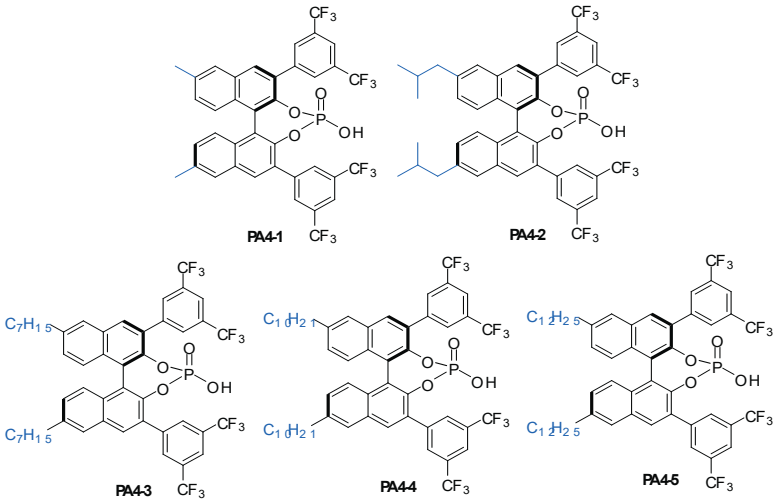
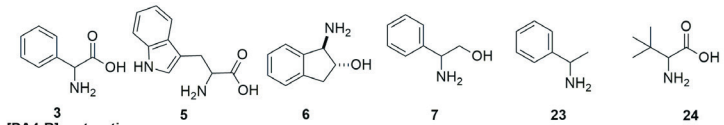


Figure 12: Structures of PA4-1 to PA4-5, a variety of 6,6′-dialkylsubstituted-3,3′-aryl BINOL derived chiral phosphoric acids

Application of PA4-1-5 in ELLE

Following the above mentioned synthesis, The five 6,6′-alkyl functionalized BINOL derived chiral phosphoric acid hosts derived from **PA4** were obtained. We then applied these obtained phosphoric acids to the ELLE of various guests. First however, we set to investigate the potentially increased solubility in organic solvents. Therefore several host solutions were prepared, at 1.0 mM, 5.0 mM and saturation level in chloroform[77]. We then presented these solutions to a similar guest scope as used for **PA4**, for optimal comparison.[11] All extraction experiments were carried out *in triplo* in the presence of a control experiment ([host] = 0.0) under standard ELLE conditions (6 °C, pH = 5.0). The physical partitioning was observed to be 0.0 for all guest at standard ELLE conditions using chloroform as solvent.



3	5	6	7	23	24
[PA4-R]=saturation					
PA4-1: α_{op}: 1.1 PA4-2: α_{op}: 1.1 PA4-3: α_{op}: 1.1 PA4-4: α_{op}: 1.1 PA4-5: α_{op}: 1.4	PA4-1: α_{op}: 1.0 PA4-2: α_{op}: 1.0 PA4-3: α_{op}: 1.0 PA4-4: α_{op}: 1.0 PA4-5: α_{op}: 1.2	PA4-1: α_{op}: 2.0 PA4-2: α_{op}: 1.9 PA4-3: α_{op}: 1.5 PA4-4: α_{op}: 1.9 PA4-5: α_{op}: 2.9	PA4-1: α_{op}: --- PA4-2: α_{op}: --- PA4-3: α_{op}: --- PA4-4: α_{op}: --- PA4-5: α_{op}: ---	PA4-1: α_{op}: 1.2 PA4-2: α_{op}: 1.3 PA4-3: α_{op}: 1.2 PA4-4: α_{op}: 1.2 PA4-5: α_{op}: 1.2	PA4-1: α_{op}: 1.0 PA4-2: α_{op}: 1.0 PA4-3: α_{op}: 1.0 PA4-4: α_{op}: 1.0 PA4-5: α_{op}: 1.1
[PA4-R]=5,0 mM					
PA4-1: α_{op}: 1.1 PA4-2: α_{op}: 1.1 PA4-3: α_{op}: 1.1 PA4-4: α_{op}: 1.2 PA4-5: α_{op}: 1.4	PA4-1: α_{op}: 1.0 PA4-2: α_{op}: 1.0 PA4-3: α_{op}: 1.0 PA4-4: α_{op}: 1.0 PA4-5: α_{op}: 1.0	PA4-1: α_{op}: 1.1 PA4-2: α_{op}: 1.5 PA4-3: α_{op}: 1.1 PA4-4: α_{op}: 1.5 PA4-5: α_{op}: 2.2	PA4-1: α_{op}: --- PA4-2: α_{op}: --- PA4-3: α_{op}: 1.3 PA4-4: α_{op}: --- PA4-5: α_{op}: ---	PA4-1: α_{op}: 2.0 PA4-2: α_{op}: 1.1 PA4-3: α_{op}: 1.1 PA4-4: α_{op}: 1.0 PA4-5: α_{op}: 1.0	PA4-1: α_{op}: 1.0 PA4-2: α_{op}: 1.0 PA4-3: α_{op}: 1.0 PA4-4: α_{op}: 1.0 PA4-5: α_{op}: 1.1
[PA4-R]=1,0 mM					
PA4-1: α_{op}: 1.0 PA4-2: α_{op}: 1.0 PA4-3: α_{op}: 1.0 PA4-4: α_{op}: 1.1 PA4-5: α_{op}: 1.4 PA4: α_{op}: 1.0	PA4-1: α_{op}: 1.0 PA4-2: α_{op}: 1.0 PA4-3: α_{op}: 1.0 PA4-4: α_{op}: 1.0 PA4-5: α_{op}: 1.0 PA4: α_{op}: 1.0	PA4-1: α_{op}: 1.1 PA4-2: α_{op}: 1.1 PA4-3: α_{op}: 1.0 PA4-4: α_{op}: 1.1 PA4-5: α_{op}: 1.3 PA4: α_{op}: 1.4	PA4-1: α_{op}: 1.1 PA4-2: α_{op}: 1.2 PA4-3: α_{op}: 1.2 PA4-4: α_{op}: 1.1 PA4-5: α_{op}: 1.1 PA4: α_{op}: 1.9	PA4-1: α_{op}: 1.0 PA4-2: α_{op}: 1.0 PA4-3: α_{op}: 1.0 PA4-4: α_{op}: 1.0 PA4-5: α_{op}: 1.0 PA4: α_{op}: 1.6	PA4-1: α_{op}: 1.0 PA4-2: α_{op}: 1.0 PA4-3: α_{op}: 1.0 PA4-4: α_{op}: 1.0 PA4-5: α_{op}: 1.0 PA4: α_{op}: 1.0

Table 4: Results of ELLE screening of chiral substrate classes with PA4-1 to PA4-5. Conditions: 2 mM guest solution (H_2O, pH 5 phosphate buffer) vs given mM host solution ($CHCl_3$), 6 °C. Determination of the ee, distribution and α_{op} via reverse phase HPLC of aqueous phase aliquots.

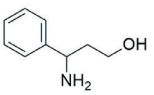
From the data presented in Table 4, the influences of the 6,6'-alkyl substituents becomes apparent. At levels where the host concentration is at saturation level we see that there is hardly any enantiodiscrimination in the extraction of the amino acids **3**, **5** and **39**, which is in line with the results obtained for original **PA4** (albeit at lower concentrations).[11] An exception in this case is **PA4-5**, which is, to the best of our knowledge, the only currently known BINOL derived chiral phosphoric acid capable of efficient enantiodiscrimination between two enantiomers of an α-amino acid (**3**). In the case of guest **7**, at high host concentrations full extraction of the guest was observed. The depletion of the aqueous phase makes an effective analysis impossible (Table 4, column 4). At saturated host concentrations good results are observed for guest **6**, all exceeding an α_{op} of 1.5 (Table 1, entry a). The best results are obtained using the dodecyl- (**PA4-5**) and methyl- (**PA4-1**) 6,6'-substituents with an α_{op} of 2.9 and 2.0, respectively (Table 4, column 3). In the case of guest **24**, at saturated host concentrations, operational selectivity is lower than the original 1.6 obtained for 1.0 mM **PA4**, which is explained by the decrease in observed ee when comparing the two (Table 4, column 5).

At 5.0 mM host concentration, a relatively high concentration considering the relatively low solubility of BINOL derived chiral phosphoric acids in chloroform, we see similar results for guests **3**, **5** and **24**. (Table 4, Column 1, 2 and 6) In the case of guest **7**, again, analysis is unreliable due to full extraction and depletion of the aqueous phase.

Most efficient ELLE is still obtained for guest **6**, albeit less efficient than at saturated concentration. A positive result can be found for **PA4-1** and guest **23**, reaching an α_{op} of 2.0, an unprecedented record for BINOL derived chiral phosphoric acids and guest **23**.

Performing the same batch extraction reactions at standard ELLE conditions, with a standard host concentration of 1.0 mM, can provide information on the influence of the 6,6'-alkyl functionalities on the efficiency of the process. This allows for a more direct comparison to the BINOL derived chiral phosphoric acids previously described in this chapter. Whereas both **PA4** and **PA4-R** have in common that there is no enantioenrichment in the extraction of guests **5** and **24**, striking differences can be observed in all other cases (table 4). In the case of guest **3** we observed that the introduction of $C_{12}H_{25}$- chains allow for enantiodiscrimination, making **PA4-5** suitable for efficient ELLE. In the cases of guests **6**, **7** and **24** we observed a significant decrease to a complete loss in α_{op} when employing any of the **PA4-R** in comparison to the α_{op} values of 1.4, 1.9 and 1.6, respective, α_{op} obtained when employing **PA4**.

Since significant differences are observed between the efficiency of 3,3'-BINOL derived chiral phosphoric acids and 6,6'-3,3'-BINOL derived chiral phosphoric acids, at 1.0 mM host concentration a more elaborate guest screening was performed. In this extensive screening, all guests numbered **1**-**21** (*vide supra*) were tested under standard ELLE conditions employing **PA4-1** through **PA4-5**. The guests **22** (due to low solubility in the aqueous phase) and **3**, **5**, **6** and **7** (detailed ELLE was performed before) were excluded. Since the functionality available for molecular interactions, the phosphoric acid inside the cavity, is not significantly different from that present in **PA2-14**, it was not surprising that fruitful extraction was observed of almost all guests using the **PA4-R** hosts. Only in the cases of guest **1** and **8**, no reactive extraction could be observed. In most cases however, the extracted guest was racemic. Only in the case of guest **18** enantioselectivity could be observed, as indicated in Table 5.



18

PA4-1:	α_{op}: 1.2 ee:10%
PA4-2:	α_{op}: 1.2 ee: 8%
PA4-3:	α_{op}: 1.1 ee: 5%
PA4-4:	α_{op}: 1.1 ee: 5%
PA4-5:	α_{op}: 1.2 ee:10%

Table 5: ELLE screening of chiral substrate classes with PA4-1 to PA4-5. Conditions: 2 mM guest solution (H_2O, pH 5 phosphate buffer) vs given mM host solution ($CHCl_3$), 6 °C. Determination of the ee, distribution and α_{op} via reverse phase HPLC of aqueous phase aliquots.

Conclusion

In summary, in this chapter we have studied two major questions in the field of BINOL derived chiral phosphoric acids in ELLE. The first, concerns the importance of the 3,3'-aryl substituents present on the BINOL derived backbone of chiral phosphoric acids. It has become obvious that the omission of 3,3'-substituents generally results in a drastically lower or complete loss of ee, indicating their importance towards conforming to the three point rule of chirality.[9,10,31] Two of the three interactions are thought to be given by the interaction of the phosphoric acid and the amino and hydroxy groups of the guest. The third point however is not well established in literature, but is proposed to be due to steric effects of the BINOL derived backbone and the 3,3'-substituents. These sterics however should be separated in a factor of pure size of the 3,3'-substituent, and a factor of interaction of the guest with the quadrupole moment or the aryl substituent. This interaction with the quadrupole moment can of course be a favorable or an unfavorable interaction depending on the position of the charges in the quadrupole moment. Therefore, a wide variety of 3,3'-disubstituted BINOL-derived phosphoric acids were synthesized. Analyzing the results obtained from screening these PAs to a variety of chiral amines, amino alcohols and amino acids; we find it hard to predict in which cases favorable and efficient ELLE can be expected. We do however see that in some cases record-breaking operational selectivities are observed (table 2 entry 1, α_{op} = 4.2), while in other experiments no enantioselecitivity is observed involving PAs with similar quadrupole moment (**PA6** vs **PA9** guest **16**, table 2 entry 1). In other cases, relatively large changes in quadrupole moment[41-45] result in rather limited differences in ELLE processes (**PA7** vs **PA5** guest **6**, table 1 entry 1). We can conclude that the most efficient system are those involving amino-alcohol based guests, where neither the alcohol nor the amine is protected (Table 2, entry 5, 6). The highest, record breaking, operational selectivity for any BINOL derived chiral phosphoric acid in ELLE was obtained with **PA11** in combination with guest **18**. (Table 2 entry 1, α_{op} = 4.2) Moreover, the selectivity for amino alcohols was proven and taken advantage off in the selective extraction of amino alcohol 7 from mixtures. (Table 3) Here, generally, even higher operational selectivity values are obtained, proposed to be due to a salting out effect.

Further research towards the underlying principles of the interactions involved in guest-host complexation are required to fully answer the hypothesis on the role of the 3,3'-substituents in chiral recognition, however with the currently presented data it is possible to deduct that the sheer size of the aromatic substituents on the BINOL phosphoric acid has an influence (most likely an increase to a certain extent) on the

efficiency of the extraction. Based on the results obtained so far, we conclude that both the electronic properties, as well as the sterics of the aryl 3- and 3'-groups are of high importance to successful ELLE.

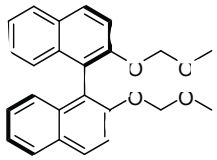
Employing alkyl chains on the 6,6'-position of chiral BINOL derived phosphoric acids, we found that, conform our hypothesis, the solubility of the chiral phosphoric acids could be drastically increased. We also observed, that in direct comparison, the introduction of 6,6'-alkyl substituents lowered the operational selectivity in most cases. (Table 4) This means that even though higher turnover numbers can be achieved due to higher host concentrations, the overall efficiency of an ELLE process would be less. The highest operational selectivity was obtained with a host-guest system based on host **PA4-5** and guest **6**. (Table 4, column 3)

Part of the experimental work in this chapter was performed by Iwan Esser and Lianne Jansen.

General information

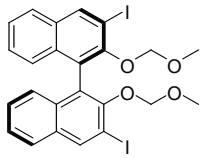
Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gels 60, 0.25 mm. Conversions of the reactions were determined by TLC unless otherwise stated. Components were visualized by UV and potassium permanganate staining. Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). ^{1}H- and ^{13}C-NMR were recorded on a Varian AMX400 (400 and 101 MHz, respectively) or a Varian VXR300 (300 and 75 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d =doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. All reactions were carried out under nitrogen or argon atmosphere in either oven dried round bottom flasks (gram scale or above) or oven dried sealed tubes (sub-gram scale) using standard Schlenk techniques. Diethyl ether, tetrahydrofuran, dichloromethane and toluene were used from the solvent purification system (MBRAUN SPS systems, MB-SPS-800). All catalysts, ligands, reagents and other solvents were purchased from commercial sources and used as received without further purification unless otherwise stated, except organo-lithium reagents which were titrated before use using diphenylacetic acid. When needed degassing of solvents was performed via the freeze, pump, thaw technique. RP-HPLC measurements were performed on a Shimadzu SIL-20A with a CTO-20AC column oven and LC-20AD pumps on a CROWNPAK® CR(-) chiral column (Daicel, Japan) equipped with a guard column. Calibration curves were prepared in the concentration range employed for the determination of the distribution. Uncertainties were typically lower than 2.0 %. General HPLC conditions for enantiomeric separation of aryl-1,2- and aryl-2,1-amino alcohols: Perchloric acid solutions (pH =1.5 or pH =1) flow = 1.0 ml/min were used as eluent, with exception of serine (**4**), phenylalanine (**18**), homoserine (**13**), 3-amino-3-phenyl-1-propanol (**16**) and normethaneprhrine (**17**) where a flow of 0,5 ml/min was applied. Column temperature was set at 20°C, with exception of 3-aminoisobuteric acid (**14**), where 0°C was applied. All materials are obtained as solid material, unless otherwise specified.

(R)- 2,2′-bis(methoxymethoxy)-1,1′-binaphthalene



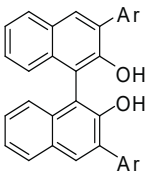
A suspension of NaH (4.5 g, 188.6 mmol, 3.6 equiv.) in 100 ml of dry THF was cooled to 0°C. Then a solution of (R)-BINOL (15.2 g, 53.1 mmol, 1 equiv.) in 100 ml of dry THF was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Subsequently it was cooled to 0°C before a dropwise addition of a solution of chloromethyl methyl ether (15.9 ml, 209.6 mmol, 4 equiv.) in 50 ml dry THF. The reaction mixture was allowed to stir overnight at room temperature, before cooling to 0°C and quenching with H_2O. Dilution with DCM was followed by washing with H_2O and brine and drying over Na_2SO_4. The solvent was evaporated *in vacuo*. The crude solid was then subjected to chromatography over a silica plug (8:2 Pentane: EtOAc) giving (R)- 2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (19.8 g, quantitative) as a white powder. (Quantitative yield) Data in accordance with literature.[31] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 9.0 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 5.10 (d, *J* = 6.8 Hz, 2H), 4.99 (d, *J* = 6.8 Hz, 2H), 3.16 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.63, 134.01, 129.87, 129.37, 127.85, 126.28, 125.54, 124.05, 121.29, 117.29, 95.20, 55.82.

(R)-3,3′-diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene



To a solution of (R)- 2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (0.508 g, 1.36 mmol, 1 equiv.) in 20 ml of dry Et_2O was added TMEDA (0.4 ml, 2.72 mmol, 2 equiv.). The reaction mixture was cooled to -78°C before adding *n*-BuLi (1.6 M, 4.08 mmol, 3 equiv.) drop wise. The reaction mixture was left to warm to room temperature and stirred for 6 h, after which it was cooled to -78°C again. Then a solution of I_2 (1.08 g, 4.2 mmol, 3.1 equiv.) in 10 ml dry Et_2O was added and the mixture was left stirring overnight at room temperature. To push to full conversion another batch of I_2 (1.09 g, 4.2 mmol, 3.1 equiv.) in 10 ml dry Et_2O was added at -78°C and the mixture was stirred for another 2 h at room temperature. Subsequently the mixture was diluted with DCM and washed with sat. aq. $NaHSO_3$, H_2O and brine and dried over Na_2SO_4. The solvent was removed *in vacuo*. The crude product was purified by FCC (97:3 Pentane:EtOAc) to get (R)-3,3′-diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (0.631 g, 76 %) as an off-white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 4.75 (dd, *J* = 34.9, 5.6 Hz, 5H), 2.60 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.20, 140.09, 132.24, 127.15, 126.77, 126.27, 125.88, 99.45, 92.20, 57.66.

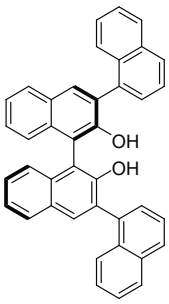
General Method Suzuki-Miyaura Cross-Coupling



A sealed tube was charged with (R)-3,3′-diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (1 equiv.), $Ba(OH)_2 \cdot H_2O$ (3 equiv.), Aryl-boronic acid (3 equiv.), $Pd(OAc)_2$ (0.1 equiv.) and PPh_3 (0.4 equiv.). To this was added 10 ml of a degassed solution of 3:1 1,4-dioxane:H_2O and the reaction mixture was heated until reflux and stirred for 72 h. The reaction mixture was allowed to cool to room temperature after which 1,4-dioxane was removed *in vacuo*. Subsequently a 1:1 mixture of DCM and 1 M aq. HCl were added followed by stirring for 30 min. Layers were separated and the organic layer was washed twice with 1 M aq. HCl and once with brine. The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo.*

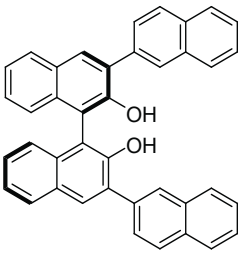
The obtained solid was dissolved in 10 ml 1,4-dioxane and 1 ml 12 M aq. HCl and stirred for a period of up to 60 h while heating to 60°C. (conversion was followed using TLC) The reaction mixture was then left to cool to room temperature before the 1,4-dioxane was removed *in vacuo*. The mixture was diluted with DCM and dried over Na_2SO_4 before removing the solvent *in vacuo*. The product was purified using FCC (10:1 Pentane:EtOAc). The compound was subsequently dissolved in toluene and washed with aq. 5 M HCl and H_2O to remove any chelating salts. The compound was dried by co-evaporation with toluene followed by drying under high vacuum, yielding a solid in the indicated yield.

(R)- [1,2′:4′,1″:3″,1‴-quaternaphthalene]-2″,3′-diol



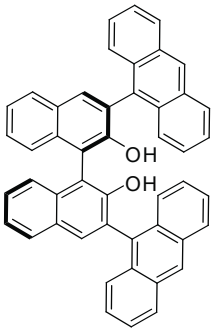
The product was obtained as a powder. Yield: 89% ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03(bs, 2H), 7.94 (m, 6 H), 7.70-7.31 (m, 16 H), 5.26-5.14 (m, 2H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.62, 150.58, 135.08, 133.90, 133.85, 133.82, 133.66, 132.27, 132.21, 129.58, 129.50, 129.37, 129.27, 128.88, 128.80, 128.60, 128.56, 128.51, 128.22, 128.12, 127.45, 126.59, 126.24, 126.19, 126.10, 125.76, 125.62, 124.82, 124.65, 124.40. (including signals due to presence of rotamers) HRMS(EI+) Calculated for $C_{40}H_{26}O_2$ m/z 538.1933 Found: 538.1915

(R) [2,2′:4′,1″:3″,2‴-quaternaphthalene]-2″,3′-diol



The product was obtained as a white solid. Yield: 86% ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 2H), 8.15 (s, 2H), 8.02-7.85 (m, 10H), 7.59-7.24 (m, 10 H), 5.46 (s, 2H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.47, 135.17, 133.63, 133.20, 132.94, 131.85, 130.80, 129.70, 128.66, 128.37, 128.08, 127.85, 127.59, 126.44, 126.39, 124.57, 124.49, 112.66. HRMS(EI+) Calculated for $C_{40}H_{26}O_2$ m/z: 538.1933 Found: 539.1991

(3r)-3,3′-di(anthracen-9-yl)-[1,1′-binaphthalene]-2,2′-diol



The product was obtained as a white solid. Yield: 76% ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58(s, 2H), 8.12-7.99 (m, 6H), 7.96-7.82 (m, 4H), 7.67 (d, J = 9 Hz, 2H), 7.59 (d, J = 9 Hz, 2H), 7.54-7.38 (m, 10 H), 7.27 (t, J = 8 Hz, 2H), 5.06 (s, 2H) 13C NMR (101 MHz, $CDCl_3$) δ 151.20, 134.13, 133.28, 131.73, 131.66, 131.06, 130.94, 129.51, 128.90, 128.77, 128.69, 127.99, 127.61, 127.35, 126.43, 126.38, 125.56, 125.07, 124.48, 113.73.

3,3′-bis(3,5-dimethylphenyl)-[1,1′-binaphthalene]-2,2′-diol

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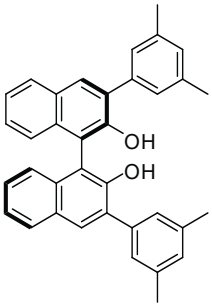
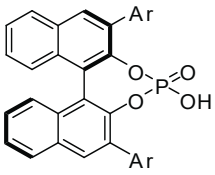


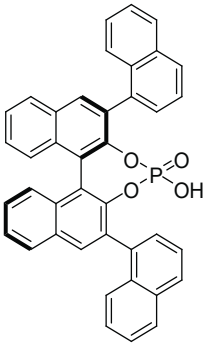
2,2′-Bis(methoxymethoxy)-1,1′-binaphthalene (374 mg, 1 mmol, 1 equiv.) was added to a Schlenk flask equipped with stirrer under a dry air atmosphere followed by the aryl chloride, (522 mg, 3 mmol) and Pd-PEPPSI-*i*Pr (14 mg, 2.0 mol%). *t*-BuLi (790 μL in heptane) was added at room temperature to the stirred mixture over a period of 10 min using a syringe pump. After the addition was completed, a saturated solution of aqueous NH4Cl was added and the mixture was extracted with Et_2O. The organic phases were combined, dried over anhydrous Na_2SO_4 and residual solvents removed under vacuum. Recrystallization from cyclohexanes afforded the desired heterocoupled product in 88% (435 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 2H), 7.91 (d, J = 8.1 Hz, 2H), 7.41 – 7.28 (m, 8H), 7.27 – 7.21 (m, 2H), 7.06 (s, 2H), 5.39 (s, 2H), 2.40 (s, 12H). 13C NMR (101 MHz, $CDCl_3$) δ 152.61, 140.81, 139.90, 135.65, 133.59, 133.49, 132.16, 132.02, 130.99, 129.97, 129.74, 127.04, 126.79, 115.41, 24.06.

General method phosphorylation and hydrolysis



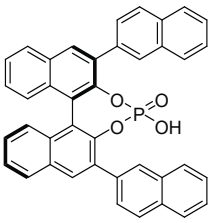
A Schlenk flask was charged with the diol starting material (1 equiv.) and brought under N_2 atmosphere. To this was added 2 ml dry DCM and the solution was cooled to 0°C. Subsequently NEt_3 (5 equiv.) and $POCl_3$ (1.5 equiv.) were added. The reaction mixture was allowed to stir overnight at room temperature. Quenching was performed using 1 ml H_2O and 0.2 ml NEt_3 while stirring for another 10 min. The solution was then acidified until pH 2 and stirred for 2 more hours. The reaction mixture was diluted with DCM and washed with H_2O and brine before drying over Na_2SO_4 and removing the solvent *in vacuo*. The compound was purified by FCC and subsequently dissolved in toluene. The organic layer was washed with 5 M HCl and H_2O to remove any chelating salts. The compound was dried by co-evaporation with toluene followed by high vacuum and obtained as a solid in the indicated yield.

4-hydroxy-2,6-di(naphthalen-1-yl)dinaphtho[2,1-d:1′,2′-f][1,3,2 dioxaphosphepine 4-oxide



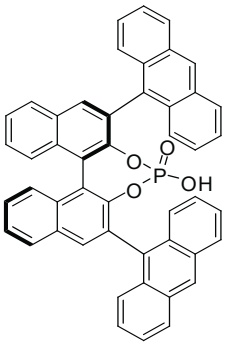
The product was obtained as a white solid. Yield: 64% ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20-7.85 (m, 6H), 7.6-7.4 (m, 4H), 7.35 (q, J = 7 Hz, 2H), 7.21 (dd, 8 H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.74, 134.59, 134.14, 133.71, 133.28, 133.16, 132.66, 132.62, 132.38, 132.12, 132.07, 131.96, 131.91, 129.17, 129.04, 128.97, 128.75, 128.68, 128.60, 128.52, 128.35, 128.30, 128.23, 127.36, 127.30, 127.19, 126.72, 126.61, 126.48, 126.18, 126.04, 125.70, 125.65, 125.48, 125.31, 125.19, 125.05. (Including signals due to presence of rotamers) ^{31}P-NMR (121 MHz, $CDCl_3$) δ 8.51 HRMS(EI+) Calculated for $C_{40}H_{25}PO_4$ m/z: 599.1490 Found: 599.1412

4-hydroxy-2,6-di(naphthalen-2-yl)dinaphtho[2,1-d:1′,2′-f][1,3,2] dioxaphosphepine 4-oxide



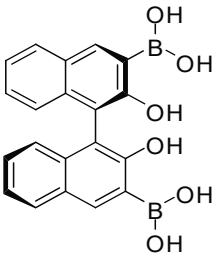
The product was obtained as a white solid. Yield: 32 % ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.16 (m, 4H), 8.06 (t, J = 9 Hz, 2H), 8.00-7.87 (m, 7H), 7.83 (d, J = 8 Hz, 1H), 7.61-7.35 (m, 10H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.95, 133.41, 132.95, 132.92, 132.44, 129.19, 128.66, 128.48, 128.42, 128.25, 127.99, 127.78, 127.74, 127.66, 127.63, 127.12, 126.74, 126.58, 126.39, 126.26. ^{31}P-NMR (121 MHz, $CDCl_3$) δ 8.51 HRMS(EI+) Calculated for $C_{40}H_{25}PO_4$ m/z: 599.1490 Found: 599.1438

(2r)-2,6-di(anthracen-9-yl)-4-hydroxydinaphtho[2,1-d:1′,2′-f][1,3,2] dioxaphosphepine 4-oxide



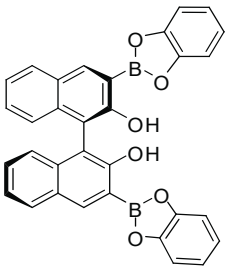
The product was obtained as a solid. Yield: 35% ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 2H), 8.02-7.93 (m, 4H), 7.86 (d, J = 9 Hz, 2H), 7.68 (d, J = 7 Hz 2H), 7.63-7.46 (m, 10H), 7.35 (t, J = 8 Hz 2H), 7.21 (d, J = 8 Hz, 2H), 7.13-7.01 (m, 4H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.57, 146.45, 133.99, 132.78, 131.53, 131.34, 130.98, 130.94, 130.89, 130.78, 130.42, 128.64, 127.98, 127.59, 127.51, 127.04, 126.21, 125.94, 125.12, 124.96, 122.43. ^{31}P-NMR (121 MHz, $CDCl_3$) δ 0.65

2,2′-Dihydroxy-1,1′-binaphthyl-3,3′-diboronic acid



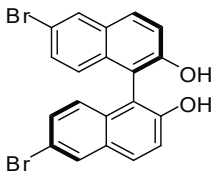
2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (4.25 g, 11.3 mmol) was dissolved in anhydrous THF, n-BuLi (15 ml 37.5 mmol) was added at -78 °C under a N_2 atmosphere. After the mixture was stirred at room temperature for 4 h, trimethoxyborane (7.6 mL, 67.8 mmol) was added dropwise at -78 °C. The reaction mixture was gradually warmed to room temperature and stirred overnight. The reaction was quenched by ice cold water at 0 °C, and extraction was carried out using ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by chromatography (hexane/ ethyl acetate: 10/1) to afford the intermediate. This intermediate was dissolved in HCl (1 M aq.) and the solution was stirred for 48 h to afford the product as a white precipitate. (yield 42%) ^{1}H NMR (300 MHz, d6-acetone) δ 8.55 (s, 2H), 7.93 (d, J = 12 Hz, 2H), 7.28 (m, 4H), 7.06 (q, J = 12Hz, 3 Hz, 2H). ^{13}C NMR (75 MHz, d6-acetone) δ 162.05, 153.94, 152.74, 133.05, 115.73, 112.16, 111.94, 110.38, 108.94, 98.13.

(R)-3,3′-bis(benzo[d][1,3,2]dioxaborol-2-yl)-[1,1′-binaphthalene]-2,2′-diol



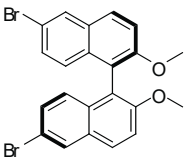
2,2′-Dihydroxy-1,1′-binaphthyl-3,3′-diboronic acid (200 mg, 0.54 mmol) and 1,2-dihydroxybenzene (108.2 mg, 1.08 mmol) were dissolved in toluene (60 mL) at 80 °C. Na_2SO_4 (ca. 6.0 g, anhydrous) was added over a period of 10 min, and the mixture was allowed to reflux overnight. After cooling to room temperature, the mixture was filtered over a glass filter. Additional toluene was used to wash. Solvent was evaporated under reduced pressure, and the product was obtained as a white solid in a nearly quantitative yield (276 mg). ^{1}H NMR (300 MHz, d6-acetone) δ ppm 8.55 (s, 1H), 7.93 (d, 1H, J = 9 Hz), 7.29 (m, 2H), 7.06 (d, J = 9 Hz, 1H), 6.84 (q, J = 3 Hz, 2H), 6.69 (q, J = 3 Hz, 2H). ^{13}C-NMR (75 MHz, d6-acetone) δ 157.07, 155.10, 154.23, 153.94, 152.74, 133.02, 129.35, 128.47, 128.15, 127.46, 127.34, 127.12, 125.94, 125.53, 115.79, 108.94.

(R)- 6,6′-dibromo-[1,1′-binaphthalene]-2,2′-diol



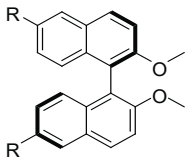
A solution of (R)-BINOL (12.5 g, 43.7 mmol) in 150 ml of anhydrous DCM at -78°C was prepared. A solution of bromine (6.07 mL, 0.6 mmol) in anhydrous DCM (50 mL) was added dropwise. The dark red/brown reaction mixture was stirred for 2 h at -78°C, before it was allowed to gradually warm to room temperature. The reaction mixture was stirred for another 2 h at room temperature. The excess bromine was quenched by slow addition of a Na_2SO_3 solution, which made the colour to fade. After quenching the organic layers were separated. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. This yielded a beige powder. (quantitative yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 2H), 7.86 (d, J=9 Hz, 2H), 7.38-7.34 (m, 4H), 6.94 (d, J=9 Hz, 2H), 4.97 (s, 1H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.93, 131.85, 130.84, 130.67, 130.55, 130.42, 125.84, 118.94, 117.99, 110.60 Mp: 89-91 ^{0}C $[\alpha]_{20}$ D = 756 (c 1.00 $CHCl_3$) HRMS (DART): 444.95, 442.96, 440.96 (calculated 443.92 (100%), 441.92 (51.4%), 445.92 (48.6%))

6,6′-dibromo2,2′-dimethoxy-1,1′-binaphthalene



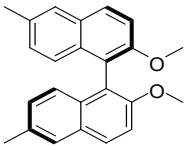
6,6′-Dibromo-[1,1′-binaphthalene]-2,2′-diol, (25.6 g, 44 mmol), K_2CO_3 (201 g, 0.14 mol) and freshly distilled acetone (245 mL) were added to a three-necked flask under nitrogen atmosphere. The yellowish suspension was stirred for 15 minutes, after which the Me_2SO_4 (12.2 g, 0.10 mol, 16.5 mL) was added dropwise and the suspension was stirred overnight. The reaction mixture was filtered. The white solid residual was washed with water, to yield the white solid product. (yield: 68%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.86 (d, J = 10 Hz, 2H), 7.44 (d, J = 10 Hz, 2H), 7.27 (d, J = 2 Hz, 1H), 7.23 (d, J = 2 Hz, 1H), 6.91 (d, J = 10 Hz, 2H), 3.74 (s, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.68, 129.86, 129.72, 128.71, 126.85, 114.92, 56.71

2,2′-dimethoxy-6,6′-di(R)-1,1′-binaphthalene



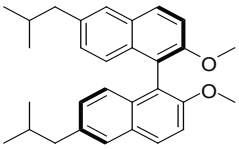
To a three-necked flask with condenser, 6,6′-dibromo2,2′-dimethoxy-1,1′-binaphthalene, (5 g, 11 mmol), $PdCl_2$(dppf) (803 mg, 1.1 mmol, 0.1 eq) and dry THF (300 mL) were added under nitrogen atmosphere. The solution was cooled to 0°C and the RMgBr (55 mmol, 5 eq) was added dropwise. After the addition the reaction mixture was refluxed for 2.5 h, which yielded a dark coloured reaction mixture. Once the reaction mixture was cooled down to room temperature, it was quenched with a saturated aqueous NH_4Cl solution (40 mL). The mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (gradient of pentane and ethyl acetate, 0%-20%). A pale yellow solid was obtained.

(R)-2,2′-dimethoxy-6,6′-dimethyl-1,1′-binaphthalene



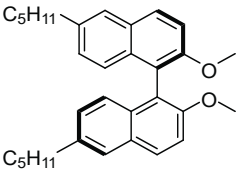
The product was obtained as a pale yellow solid. Yield: 36% ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 9 Hz, 2H), 7.60 (s, 2H), 7.39 (d, J = 9 Hz, 2H), 6.99 (s, 4H), 3.71 (s, 6H), 2.42 (s, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.42, 136.72, 132.47, 129.31, 128.74, 128.42, 127.13, 125.05, 119.76, 114.37, 57.05, 45.36, 30.05, 22.51, 22.46 Mp: 240-245°C

(R)-2,2′-dimethoxy-6,6′-diisobutyl-1,1′-binaphthalene



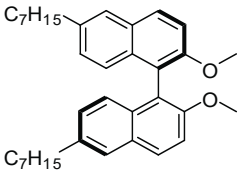
The product was obtained as a pale yellow solid. Yield: 68% ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 9 Hz, 2H), 7.57 (s, 2H), 7.40 (d, J = 9 Hz, 2H), 7.01 (s, 4H), 3.73 (s, 6H), 2.55 (d, J = 7 Hz, 4H), 1.90 (m, 2H), 0.90 (d, J = 7 Hz, 12H) ^{13}C NMR (101 MHz, CDCl3) δ 136.72, 128.73, 128.42, 127.12, 125.05, 114.37, 77.63, 76.99, 76.36, 57.05, 45.35, 30.06, 22.51, 22.45 Mp: 70-72^{0}C $[\alpha]_{20}$ D = 152 (c 1.00, $CHCl_3$) Elemental analysis: C 83.76, H 8.04 (expected C 84.47, H 8.03) HRMS (EI+): calculated for $C_{30}H_{32}O_2$ 427.2631 found: 427.2629

(R)-2,2′-dimethoxy-6,6′-dipentyl-1,1′-binaphthalene



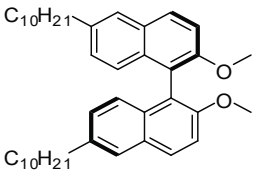
The product was obtained as a pale yellow solid. Yield: 64% ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 9.0 Hz, 2H), 7.60 (s, 2H), 7.40 (d, J = 9.0 Hz, 2H), 7.02 (s, 4H), 3.73 (s, 6H), 2.79 – 2.56 (t, 4H), 1.80 – 1.52 (m, 4H), 1.46 – 1.18 (m, 8H), 0.87 (m, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.40, 137.91, 129.39, 128.69, 127.93, 126.17, 125.18, 114.39, 57.04, 35.79, 31.59, 30.97, 22.56, 14.02 Mp: 92-93.5^{0}C $[\alpha]_{20}$ D = 212 (c 1.00, $CHCl_3$) Elemental analysis: C 84.57, H 8.56 (expected C 84.54, H 8.42) HRMS (EI+): calculated for $C_{32}H_{38}O_2$ 455.2944 found: 455.2943

(R)-2,2′-dimethoxy-6,6′-diheptyl-1,1′-binaphthalene



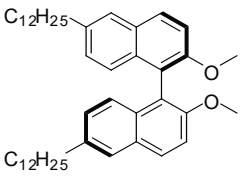
The product was obtained as a pale yellow solid. Yield: 68% ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 9 Hz, 2H), 7.60 (s, 2H), 7.39 (d, J = 9 Hz, 2H), 7.02 (m, 4H), 3.72 (s, 6H), 2.84 – 2.54 (t, 4H), 1.80 – 1.55 (m, 4H), 1.26 (m, 16H), 0.84 (t, J = 6 Hz, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.63, 138.01, 132.73, 132.70, 129.64, 128.92, 128.10, 126.43, 125.47, 119.98, 114.46, 72.08, 56.97, 37.73, 36.10, 32.12, 32.09, 31.66, 31.58, 29.96, 29.66, 29.58, 29.48, 25.91, 22.92, 14.34 Mp: 59.0-61.3^{0}C $[\alpha]_{20}$ D = 188 (c 1.00, $CHCl_3$) Elemental analysis: C 84.62, H 9.09 (expected C 84.66, H 9.08) HRMS (EI+): calculated for $C_{36}H_{46}O_2$ 511.3570 found: 511.3562

(R)-2,2′-dimethoxy-6,6′-didocyl-1,1′-binaphthalene



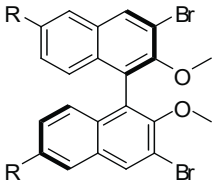
The product was obtained as a pale yellow solid. Yield: 76% ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 9 Hz, 2H), 7.62 (s, 2H), 7.42 (d, J = 9 Hz, 2H), 7.14 – 6.93 (m, 4H), 3.75 (s, 6H), 2.69 (t, 4H), 1.64 (m, 4H), 1.48 – 1.14 (m, 28H), 0.88 (t, J = 6 Hz, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.11, 132.61, 128.87, 128.12, 126.36, 125.38, 114.58, 57.23, 36.02, 32.07, 31.49, 29.79, 29.72, 29.61, 29.50, 22.85, 14.28 Mp: 48-50^{0}C $[\alpha]_{20}$ D = 184 (c 1.00, $CHCl_3$) Elemental analysis: C 84.79, H 10.12 (expected C 84.79, H 9.83) HRMS (EI+): calculated for $C_{42}H_{58}O_2$ 595.4509 found: 595.4501

(R)-2,2′-dimethoxy-6,6′-didodecyl-1,1′-binaphthalene



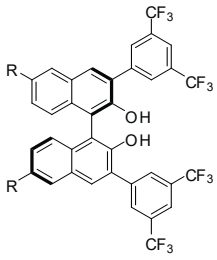
The product was obtained as a pale yellow solid. Yield: 64% ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 9 Hz, 2H), 7.60 (s, 2H), 7.40 (d, J = 9 Hz, 2H), 7.02 (s, 4H), 3.73 (s, 6H), 2.76 – 2.58 (m, 4H), 1.62 (m, 4H), 1.29-1.24 (m, 36H), 0.86 (t, J = 6 Hz, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.40, 137.92, 132.43, 129.39, 128.68, 127.93, 126.17, 125.18, 119.79, 114.39, 57.05, 35.86, 31.92, 31.34, 29.68, 29.56, 29.45, 29.35, 22.70 Mp: 58-61^{0}C $[\alpha]_{20}$ D = 124 (c 1.00, $CHCl_3$) Elemental analysis: C 84.87, H 10.43 (expected C 84.87, H 10.22) HRMS (EI+): calculated for $C_{46}H_{66}O_2$ 651.5135 found: 651.5128

3,3′-dibromo-6,6′-di(R)-2,2′-dimethoxy-1,1′-binaphthalene



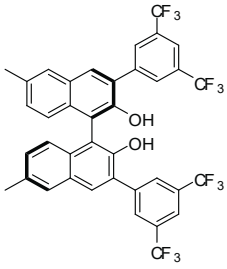
2,2′-dimethoxy-6,6′-di(R)-1,1′-binaphthalene (0.7 mmol) was added to anhydrous DCM (7 mL) under nitrogen atmosphere. The mixture was cooled down to 0°C and bromine (0.08 mL, 1.6 mmol, 2.3 eq) was added. The dark red solution was stirred for 1 hour and gradually reached room temperature. The solution was poured into a saturated $NaHSO_3$solution (11 mL) and this mixture stirred for 1 h at room temperature. The reaction mixture was extracted three times with DCM. The organic layers were combined and dried over Na_2SO_4, filtered and concentrated. Filtration over a silica plug yielded the crude product, which was used in the subsequent steps without further purification.

3,3'-bis(3,5-bis(trifluoromethyl)phenyl)-6,6'-di(R)-[1,1' binaphthalene]-2,2'-diol



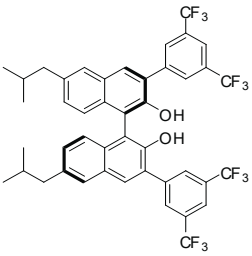
The products from the 3,3'-bromination (1.48 mmol) was dissolved in DME in a 20 mL screw-capped vial. The (3,5-bis(trifluoromethyl)phenyl)boronic acid (1.4 gram, 5.18 mmol, 3.5 eq) and an aqueous solution of K_2CO_3 (2M, 1 mL) were added to the solution. This mixture was degassed and placed under argon. The $Pd(PPh_3)_4$ (256 mg, 0.22 mmol, 0.15 eq) was added and the reaction mixture was degassed another time and placed under argon. The screw-capped vial was closed and heated to 95°C. The reaction mixture was stirred at 95°C for 16 h. The obtained dark solution was filtered over celite and the solvent was removed. The crude product was dissolved in DCM, washed with saturated aqueous NH_4Cl, water and brine, dried over Na_2SO_4 and concentrated. The crude product was dissolved in anhydrous DCM (2 mL) under nitrogen atmosphere. The $BF_3{\cdot}SMe_2$-complex (858 mg, 0.7 mL, 6.6 mmol, 6 eq) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with methanol, this changed the colour from orange to dark brown. The mixture was evaporated and the residual was filtered and then separated on silica gel column (automated column, gradient pentane/ether). This yielded a yellow oil.

3,3'-bis(3,5-bis(trifluoromethyl)phenyl)-6,6'-dimethyl-[1,1'-binaphthalene]-2,2'-diol



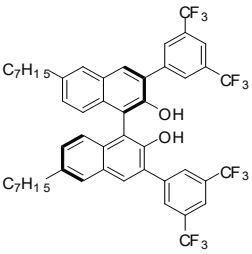
The product was obtained as a pale yellow solid. Yield: 41% ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 2H), 7.85 (d, J = 12.6 Hz, 4H), 7.43 – 7.13 (m, 8H), 4.99 (s, 2H), 2.18 (s, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.81, 144.71, 138.24, 134.96, 134.77, 134.63, 134.49, 133.13, 133.00, 132.95, 131.31, 131.07, 127.46, 127.41, 120.95, 114.16, 23.05.

3,3′-bis(3,5-bis(trifluoromethyl)phenyl)-6,6′-diisobutyl-[1,1′-binaphthalene]-2,2′-diol



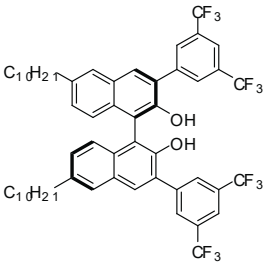
The product was obtained as a pale yellow solid. Yield: 35% ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, ^{1}H), 8.02 (s, 2H), 7.83 (d, J = 9.8 Hz, 3H), 7.44 – 7.14 (m, 8H), 5.02 (s, 2H), 2.29 (d, J = 7.3 Hz, 4H), 1.87 – 1.66 (m, 2H), 0.89 (t, J = 6 Hz, 3H), 0.77 (t, J = 6 Hz, 9H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.99, 144.65, 140.32, 138.32, 138.29, 135.90, 134.67, 133.74, 133.62, 133.31, 131.69, 131.09, 127.56, 127.36, 126.00, 121.43, 120.81, 114.05, 113.97, 44.97, 31.95, 25.08.

3,3′-bis(3,5-bis(trifluoromethyl)phenyl)-6,6′-diheptyl-[1,1′-binaphthalene]-2,2′-diol



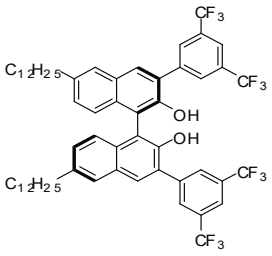
The product was obtained as a pale yellow solid. Yield: 62% ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 2H), 7.87 (d, J = 11.7 Hz, 4H), 7.45 – 7.13 (m, 8H), 5.12 (s, 2H), 2.50 – 2.29 (m, 4H), 1.55 – 1.05 (m, 16H), 0.99 – 0.71 (m, 10H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.94, 144.52, 141.38, 139.48, 135.79, 134.59, 133.34, 132.47, 131.60, 131.26, 131.02, 127.57, 126.92, 126.32, 121.45, 120.82, 113.94, 113.83, 39.87, 36.14, 34.49, 34.22, 32.88, 32.17, 32.00, 31.83, 31.55, 31.54, 25.34, 25.19, 16.75, 16.60. (heptyl chains are chemically inequivalent)

3,3′-bis(3,5-bis(trifluoromethyl)phenyl)-6,6′-diheptyl-[1,1′-binaphthalene]-2,2′-diol



The product was obtained as a pale yellow solid. Yield: 24% ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 2H), 7.85 (d, J = 6.5 Hz, 4H), 7.41 – 6.92 (m, 8H), 5.02 (s, 2H), 2.93 (m, 4H), 2.39 (m, 4H), 1.66 (m, 4H), 1.49 – 1.05 (m, 20H), 0.83 (m, 10H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.94, 144.52, 141.38, 139.48, 135.79, 134.59, 133.34, 132.47, 131.60, 131.26, 131.02, 127.57, 126.92, 126.32, 121.45, 120.82, 113.94, 113.83, 39.87, 36.14, 34.49, 34.22, 32.88, 32.17, 32.00, 31.91, 31.72, 31.83, 31.78, 31.76, 31.65, 31.55, 31.54, 25.37, 25.34, 25.19, 16.75, 16.60. (decyl chains are chemically inequivalent)

3,3′-bis(3,5-bis(trifluoromethyl)phenyl)-6,6′-diheptyl-[1,1′-binaphthalene]-2,2′-diol

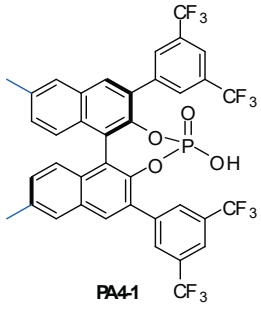


The product was obtained as a pale yellow solid. Yield: 69% ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 2H), 7.84 (d, J = 10.0 Hz, 4H), 7.44 – 7.04 (m, 8H), 4.98 (s, 2H), 2.45 – 2.23 (m, 4H), 1.43 (m, 4H), 1.33 – 0.99 (m, 36H), 0.84 (t, J = 6.6 Hz, 6H) 13C NMR (101 MHz, $CDCl_3$) δ 154.94, 144.52, 141.38, 139.48, 135.79, 134.59, 133.34, 132.47, 131.60, 131.26, 131.02, 127.57, 126.92, 126.32, 121.45, 120.82, 113.94, 113.83, 39.87, 36.14, 34.49, 34.22, 32.88, 32.17, 32.00, 31.91, 31.72, 31.83, 31.78, 31.76, 31.65, 31.55, 31.54, 25.37, 25.34, 25.19, 18.67, 18.42, 17.24, 17.14, 16.75, 16.60. (dodecyl chains are chemically inequivalent)

General procedure for phosphorylation of 6,6′-disubstituted-3,3′-bis(3,5-bis(trifluoromethyl)phenyl BINOLs

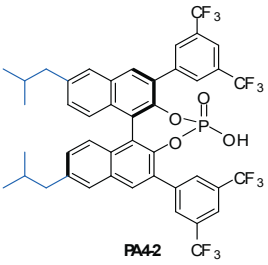
The corresponding diol (0.19 mmol) was dissolved in freshly distilled pyridine (1.5 mL) under nitrogen atmosphere. $POCl_3$ (87.5 mg, 0.05 mL, 0.57 mmol, 3 eq) was added and the resulting mixture was refluxed overnight. The dark red solution was allowed to cool to room temperature and water was (carefully) added. The resulting brownish slurry was refluxed for 3 h. Once the reaction mixture was cooled down to room temperature DCM (5 mL) was added. A concentrated HCl-solution (1.5 mL) was added. The organic layer was concentrated *in vacuo* and was purified by reverse phase column chromatography (automated column, gradient methanol/water). This yielded a white or brownish solid in the indicated yield.

(4R)-2,6-bis(3,5-bis(trifluoromethyl)phenyl)-4-hydroxy-9,14-dimethyldinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4 – oxide



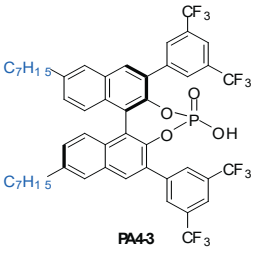
The product was obtained as a pale white solid. Yield: 55% ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 27 Hz, 4H), 7.59 (s, 2H), 7.33 (d, J = 8.8 Hz, 4H), 7.18 (d, J = 8.8 Hz, 4H), 2.12 (s, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.86, 135.11, 132.86, 132.15, 131.02, 130.36, 130.08, 128.99, 127.86, 127.39, 121.97, 121.46, 121.29, 20.43 ^{31}P-NMR (121 MHz, $CDCl_3$) δ 5.38 (s) ^{19}F-NMR (282 MHz, $CDCl_3$) δ -62.83 (s), -62.98 (s) $[\alpha]_{20}$ D = 1130 (c 1.00, $CHCl_3$) HRMS (EI+): calculated for $C_{42}H_{58}O_2$ 801.1058 found: 801.1051

(4R)-2,6-bis(3,5-bis(trifluoromethyl)phenyl)-4-hydroxy-9,14-diisobutyldinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4 – oxide



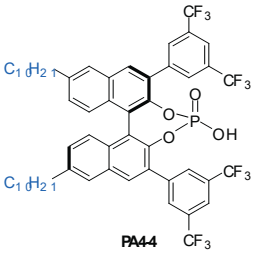
The product was obtained as a pale white solid. Yield: 45% ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 16.3 Hz, 4H), 7.67 (s, 2H), 7.49 – 7.03 (m, 8H), 2.24 (m, 4H), 1.75 (m, 2H), 0.89-0.65 (m, 12H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.64, 136.93, 135.27, 131.86, 131.41, 130.87, 128.46, 124.91, 121.29, 42.26, 29.95, 29.84, 22.33, 22.28, 22.15, 22.01 141.86, 135.11, 132.86, 132.15, 131.02, 130.36, 130.08, 128.99, 127.86, 127.39, 121.97, 121.46, 121.29, 20.43 ^{31}P-NMR (121 MHz, $CDCl_3$) δ 5.02 (s)^{19}F-NMR (282 MHz, $CDCl_3$) δ -63.20 (s), -63.36 (s) $[\alpha]_{20}$ D = 1008 (c 1.00, $CHCl_3$) HRMS (EI+): calculated for $C_{30}H_{31}PO_4$ 885.1997 found: 885.1993

(4R)-2,6-bis(3,5-bis(trifluoromethyl)phenyl)-4-hydroxy-9,14-diheptyldinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4 – oxide



The product was obtained as a pale white solid. Yield: 35% ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 21.6 Hz, 4H), 7.50 (s, 2H), 7.31 – 7.13 (m, 4H), 7.11 – 6.97 (m, 4H), 2.17 (m, 4H), 1.24 (m, 4H), 0.85 (m, 16H), 0.61 (m, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.83, 147.71, 141.78, 137.85, 134.75, 132.41, 131.97, 131.53, 131.04, 130.61, 130.35, 129.05, 128.21, 128.03, 127.67, 126.60, 125.15, 125.04, 121.98, 121.57, 121.42, 121.31, 35.36, 33.54, 31.65, 31.50, 31.40, 31.32, 29.27, 29.10, 29.02, 28.80, 28.69, 25.55, 22.55, 22.54, 22.46, 22.32, 13.97, 13.89, 13.77 ^{31}P-NMR (121 MHz, $CDCl_3$) δ 3.69 (s) ^{19}F-NMR (282 MHz, $CDCl_3$) δ -62.96 (s), -63.03 (s) $[\alpha]_{20}$ D = 996 (c 1.00, $CHCl_3$) HRMS (EI+): calculated for $C_{36}H_{45}PO_4$ 969.2936 found: 969.2934

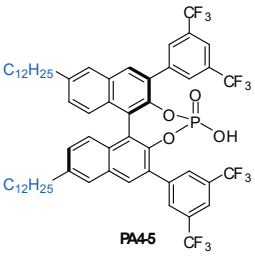
(4R)-2,6-bis(3,5-bis(trifluoromethyl)phenyl)-4-hydroxy-9,14-didocyldinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4 – oxide



PA44

The product was obtained as a pale white solid. Yield: 12% 1H NMR (400 MHz, CDCl3) δ 7.83 (d, J = 24.2 Hz, 4H), 7.65 (s, 2H), 7.25-7.20 (m, 8H), 2.80 (m, 4H), 2.30 (m, 4H), 1.55 (m, 4H), 1.15 (m, 24H), 0.85 (m, 6H) 13C NMR (101 MHz, $CDCl_3$) δ 141.70, 139.49, 137.74, 134.62, 132.00, 130.93, 130.21, 128.27, 123.66, 121.86, 37.27, 33.57, 31.89, 31.82, 31.39, 29.93, 29.61, 29.44, 29.33, 29.18, 29.12, 22.65, 22.60, 14.05, 14.02 31P-NMR (121 MHz, $CDCl_3$) δ 6.46 (s) 19F-NMR (282 MHz, $CDCl_3$) δ -62.82 (s), -62.93 (s) [α]20 D = 1432 (c 1.00, $CHCl_3$) HRMS (EI+): calculated for C42H57PO4 1053.3875 found: 1053.3866

(4R)-2,6-bis(3,5-bis(trifluoromethyl)phenyl)-4-hydroxy-9,14-didodecyldinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4 – oxide



PA45

The product was obtained as a pale white solid. Yield: 4% ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 24.3 Hz, 4H), 7.57 (s, 2H), 7.45 – 7.03 (m, 8H), 2.65 (m, 4H), 2.35 – 2.16 (m, 4H), 1.38 (m, 4H), 1.13 (m, 36H), 0.80 (t, J = 6.6 Hz, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.72, 137.69, 134.62, 131.42, 130.99, 130.55, 130.02, 128.03, 122.12, 121.32, 33.51, 31.84, 31.37, 29.55, 29.52, 29.48, 29.42, 29.34, 29.26, 29.11, 22.61, 14.02 ^{31}P-NMR (121 MHz, $CDCl_3$) δ 6.46 (s) ^{19}F-NMR (282 MHz, $CDCl_3$) δ -62.90 (s), -63.01 (s) $[\alpha]_{20}$ D = 940 (c 1.00, $CHCl_3$) HRMS (EI+): calculated for $C_{46}H_{65}PO_4$ 1109.4501 found: 1109.4500

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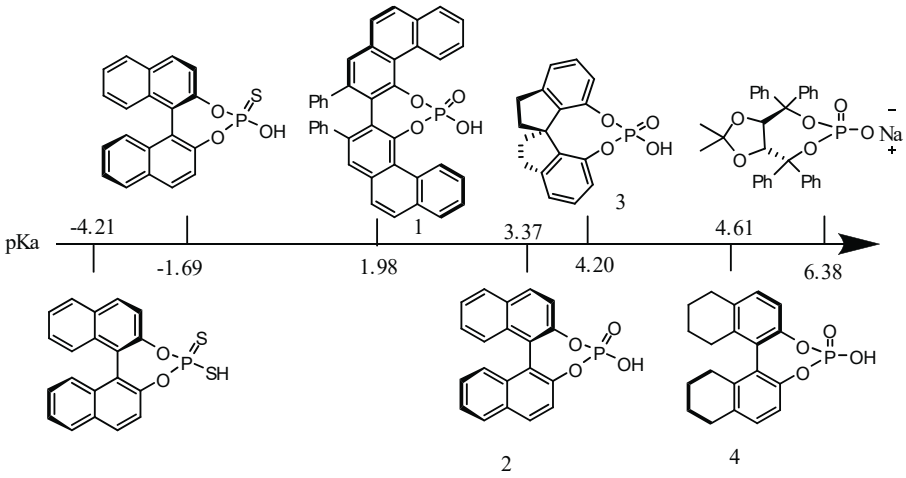
Chapter 3

Highly efficient enantioselective liquid-liquid extraction of 1,2-amino-alcohols using SPINOL based phosphoricacid hosts

Introduction

In the previous chapter, the importance of the 3,3'-aryl substituents on the BINOL backbone of a chiral BINOL derived phosphoric acid has been established. Several other parameters are also involved in determining the steric hindrance and electronical properties around/of the phosphoric acid moiety.[1] These parameters can have a major influence on the molecular interactions with the guest molecules and potentially have a large impact on the efficiency of ELLE.[2] By substitution or derivatization of the BINOL backbone, the bite angle (the angle under which the two naphthalene halves are set) as well as the electronic properties of the backbone can be altered. Both will have an influence on the pKa of the phosphoric acid.[3] Some adaptations of the BINOL backbone, the substitution at the 6,6'-position, have been shown already (Chapter 2). However, chiral phosphoric acids with different backbones have been reported in literature[4], together with their corresponding pKa values, obtained via DFT calculations.1 Their commonly accepted names, in order of pKa value (ascending), are the VAPOL, SPINOL, H8-BINOL and TADDOL backbone based chiral phosphoric acids (Scheme 1). Thiophosphoric[5] and dithiophosphoric BINOL derived acids are also presented with their respective calculated pKa values. Unfortunately in our hands reproduction of the only example given in literature of a BINOL derived thiophosphoric acid with 3,3'-substituents, resulted in no conversion towards the desired product, with full recovery of starting material[6]. They will therefore not be considered here. Now that the importance of sterical hindrance around the phosphoric acid moiety has been highlighted (chapter 2), investigation of the changes of backbone and their corresponding impact on the sterical environment of the host-guest binding pocket will be investigated next. In this chapter, the synthesis and application of the more rigid SPINOL derived phosphoric acids (Figure 1) in enantioselective liquid-liquid extraction of chiral amines will be evaluated.[7]



Scheme 1: Various chiral phophoric and thiophosphric acids with their corresponding calculated pKa values[1]

There is a large demand for enantiopure compounds, not only for the pharmaceutical and fine chemical industries,[8,9] but also for the fragrance & flavour, agrochemical and food & feed industries.[10] Some chiral molecules can be obtained from agriculture or fermentation, in the past referred to as the "chiral pool", however, the number of chiral compounds obtained in this way is rather limited.[9,11,12,13] Therefore the development of efficient methods to obtain chiral compounds in enantiopure form has been the centre of much attention over the past decades. Two distinctive pathways have been mainly used to obtain chiral compounds. The synthetic approach relies on the asymmetric transformation to create enantiopure compounds *via* such methods as the reaction of prochiral compounds to single enantiomers using chiral catalysts or the differentiation of the enantiomers *via* kinetic resolution.[14] The resolution approach relies on selectively removing one enantiomer from a racemate via crystallisation or chromatography.[15,16] While asymmetric synthesis has clearly shown to be incredibly powerful in answering the need for chiral molecular diversity, it needs longer development times and thus struggles to achieve the requirements defined by time to market pressure, although this problem can largely be abated by the use of high throughput experimentation.[17,18] In addition, many reported catalytic procedures are too slow to be cost-effective and require extensive development to increase the turnover frequency. In contrast, resolution of racemates is still a preferred method as often the cost of the racemate is rather low and the processes are easy to develop. One example of this is the production of enantiopure BINOL via entrainment crystallisation.[19] Although these crystallisation methods fit better with

the time to market demands, there is only a limited number of low-cost resolving agents available. In addition, these processes often suffer from solids handling issues in the plant.[20,21,22,23,24] Other resolution techniques such as chromatography, electrophoresis, or the use of membranes are either too slow or require high cost systems hindering large sale applications.[25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41]{Baragana, 2002 #167}{Baragana, 2002 #167}

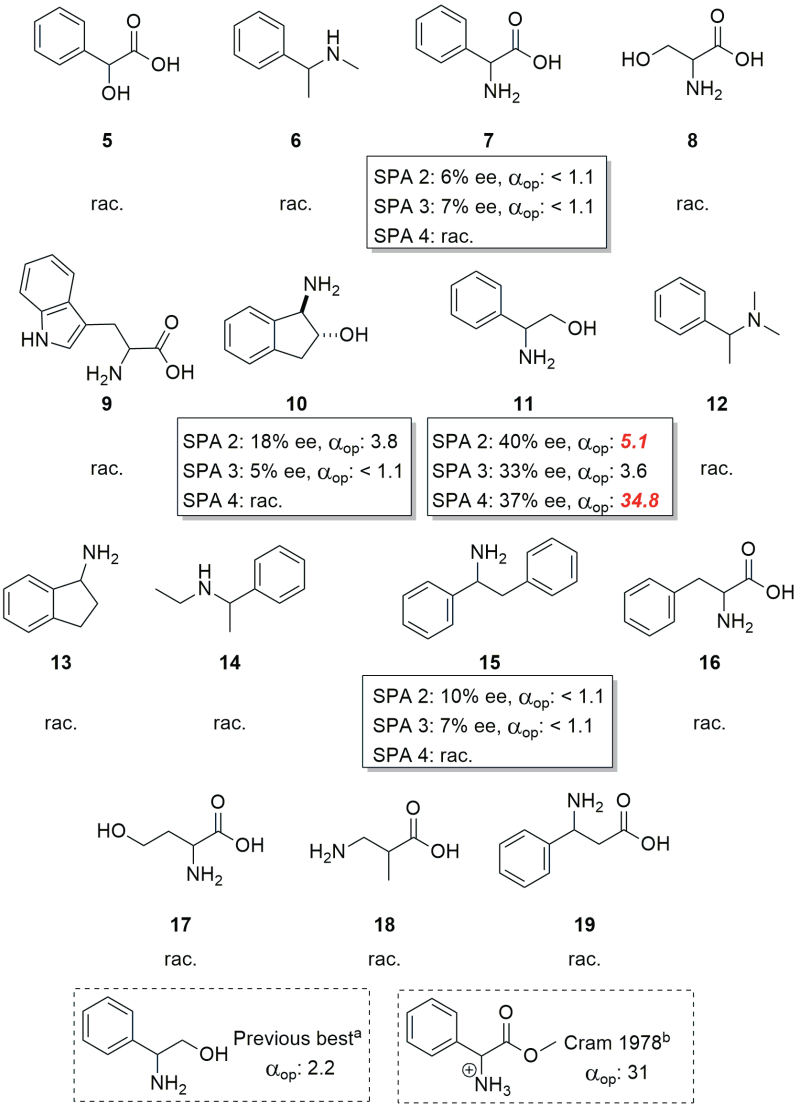


Figure 1: SPINOL derived dhiral hosts for application in ELLE

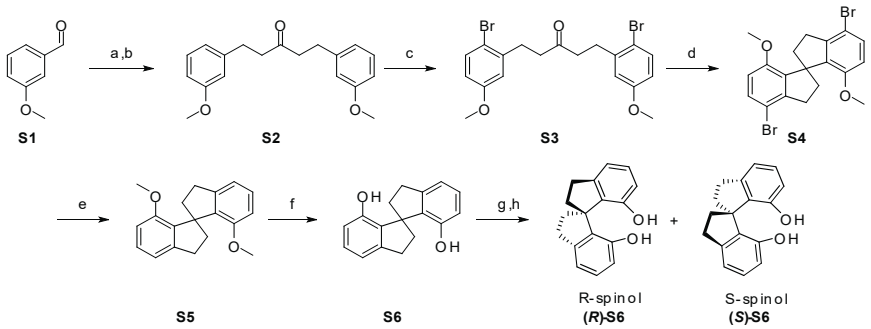
Enantioselective Liquid-Liquid Extraction (ELLE) has been well-studied to solve these issues and many reports as to the potential efficiency, scalability and costs have been published.[28,42,43,44,45,46,47,48,49,50] This method relies on the catalytic use of a chiral host and since mixing and a separation of the two phases are the two major unit operations used, it has a much reduced operational cost. In addition, the method can be scaled up quite easily as was shown earlier by us, for instance through the use of existing centrifugal contactor-separators.[51,52] This means that it has the potential to be even more viable, both economically and environmentally, than crystallisation. However, despite all the potential advantages of ELLE, it has, to the best of our knowledge, never been applied in large-scale production due to the fact that few developed chiral hosts are sufficiently selective ($\alpha_{op} > 3$; for an explanation of how this value is obtained see below), to allow a reduction of the number of extractions (stages).[8,51] Most of the reported host structures,[51] such as crown ethers, BINOL derivatives, metal complexes (Pd, Cu, Ln, Zn, Co, Ru), tartrates, Cinchona alkaloids or guanidinium derivatives or our own BINOL based phosphoric acid system, though promising,[53] function only at a proof of concept level with extraction values falling just short of applicability. Another underlying issue within these systems is that the fundamental chemical principles (kinetics, interactions, active complexes…) that drive them are poorly understood making further optimisation and developments difficult. As a direct result the developments in the field of ELLE has seen only slow progress with only a few recent results appearing such as the work of the groups of Schuur[54] and Tang[55]. Therefore a more detailed understanding of these systems is of paramount importance for the development of new, highly selective, hosts.

With the recent advancements in the field of organocatalysis, numerous new selector candidates have emerged. Their identification and study may provide the required insight into the core principles behind ELLE to bridge the gap between concept and application and explain the dependencies of the enantioselection on different parameters. Herein, we describe the results of an in depth study, from a fundamental point of view, of the interactions and parameters determining the efficiency of the resolution of chiral aminoalcohols by several new selector candidates. These hosts are capable of separating aminoalcohols with sufficient operational selectivity (vide infra) to reach the required level of efficiency to become industrially viable.

Results and Discussion

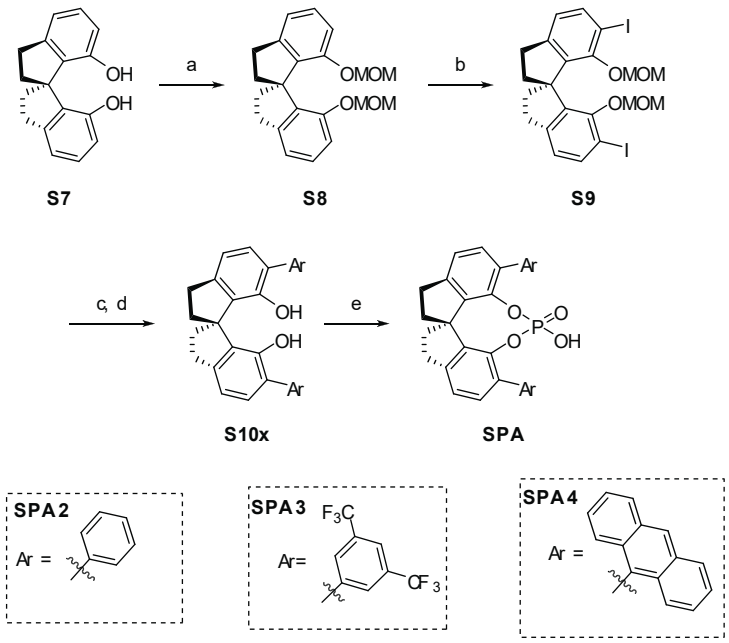
Host Family Studied

SPINOL derived ligands have been used for highly enantioselective metal-catalysed transformations, outperforming in many cases the more traditional BINOL and H8-BINOL derived alternatives, in terms of enantiodiscrimination.[56],[57] However, these ligands require a significantly greater synthetic effort to obtain compared to the other backbones and are therefore underused in fields outside asymmetric catalysis. Nevertheless, SPINOL-based hosts could be highly suited for ELLE as long as they are stable under the conditions of the extraction and if sufficient turnovers can be obtained. For this study we have selected four well-described SPINOL based phosphoric acids[58,59,60] as potential hosts, (Figure 1) which we obtained via known synthetic routes.61 An overview of the synthesis route is given below. SPINOL, the key chiral intermediate from which the 4 hosts are derived, was synthetized as follows according to an adapted and improved procedure described by Birman et al.[61] All spectroscopic data are matching, and the SPINOL intermediate was resolved according to method described by Deng and Ye.[62] (Scheme 2) Modifications of the existing procedure described by Birman et al. can be found most prominently in step d, where the use of polyphosphoric acid was circumvented. This, to prevent extensive difficulties during aqueous workup, in which highly stable emulsions drastically reduced the yield of the reaction. Instead, the starting material was brought onto pre-acidified silica where the reaction occurred under neat conditions. Work-up was significantly simplified to extensive extraction with DCM and recrystallization from hexane. Apart from synthetic ease, a significant increase in yield (from ~25% to 65%) was obtained. We would like to emphasize the importance of the lack of trace palladium (for example from cross contamination via stir bars) in the reaction mixture for step e, as this would lead to unwanted cross coupling reactions as described in chapter 5.



Scheme 2: Synthetic route towards (R)- and (S)-spinol. Reaction conditions: a) Me_2CO, NaOH, 50% EtOH-H_2O, r.t, 60%. b) Raney Ni, H_2, Me_2CO, r.t 95% c) Br_2, pyridine, DCM, 0°C. 95% d) SiO_2-SOOH, r.t, neat, 65%. e) ^{n}BuLi, THF, -78°C, 95%. f) BBr_3, DCM, -78°C, 85%. g) N-Benzylcinchonidinium chloride, toluene, reflux. h) HCl, (R)-spinol 90%, >99% ee, (S)-spinol 80%, >99% ee.

After resolution of the enantiomers of the key intermediate SPINOL using co-crystallisation with N-benzylcinchonidinium chloride, subsequent derivatization introducing the three different aryl groups on the 3,3'-positions was performed. (Scheme 3) To be able to obtain the desired SPINOL derived phosphoric acids, a similar route as for conventional BINOL derived hosts described in chapter 2 was employed. Enantiopure (R)-SPINOL was protected using a suitable MOM protecting group and selectively lithiated and halogenated at the 3,3'-positions. A subsequent Suzuki cross coupling for introduction of the aryl groups was employed and finally phosphorylation and hydrolysis yielded the desired hosts (**SPA2-4**) in relative overall good yield (59-90%). All spectroscopic data were found to be matching with literature values.[63] We note however that extensive drying of the obtained SPINOL derived phosphoric acid is required, as removal of residual water can be troublesome, resulting in a shift in signals when applying NMR spectroscopy. Research towards improving the current synthesis route towards SPINOL scaffold derivatives is a hot topic.[63,64]



Scheme 3: Synthetic route towards SPA 2-4. Reaction conditions: a) NaH, THF then MOMCl r.t 85%. b) ^{n}BuLi, TMEDA, TBME, then I_2 r.t 70%, c) for S10a and S10b $ArB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, THF, MeOH, H_2O reflux; for S10c $ArB(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, DME, reflux. d) HCl, dioxane, reflux. e) $POCl_3$, pyridine, reflux then dioxane, H_2O reflux or Na_2CO_3, H_2O, reflux[73]

Evaluation of the Enantioselective Liquid Liquid Extraction of Various Racemates by the SPINOL-based Hosts

Having successfully synthesised these chiral hosts, they were tested in the two-phase enantioselective extraction of a range of chiral compounds that are often used in enantiopure form as building blocks in organic synthesis () and highly promising initial results were obtained. Use of 6,6′-Unsubstituted SPINOL phosphoric acid (**SPA1,** Figure 1) resulted in racemic extraction of all families of guests whereas 6,6′-phenyl substituted **SPA2** showed modest enantio-discrimination for phenylglycine (**7**, 6% ee) and 1,2-diphenylethan-1-amine (**15**, 10% ee) and good to excellent selectivities in the cases of 1-amino-2,3-dihydro-1H-inden-2-ol (**10**, 18% ee) and phenylglycinol (**11**, 40% ee). 6,6′-(3,5-diCF_3)phenyl-substituted **SPA3** showed a similar trend though, overall, with slightly lower selectivities, while 6,6′-(5-anthracyl) substituted **SPA4** proved selective only for phenylglycinol (**11**, 37%). Highly encouraged by these results we next measured the α_{op} for the most selective host-guest pairs. We obtained in the case of *trans*-inden-2-ol (**10**) an α_{op} of 3.8 when using **SPA2**, while for

phenylglycinol (**11**) we obtained, respectively, 5.1 and 3.6 for **SPA2**, **SPA3** as well as and an exceptional α_{op} of 34.8 for **SPA4**. These results are significantly better than anything previously reported[47] and open the way towards industrial application. The result obtained with **SPA4** in the resolution of **11** is particularly striking as its efficiency is, to the best of our knowledge, higher than any previously reported system including the pioneering work of Cram who obtained with his best system an α_{op} of 31 for phenylglycine methyl ester.[56] In all cases the (*R*)- enantiomer of the SPINOL based hosts preferentially extracts the (*R*)- enantiomer of the corresponding amino acid or amino alcohol.

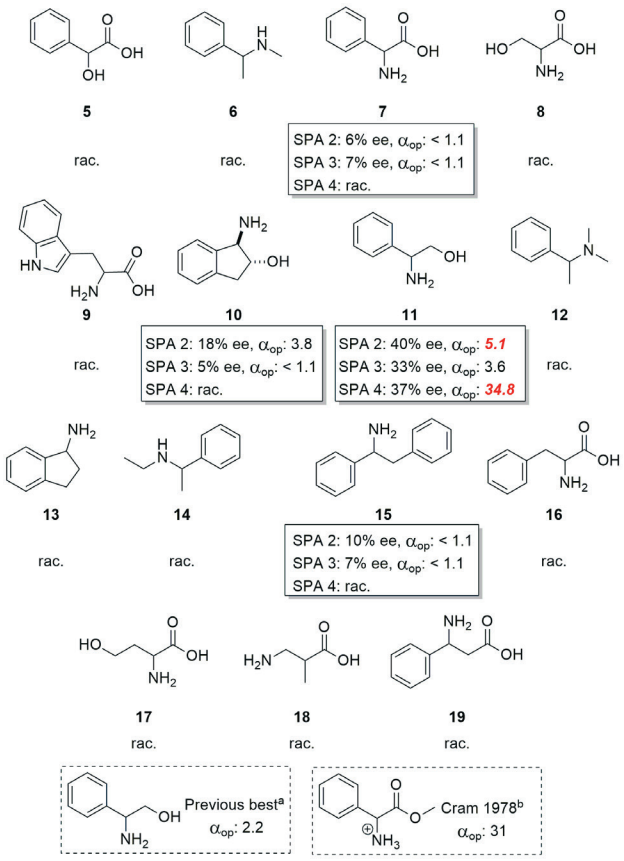


Figure 1: Screening of various classes of chiral compounds. Conditions: All extraction experiments were conducted in 2 ml auto-sampler vials with crimp cap seals equipped with stir bars. A solution of the racemic guest (0.4 ml, 2 mM) dissolved in a phosphate buffer solution (buffer strength 0.1 M, pH 5.0) was carefully added to a solution of the corresponding host in chloroform (0.4 ml, 1.0 mM). The two-phase system was then cooled to 6°C and stirred at 900 rpm for 16 h. The phases were then allowed to separate over a period of 2 min. The aqueous phase was removed and an aliquot injected into a chiral reverse phase HPLC for determination of the ee, distribution and α_{op}. All extraction experiments were carried out in triplo and with a simultaneous blank reaction (concentration of host = 0.0 mM).

Study and Optimisation of the ELLE of Amino-Alcohols by the SPINOL-based Hosts

In view of these exceptional results we further examined the parameters affecting the ELLE of phenylglycinol (**11**) using **SPA2** and **SPA4** to gain insight into the mode of action of these hosts.

The temperature of the extraction usually strongly affects the operational selectivity; prior experience has taught us that a delicate balance between solubility and selectivity exists with an optimum often at around 6°C and that small changes can strongly impact the process. We therefore studied the variation of ELLE over a 2-40 °C temperature range using the two best hosts (A). Interestingly, both revealed unexpected differences in behaviour. With **SPA2** the highest ee and α_{op} were obtained at 2°C (48% ee, α_{op} = 15.3) with diminishing results at increasing temperatures although it retained much of its exceptional selectivity even at 40°C (33% ee, α_{op} = 3.5). At 6 °C, a maximum in the amount extracted was observed, however, at lower ee's. **SPA4** showed a far greater sensitivity towards temperature. The highest ee's and α_{op}'s are obtained in a very small window around 6°C (37% ee, α_{op} = 34.8). Much lower enantioselection was observed at both lower and higher temperatures even though these results remain exceptionally high for ELLE (α_{op} = 3.6-4.3). Interestingly, this exceptionally high α_{op} is due to a reduction in the overall amounts extracted at 6 °C which results in near perfect selectivity for one enantiomer rather than any enhancement of extraction of the desired enantiomer. This therefore results in fewer steps needed to achieve high ee's and therefore an overall increase in efficiency. A similar behaviour is observed with **SPA2** at 2 °C. Initially all measurements were performed in a two to one guest to host (G/H) ratio for there to be an equivalent of each enantiomer available to the chiral host. However, we were also interested in the effect the G/H ratio had on our system. To put this in perspective: In a continuous extractive separation, the host is used in catalytic amounts with respect to the total amount of guest. Nevertheless, in each separatory stage the concentrations of host and racemate can be varied to achieve the optimum result. This could even include a situation where the concentration of host is higher than that of the racemate. We thus measured the effectiveness of the ELLE process with **SPA2** and **SPA4** over a G/H range of 0.25 to 3.0 (B). We observe that when an excess of guest over host is used (G/H > 2) a progressive erosion of ee and alpha is observed as expected due to a decreasing proportion of guest which can be extracted which mathematically leads to lower distribution values and therefore ee's and α_{op}. When a sub-stoichiometric amount of total guest to host is used (G/H < 1) the host extracts more guest regardless of configuration and an erosion of ee and alpha can be observed.

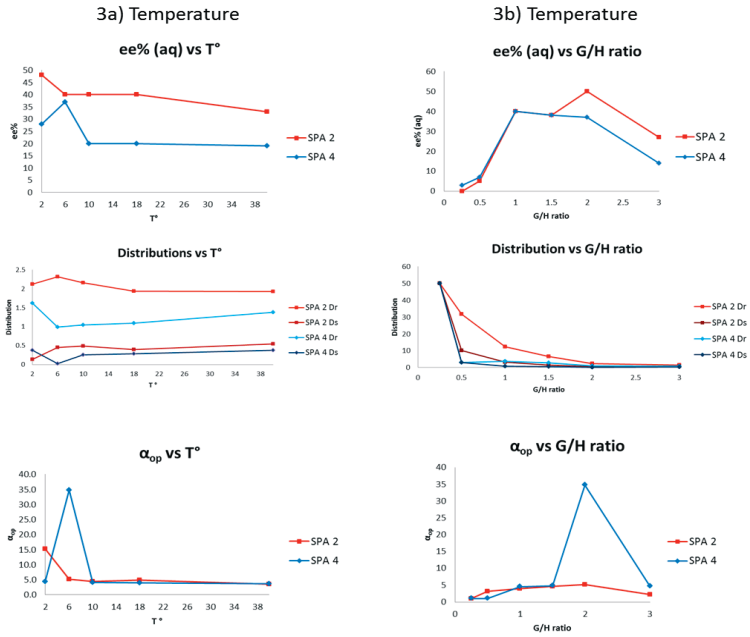


Figure 2: T° and G/H screenings. Conditions: All extraction experiments were conducted in 2 ml auto-sampler vials with crimp cap seals equipped with stir bars. a) A solution of racemic 11 (0.4 ml, 2 mM) dissolved in a phosphate buffer solution (buffer strength 0.1 M, pH 5.0) was carefully added to a solution of the corresponding host in chloroform (0.4 ml, 1.0 mM). The bi-phasic system was immediately cooled to the indicated temperature and stirred at 900 rpm for 16 h. b) A solution of racemic 11 (0.4 ml, indicated concentration) dissolved in a phosphate buffer solution (buffer strength 0.1 M, pH 5.0) was carefully added to a solution of the corresponding host in chloroform (0.4 ml, 1.0 mM) The two-phasic system was then immediately cooled to 6 °C and stirred at 900 rpm for 16 h. In all cases, the phases were then allowed to separate over a period of 2 min. The aqueous phase was removed and an aliquot injected into a reverse phase HPLC equipped with chiral columns for determination of the ee, distribution and α_{op}. All extraction experiments were carried out in triplo and with a simultaneous blank reaction (concentration of host = 0.0 mM).

The more interesting behaviour of these systems appears in the 1-2 G/H range (excess of total guest, substoichiometric amount of each enantiomer) were loss in selectivity is less than expected. This may indicate that the extraction is not solely determined by a competition between enantiomers for the host which, one would expect, would give a linear erosion of selectivity as observed when G/H < 1 but appears to also be determined by the two association constants between each enantiomer and host.
We next determined the effect of the pH on the enantioselectivity of the extraction. As the recognition between host and guest relies on acid-base interactions, we reasoned that pH could prove a crucial parameter for enantiodiscrimination. While surprisingly little pH dependency was noted when BINOL derived phosphoric acids were used[57] (estimated pKa 3.5-3.9),[1] SPINOL based phosphoric acids have predicted pKa's (around 4.9)[1] far closer to the pKb of phenylglycinol (around 5.5)[65] which could

have a positive effect as to the selectivity. We therefore studied the effect of the pH over a range of pH = 2-12 (Figure 3). Both S**PA2** and **SPA4** showed similar behaviours in terms of ee of the extraction with two significant maxima for each, a first one at pH 5 (40 and 37% ee, respectively) and a second one, at respectively pH 9.6 (44% ee) and pH 8.4 (52% ee). From the measured distributions it is clear that above pH 7 the amounts extracted are too high for good selectivity, this is, however, due to some solubility of the neutral guest into the organic phase,[66] though the effect of the catalyst remains visible. Below pH = 7, where the extraction is host-controlled, both **SPA2** and **SPA4** show interesting behaviour. **SPA2** has a maximum in extraction at pH 5 while **SPA4** is in a local minimum with the amount of undesired enantiomer extracted dropping to almost zero. In both cases these local variations result in optimal α_{op} values, making any attempts at determining structure-activity relationships difficult.

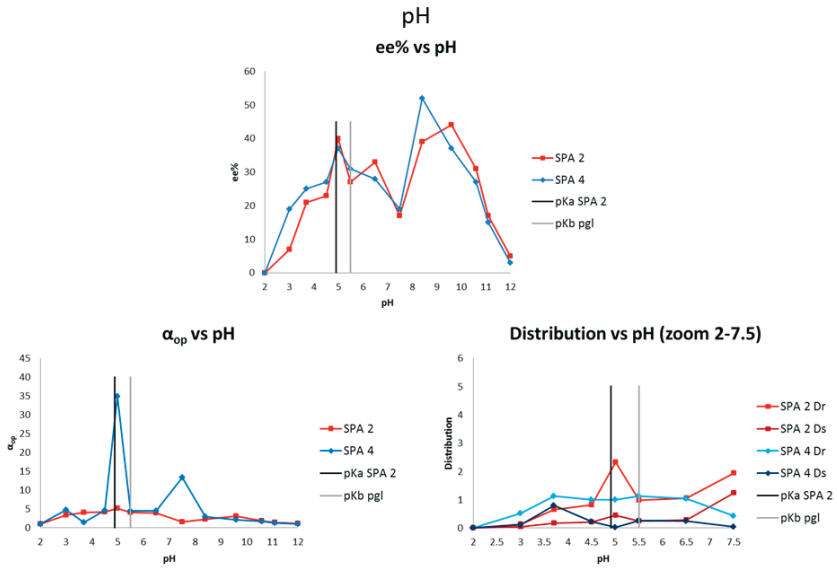


Figure 3: pH screenings for SPA2 and SPA4 in combination with guest 11. Conditions: All extraction experiments were conducted in 2 ml auto-sampler vials with crimp cap seals equipped with stir bars. A solution of racemic 11 (0.4 ml, 2 mM) dissolved in a phosphate buffer solution (buffer strength 0.1 M, indicated pH) was carefully added to a solution of the corresponding host in chloroform (0.4 ml, 1.0 mM). The two-phase system was then immediately cooled to 6 °C and stirred at 900 rpm for 16 h. In all cases, the phases were then allowed to separate over a period of 2 min. The aqueous phase was removed and an aliquot injected into a reverse phase HPLC system employing a crownpack (+) column for determination of the ee, distribution and α_{op}. All extraction experiments were carried out in triplo and with a simultaneous blank reaction (concentration of host = 0.0 mM).

One hypothesis towards explaining this high pH dependency would be that the changing ionic strength of the media affects the ion-pairing distance of the G/H complex, altering the chiral recognition between guest and host. At a pH close to both

the pKa of the host and pKb of the guest, the complex might form tighter ion pairs with stronger interactions which would explain the ee optimum at pH 5. As a control to check the influence of the buffer on the system, an extraction without buffer was performed and we obtained an ee of 37% and an α_{op} of 5.6 which showed that the buffer was not key to the extraction mechanism but important for maintaining an optimal pH as it varied strongly over the course of the extraction.

Finally we turned our attention to the solvent effect on the ELLE with these hosts. Due to limitations in solvent miscibility and the requirement that the guest must only be soluble in one phase, we limited our study to various halogenated and aromatic solvents (Figure 4). Both **SPA2** and **SPA4** show similar trends with chloroform, which was the optimal solvent in both cases (40% ee, α_{op} = 5.1; 37% ee, α_{op} = 34.8, respectively). When switching to DCM or tetrachloromethane, a loss of ee and lower extraction efficacy is observed. Most astonishingly[67,68], when switching from chlorinated solvents to toluene with both hosts we observed a reversal in selectivity, with near perfect retention of α_{op} in the case of **SPA4** (-8% ee, α_{op} = 3.8; -39% ee, α_{op} = 35.0, respectively).

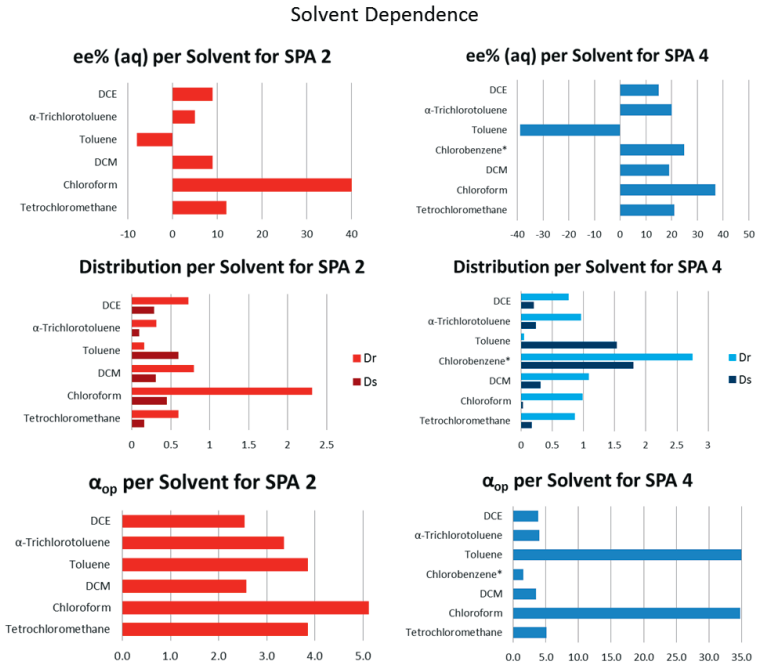


Figure 4: Solvent screenings for on the left SPA2 and on the right SPA4. Conditions: All extraction experiments were conducted in 2 ml auto-sampler vials with crimp cap seals equipped with stir bars. A solution racemic 11 (0.4 ml, 2 mM) dissolved in a phosphate buffer solution (buffer strength 0.1 M, pH 5.0) was carefully added to a solution of the corresponding host in the indicated solvent (0.4 ml, 1.0 mM). The two-phasic system was then immediately cooled to 6 °C and stirred at 900 rpm for 16 h. In all cases, the phases were then allowed to separate over a period of 2 min. The aqueous phase was removed and an aliquot injected into a reverse phase HPLC equipped with chiral columns for determination of the ee, distribution and α_{op}. All extraction experiments were carried out in triplo and with a simultaneous blank reaction (concentration of host = 0.0 mM).

In order to further investigate this solvent dependent behaviour we tested halogenated aromatic solvents such as chlorobenzene or trichlorotoluene but did not see any significant effect, with α_{op} values remaining in the same range as with DCM. Mechanistic investigations were attempted to better understand the peculiarities observed with this system. However, attempts at DFT modelling of the system, crystal growth of the host-guest complex or its NMR characterisation proved unsuccessful. Nevertheless, observation of a basic molecular model leads us to believe that a key π-π interaction exits between the guest and the host backbone. In the absence of toluene, one enantiomer can interact favourably with the backbone whereas the other cannot, determining the selectivity of the extraction. When toluene is present it can act as a π-π interaction relay allowing for the second enantiomer to also interact with the backbone. This, in addition to being the less sterically hindered of the two enantiomers results in an inversion of selectivity. Further investigations into these host-guest complexes are ongoing.

It has often been observed in ELLE that the interactions between host and guest are so specific that even slight changes in guest structure significantly alter the outcome of the extraction, making generalisation of a method over a family of compounds highly difficult. However, in view of the efficiency of our system we were curious as to the behaviour of these hosts towards other amino alcohols. We therefore selected a family of similar amino-alcohols and tested their resolution *via* ELLE using **SPA2** and **SPA4** under the optimized conditions (Figure 5).

We first studied the importance of the 1,2-amino-alcohol moiety. When cyclic *trans*-1-hydroxy-2-amino compound **10** was used only **SPA2** retained some selectivity (α_{op} = 3.8), 1,3-aminoalcohol **20,** N-isopropyl phenylglycinol **21** and O-methyl phenylglycinol **22** were extracted as a racemate by both hosts. 1-Amino-2-hydroxy compound **23** was extracted with moderate selectivity (**SPA4**, α_{op} = 1.5). We also tested a similar norepinephrine metabolite, normetanephrine (**24**), which is cheaply available in the racemic version but only available in the enantiopure form by total synthesis. With this compound we obtained an α_{op} of above 3 with **SPA2,** which is sufficient for efficient large scale resolution of this biologically relevant molecule.[69] Overall, this shows how important the 1,2-amino-alcohol motif is and how specific its interactions with the phosphoric acid via H-bonding are. Altering the chain length between moieties, increasing the steric bulk around these positions or removing H-bond donor or acceptor positions results in a total loss of selectivity.

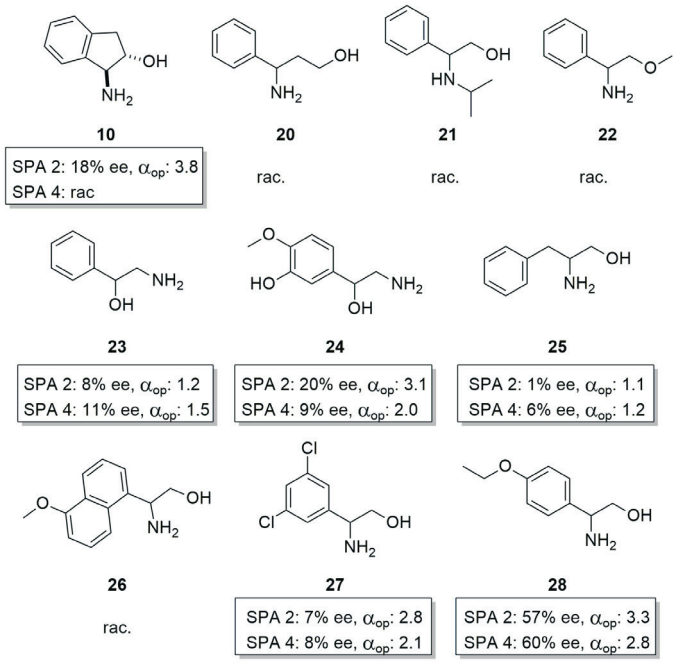


Figure 5: Amino-alcohol screening. Conditions: All extraction experiments were conducted in 2 ml auto-sampler vials with crimp cap seals equipped with stir bars. In a standard experiment, a solution of the racemic guest (0.4 ml, 2 mM) dissolved in a phosphate buffer solution (buffer strength 0.1 M, pH = 5.0) was carefully added to a solution of the corresponding host in chloroform (0.4 ml, 1.0 mM). The two-phasic system was then immediately cooled to 6 °C and stirred at 900 rpm for 16 h. The phases were then allowed to separate over a period of 2 min. The aqueous phase was removed and an aliquot injected into a chiral reverse phase HPLC equipped with chiral columns for determination of the ee, distribution and α_{op}. All extraction experiments were carried out in triplo and with a simultaneous blank reaction (concentration of host = 0.0 mM).

We then studied the importance of the aromatic ring of the guest in terms of selectivity. When phenylalaninol (**25**) was used only minor selectivity could be observed (**SPA 4**, α_{op} = 1.24) in its extraction. Naphthyl substituted aminoalcohol **26** was too insoluble in water for ELLE, whereas substituted phenylglycinol derivatives **27** and **28** could be extracted with lower but still significant selectivities (**SPA2**, α_{op} = 2.8 and **SPA2**, α_{op} = 3.3). Overall this confirmed that π-stacking was significantly involved in determining the guest-host binding affinity.

In view of the extraordinary sensitivity of the extraction of **11** towards the pH of the aqueous phase, we decided to further optimise the pH for the extraction of **28** (Figure 6). This resulted in a pH dependency which had a similar profile to that of **11** with local maxima and minima arranged around the estimated pKb/pKa ranges of the host-guest system with the highest ee at pH 5 (57% and 60% ee for **SPA2** and **SPA4**, respectively). However, the distribution of the preferred enantiomer showed a drop in extraction at that pH whereas extraction of the other enantiomer

remained at the same level unlike in the case of **11**. This caused the operational selectivity to be at a minimum at pH 5. The optimum pH for the extraction of **28** was 3.5 with α_{op}'s nearly doubling, reaching 6.4 for **SPA2** and 5.3 for **SPA4**. (Figure 6) While this shows how hard it is to predict what the optimal extraction pH will be for each individual compound as no trend can be observed, it also demonstrates that these hosts can be efficiently applied to many different amino alcohols.

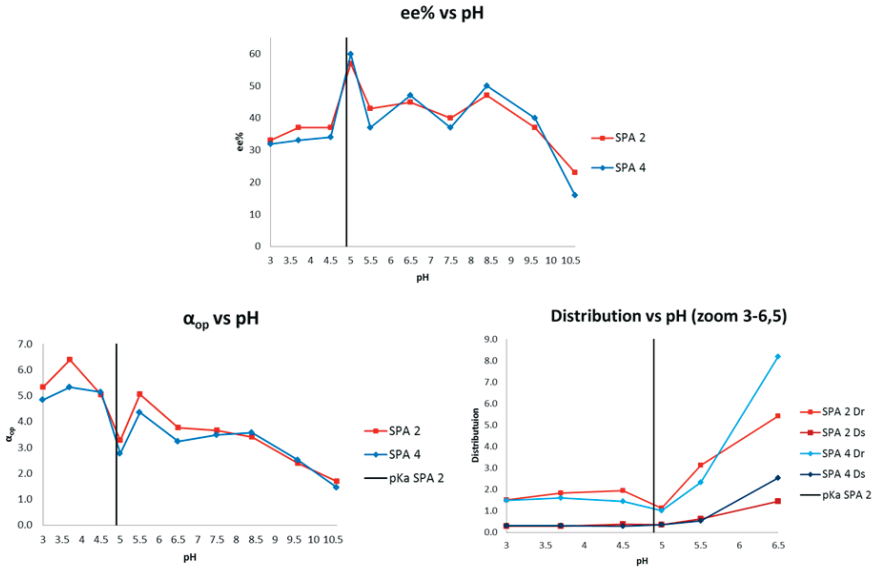
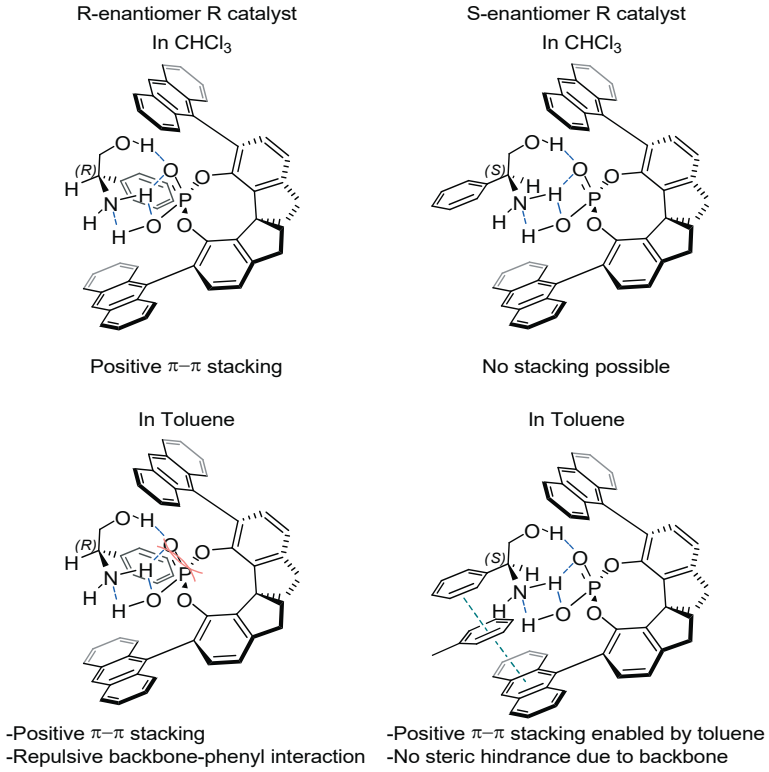


Figure 6: pH dependency of **28**. *Conditions: All extraction experiments were conducted in 2 ml auto-sampler vials with crimp cap seals equipped with stir bars. In a standard experiment, a solution of racemic 28 (0.4 ml, 2 mM) dissolved in a phosphate buffer solution (buffer strength 0.1 M, pH = 5.0) was carefully added to a solution of the corresponding host in chloroform (0.4 ml, 1.0 mM). The two-phasic system was then immediately cooled to 6 °C and stirred at 900 rpm for 16 h. The phases were then allowed to separate over a period of 2 min. The aqueous phase was removed and an aliquot injected into a reverse phase HPLC equipped with chiral columns for determination of the ee, distribution and* α_{op}. *All extraction experiments were carried out in triplo and with a simultaneous blank reaction (concentration of host = 0.0 mM). For numerical values see S. I.*

With this information in hand, we can attempt to rationalise a mode of action of SPINOL derived phosphoric acid hosts and propose the following model (Scheme 4) which is in accordance to the aforementioned observations.[61] In the case of an *R*-host and *R*-guest in chloroform we propose that the phosphoric acid will interact in a bidentate fashion with the amino-alcohol moiety forming multiple H-bonds. The phenyl substituent can complete the 3-point interaction by aligning with the phenyl ring in the SPINOL backbone via π-π stacking; Molecular models show that this latter interaction is only possible due to the unique structure of the catalyst. It

is to be noted that the 3,3′-substituents in combination with the twisted shape of the backbone would induce some steric interaction with the guest. In the case of the *S*-guest, while the amino-alcohol/phosphoric acid interactions are unchanged, the phenyl ring will orient into the centre of the chiral pocket too far away from the



Scheme 4: Proposed interaction model between SPA4 and 11, and the solvent influence of toluene towards the outcome of extraction experiments.

anthracene rings and the backbone to result in any stabilisation. However, when toluene is present, we propose that π-π stacking can occur via inclusion of a relay toluene ring between the phenyl moiety of the guest and the anthracene which overall will result in a more stabilised complex than the *R*-enantiomer, suffering from some steric interaction with the backbone of the catalyst. This behaviour is potentially specific for toluene as in the presence of α,α,α-trichlorotoluene and chlorobenzene as solvents no full inversion of enantioselectivity was observed.[6] The application of DFT calculations to support the abovementioned model did not yield the desired evidence due to the small energy differences involved and the error margin of the calculations. Attempts at crystallisation of the guest-host complex resulted in either separate crystals of both the host and the guest, or in complex mixtures of several crystalline

structures (as indicated by collaborations with the group of Prof. Dr. Cyranski). Further investigations are therefore needed to better understand this unique behaviour.

Applicability and Scalability

With this highly efficient, optimized system in hand we turned our attention to the scalability of the process toward multistage reactors, running a U-tube experiment (a modified version of a resolving device described by Cram) which serves as a useful test to judge the capacity of a host to deliver a guest from a feeding to a release phase in a catalytic manner (Figure 7A).[50] A blank run showed that at pH 5 there was no leaching of guest into the second aqueous phase over 24 h so any transfer observed can solely be attributed to the host.

When a 2 mM guest solution was used as feeding phase an ee of 41% could be measured in the receiving phase after an hour. (Table 1) However, further aliquots after two and three hours showed that a slow erosion of ee occurred over time. This is due to a depletion of the desired enantiomer of the guest in the feeding phase and subsequent transport of the other enantiomer as was observed earlier by us,[56] indicating as well that the host was undergoing multiple transport release cycles. When a 20 mM feeding phase was used to overcome this issue, a 50% ee could be observed in the receiving phase after just 10 min with the ee staying globally constant over several hours while the amount of guest accumulated in the receiving phase rose steadily. (Table 2) Only after 24 h was a notable loss in ee observed (29%) due, again, to depletion of the feeding phase. This showed that this system could be adapted to multistage reactors with high efficiency and that a catalytic process was achieved with multiple turnovers, the first turnover being achieved in approximately 40 min.

Aliquot 1	Extraction Time	ee% Receiving Phase
1	1 h	41
2	2 h	35
3	3 h	29
4	72 h	9

Table1: Results obtained from U-tube extractions over time. Temperature: 6 °C, host phase: **SPA 4** *in chloroform (10 ml, 0.5 mM). Feeding phase: 5 ml of a 2 mM solution of racemic phenylglycinol dissolved in a phosphate buffer solution (buffer strength 0.1 M) pH= 5.0. Receiving phase: 5ml of a HCl solution in doubly distilled water such as pH = 2.0.*

Aliquot	Extraction Time	ee% Receiving Phase
1	10 min	50
2	20 min	52
3	1 h	52
4	2 h	55
5	3 h	50
6	4 h	47
7	24 h	29

Table2: Results obtained from U-tube extractions over time. Temperature: 6 °C, host phase: SPA 4 in chloroform (10 ml, 0.5 mM). Feeding phase: 5 ml of a 20.0 mM solution of racemic phenylglycinol dissolved in a phosphate buffer solution (buffer strength 0.1 M) pH= 5.0. Receiving phase: 5ml of a HCl solution in doubly distilled water such as pH = 2.0.

In addition, the unique solvent dependency of SPINOL derived chiral phosphoric acids can also be exploited in a novel fashion *via* simultaneous extraction of both enantiomers with a single catalyst in a vertical variation of the W-tube first suggested by Cram.[70] When a triphasic system is set-up as shown below (Figure 7B) with the bottom phase containing the host in chloroform ((*R*)-Host phase 1), the middle phase containing the aqueous racemic guest solution (2 mM, feeding phase, pH is 5) and the top phase containing the host in toluene ((*R*)-Host phase 2) extraction of the guest occurs from the feeding phase into both host phases which yield, after back-extraction,[71] an ee of 41% for the chloroform phase and an ee of 48% of the opposite enantiomer for the toluene phase.

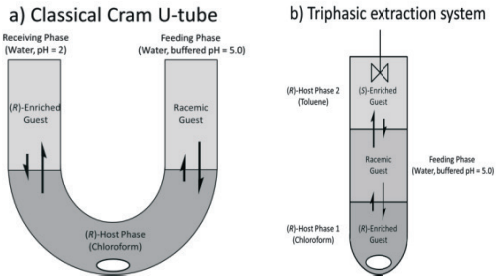


Figure 7: U-tube and tri-phasic reactor. Internal diameters: 1.0 cm, 0.9 cm, respectively. Stirring: for both 900 rpm, Temperature: for both: 6 °C Initial set-up: a) (R)-host phase: SPA 4 in chloroform (10 ml, 0.5 mM). Feeding phase: 5 ml of a 2 or 20.0 mM solution of racemic phenylglycinol dissolved in a phosphate buffer solution (buffer strength 0.1 M) pH= 5.0. Receiving phase: 5ml of a HCl solution in doubly distilled water such as pH = 2.0. At regular intervals an aliquot of the receiving phase was injected into a reverse phase HPLC equipped with a chiral column for determination of the ee, distribution and αop. b) (R)-host phase 1: SPA 4 in chloroform (3 ml, 1.0 mM) Feeding phase: 5 ml of a 2.0 mM solution of racemic phenylglycinol dissolved in a phosphate buffer solution (buffer strength 0.1 M) pH= 5.0. (R)-host phase 2: SPA 4 in toluene (3 ml, 1.0 mM). All extraction experiments were carried out in triplo and with a simultaneous blank reaction (concentration of host = 0.0 mM).

The triphasic system therefore allows for the simultaneous extraction of both enantiomers with a single host. This is, to the best of our knowledge, unique and opens many new possibilities for ELLE.

Conclusions

In summary, in this chapter we have studied the efficiency of a previously unexplored family of chiral hosts towards the enantioselective liquid-liquid extraction of a range of 1,2-aminoalcohols, including biologically relevant ones. These chiral 3,3'-substitued SPINOL phosphoric acids were shown to be highly efficient at the resolution of this type of substrates reaching unprecedented levels of selectivity. (Figure 3) The operational selectivity of the extractions is highly dependent on the organic solvent, the pH and the temperature. Much more so, than the previously described BINOL derived phosphoric acids. This led to formation of an optimal regime, anticipated to be between the pKa of the phosphoric acid and the pKb of the 1,2-aminoalcohol, indicating the delicacy of the interactions involved. (Figure 5) The distinct solvent dependency and unexpected behaviour when involving toluene led to the formation of several hypotheses on the interactions between the 1,2-aminoalcohol and the backbone of the phosphoric acid. Attempts at crystallisation of the guest-host complex resulted in either separate crystals of both the host and the guest, or in complex mixtures of several crystalline structures (as indicated by collaborations with the group of Prof. Dr. Cyranski). Moreover, DFT calculations were found to be inconclusive in describing the interactions involved for complexes of this size and nature. We have also validated these systems towards multistage processes by demonstrating their catalytic efficiency in a U-tube system, obtaining unprecedented ee (Figure 5, SPA4 and guest 11) values for chiral phosphoric acid hosts, and have taken advantage of its unique properties to develop a novel triphasic extraction system in which both enantiomers are extracted simultaneously (Figure 9B). We conclude that these hosts, in view of the results obtained, could be used in an industrial-scale racemate separation process.

General information

Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gels 60, 0.25 mm. Conversions of the reactions were determined by TLC unless otherwise stated. Components were visualized by UV and potassium permanganate staining. Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). ^{1}H-and ^{13}C-NMR were recorded on a Varian AMX400 (400 and 101 MHz, respectively) or a Varian VXR300 (300 and 75 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. All reactions were carried out under nitrogen or argon atmosphere in either oven dried round bottom flasks (gram scale or above) or oven dried sealed tubes (sub-gram scale) using standard Schlenk techniques. Diethyl ether, tetrahydrofuran, dichloromethane and toluene were used from the solvent purification system (MBRAUN SPS systems, MB-SPS-800). All catalysts, ligands, reagents and other solvents were purchased from commercial sources and used as received without further purification unless otherwise stated, except organo-lithium reagents which were titrated before use using diphenylacetic acid. When needed degassing of solvents was performed via the freeze, pump, thaw technique. SFC measurements were performed on a Waters Thar SFC system on a Chiralpak IA using as conditions 85% CO_2 / 15% CH_3OH, 150 bar, 4 mL/min. RP-HPLC measurements were performed on a Shimadzu SIL-20A with a CTO-20AC column oven and LC-20AD pumps on a CROWNPAK® CR (-) chiral column (Daicel, Japan) equipped with a guard column. Calibration curves were prepared in the concentration range employed for the determination of the distribution. Uncertainties were typically lower than 2.0%. General HPLC conditions for enantiomeric separation of aryl-1,2- and aryl-2,1-amino alcohols: Perchloric acid solutions (pH =1,5 or pH =1) flow = 1.0 ml/min were used as eluent, with exception of serine (**8**), phenylalanine (**16**), homoserine (**17**), 3-amino-3-phenyl-1-propanol (**19**) and normetanephrine (**24**) where flow of 0,5 ml/min was applied. Column temperature was set at 20°C, with exception of 3-aminoisobuteric acid (**18**), where 0°C was applied.

GP 1) General procedure for biphasic batch extraction experiments

All extraction experiments were conducted in 2 ml auto-sampler vials with crimp cap seals equipped with stir bars. In a standard experiment, a solution of the racemic guest (0.4 ml, indicated concentration) dissolved in a phosphate buffer solution (buffer strength 0.1 M, indicated pH) was carefully added to a solution

of the corresponding host in the indicated solvent (0.4 ml, 1.0 mM). The bi-phasic system was then cooled to the indicated temperature and stirred at 900 rpm for 16 h. The phases were then allowed to separate over a period of 2 min. The aqueous phase was removed and an aliquot was analyzed by reverse phase HPLC for determination of the ee, distribution and α_{op}. All extraction experiments were carried out *in triplo* and with a simultaneous blank reaction (concentration of host = 0.0 mM).

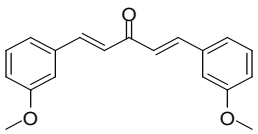
GP 2) General procedure for the U-tube reactor experiments

To a U-shaped reactor vessel (Figure 7a, inner diameter = 1.0 cm) equipped with a stir bar, was added a solution of SPA 4 in chloroform (10 ml, 0.5 mM). The vessel with the solution was cooled to 6°C and both the feeding phase (5 ml of a 2 or 20.0 mM solution of racemic phenylglycinol dissolved in a phosphate buffer solution (buffer strength 0.1 M) pH= 5.0) and the receiving phase (5ml of a HCl solution in doubly distilled water at pH = 2.0) were added simultaneously to the right and left legs of the U-tube. Stirring was set to 900 rpm and aliquots of 0.2 ml were removed from the receiving phase at given intervals. Each aliquot was replaced by an equal amount of fresh receiving phase.

GP 3) General procedure for the triphasic reactor system experiments

To a tube-shaped reactor vessel, as described in Figure 7b (inner diameter = 0.9 cm), equipped with a stir bar and overhead stirrer, was added the first host phase comprised of a solution of SPA 4 in chloroform (3 ml, 1.0 mM). The vessel was cooled to 6°C and then was carefully added so as no mixing of phases could be observed, in the following order, the feeding phase (5 ml of a 2.0 mM solution of racemic phenylglycinol dissolved in a phosphate buffer solution (buffer strength 0.1 M) pH= 5.0) and the second host phase comprised of a solution of SPA 4 in toluene (3 ml, 1.0 mM). Stirring was set at a rate of 900 rpm to ensure that all three phases were stirred but no mixing occurred and this was continued for 16 h. The organic phases were removed from the reactor and each independently extracted with a 3 ml of a solution of HCl in doubly distilled water pH = 2.0. The extracted aqueous phases were sampled for measuring in reverse phase HPLC.

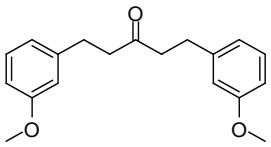
S1: 1,5-bis(3-methoxyphenyl)penta-1,4-dien-3-one[61]



A solution of *m*-anisaldehyde (10.0 g, 73.4 mmol, 2 equiv) and acetone (2.70 ml, 36.8 mmol, 1 equiv) in ethanol (20 ml) was added dropwise to a solution of NaOH (7.5 g, 190 mmol, 2.5 equiv) in 120 ml of ethanol/H_2O (1:1, 0.25 M) at 0 °C. The mixture was stirred for 3 h, then diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and purified by FCC (PE/AcOEt, 9/1) to give 6.6 g of **1,5-bis(3-methoxyphenyl)pentan-3-one** (62% yield).

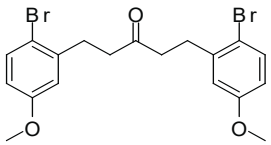
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 16 Hz, 2H), 7.34 (t, *J* = 8 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H), 7.13 (s, 2H), 7.07 (d, *J* = 16 Hz, 2H), 6.97 (dd, *J* = 8, 2 Hz, 2H), 3.86 (s, 6H). ^{13}CNMR(100MHz,$CDCl_3$):δ189.0,160.0,143.3,136.2,130.0,125.7,121.1,116.4,113.3,55.4.

S2: 1,5-bis(3-methoxyphenyl)pentan-3-one[61]



A mixture of 1,5-bis(3-methoxyphenyl)penta-1,4-dien-3-one (20.0 g, 68 mmol, 1 equiv) in acetone (200 ml, 0.35 M) and Raney Ni (2 g) under an atmosphere of hydrogen at rt under very vigorous stirring (1500 rpm, large stir bar, formation of a big vortex) for 1h. If the stirring is not strong enough the reaction can take up to 48 h to complete. The suspension was filtered on Celite (AcOEt) and concentrated under vacuum to give 19.65 g pure 1,5-bis(3-methoxyphenyl)pentan-3-one (95% yield).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (t, J = 8 Hz, 2H), 6.75-6.69 (m, 6H), 3.78 (s, 6H), 2.86 (t, J = 8 Hz, 4H), 2.71 (t, J = 8 Hz, 4H) 13C NMR (100 MHz, $CDCl_3$): δ 209.0, 159.6, 142.6, 129.4, 120.6, 114.1, 111.4, 55.1, 44.4, 29.8.

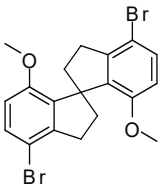
S3 1,5-bis(2-bromo-5-methoxyphenyl)pentan-3-one[61]



Crude **1,5-bis(3-methoxyphenyl)pentan-3-one** (19.65 g, 66 mmol, 1 equiv) was dissolved in CH2Cl2 (220 ml, 0.3 M total), pyridine (15.95 ml, 198 mmol, 3 equiv.) was added, and the mixture was cooled to 0 °C. A solution of bromine in CH2Cl2 (10% v/v, 8.5 ml, 165 mmol, 2.5 equiv.) was added drop wise. The reaction mixture was allowed to warm to rt and stirred until the starting material had disappeared (by NMR, 3h). The mixture was diluted with DCM, washed with aqueous $NaHSO_3$ to remove excess bromine, then with 1M aq. HCl and water, dried over Na_2SO_4 and concentrated under vacuum to give 30.5 g of 1,5-bis(2-bromo-5-methoxyphenyl)pentan-3-one (95% yield).

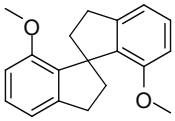
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 9 Hz, 2H), 6.77 (d, J = 3 Hz, 2H), 6.63 (dd, J = 9, 3 Hz, 2H), 3.78 (s, 6H), 2.96 (t, J = 8 Hz, 4H), 2.72 (t, J = 8 Hz, 4H) 13C NMR (100 MHz, $CDCl_3$): δ 208.6, 159.1, 141.3, 133.5, 116.3, 114.8, 113.8, 55.6, 42.7, 30.7.

S4: 4,4′-dibromo-7,7′-dimethoxy-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene] 61[c+]



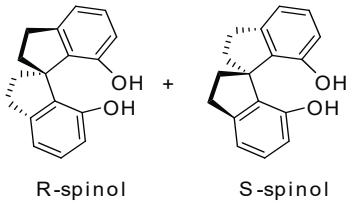
To a solution of 1,5-bis(2-bromo-5-methoxyphenyl)pentan-3-one (5g, 11.45 mmol, 1 equiv) in DCM (112ml, 0.1M) at 0°C was added 50g of silica-sulfuric acid.[72] The red suspension was evaporated to dryness at room temperature to avoid degradation of the substrate and left to stand for 3 h after which the brownish solid was filtered over a pad of silica with DCM and concentrated in vacuo. The residue was recrystallized from hexane to give 3.25g of solid 4,4′-dibromo-7,7′-dimethoxy-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene]65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 8.6 Hz, 2H), 6.52 (d, J = 8.6 Hz, 2H), 3.52 (s, 6H), 3.14-2.84 (m,42H), 2.40-2.26 (m, 2H), 2.23-2.07 (m, 2H).13C NMR (75 MHz, $CDCl_3$): δ 155.6, 144.8, 138.0, 130.3, 110.8, 110.5, 61.9, 55.4, 55.4, 37.9, 33.2.

S5: 7,7′-dimethoxy-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene] [61]



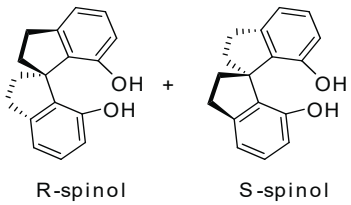
To a solution of crude 4,4′-dibromo-7,7′-dimethoxy-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene] (7.5 g, 17.2 mmol, 1 equiv) in THF (170 ml, 0.1 M) cooled to -78 °C was added n-BuLi (1.6 M in hexanes, 45 ml, 68.8 mmol, 4 equiv) and stirred for 1 h. The reaction mixture was then quenched with 10 ml of ethanol and returned to r.t and most of the THF was removed under vacuum. The remaining solution was diluted in DCM and washed with water and dried over Na_2SO_4. The thus obtained 4.6 g of 7,7′-dimethoxy-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene] (96%) proved to be >95% pure by ^{1}H-NMR and was used as such in the next step. (if needed it can be recrystallized from hexanes) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 (t, J = 7.7 Hz, 2H), 6.87 (dd, J = 7.7 Hz, 2H), 6.63 (d, J = 8.1 Hz, 2H), 3.54 (s, 6H), 3.13-2.92 (m, 4H), 2.43-2.28 (m, 2H), 2.25-2.08 (m, 2H). 13C NMR (75 MHz, $CDCl_3$) δ 156.4, 145.3, 136.8, 127.5, 116.7, 108.5, 59.1, 55.1, 55.1, 38.7, 31.5.

3: Spinol[61]



To a solution of 7,7′-dimethoxy-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene] (6.43 g, 23.0 mmol, 1 equiv) in DCM (115 ml, 0.2 M) cooled to -78 °C, was slowly added BBr3 (neat, 5.0 ml, 52 mmol, 2.3 equiv) and the reaction mixture was slowly returned to room temperature overnight. The reaction mixture was then diluted with DCM and a few milliliters of water were carefully added. When the excess of BBR3 was quenched the mixture was washed with aq. sat. $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by FCC (PE/AcOEt , 9/1) and if needed recrystallized from hexanes to give 4.9 g pure spinol (84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (t, J = 7.7 Hz, 2H), 6.90 (dd, J = 7.4, 1.0 Hz, 2H), 6.68 (d, J = 8.1 Hz, 2H), 4.59 (brs, 2H), 3.34-2.89 (m, 4H), 2.43-2.26 (m, 2H), 2.26-2.12 (m, 2H). 13C NMR (75 MHz, $CDCl_3$): δ 153.0, 146.0, 130.6, 130.1, 117.9, 114.5, 57.6, 37.6, 31.4.

3′: S/R-spinol[62]

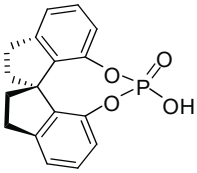


To a solution of racemic spinol in toluene was added N-Benzylcinchonidinium chloride. The suspension was heated to reflux for 1.5 h and then returned to room temperature. The white solid was filtered on a sintered funnel to afford the S-spinol/ N-Benzylcinchonidinium chloride complex and the filtrate evaporated to afford R-spinol. The complex is suspended in AcOEt and aq. HCl 1M is added till the pH reaches 3 (stable over 5 min, going lower than pH 2 will cause degradation). The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue is filtered on a pad of silica (AcOEt) to remove any trace salts remaining, concentrated and recrystallized from hexanes to give pure (S)-(-)-spinol (78% yield, >99% ee). The white solid obtained from the filtrate was filtered over a pad of silica (AcOEt) to remove any trace salts remaining, concentrated and recrystallized from hexanes to give pure (R)-(+)-spinol (68% yield, >99% ee as determined by HPLC).

Synthesis of Spinol based phosphoric acids

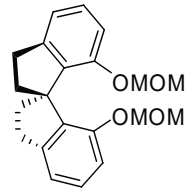
The following spinol based phosphoric acids and intermediates leading to these were synthesized according to the procedures reported by List *et al*.[73]

SPA 1: (S)-12-hydroxy-4,5,6,7-tetrahydrodiindeno[7,1-de:1′,7′-fg][1,3,2]dioxaphosphocine 12-oxide[73]



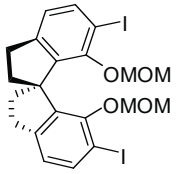
To a solution of (S)-spinol (50 mg, 0.20 mmol, 1 equiv) in pyridine (1.3 ml, 0.15 M) was added POCl3 (56 µl, 0.6 mmol, 3 equiv). The mixture was then stirred for 6 h before dioxane/water was added (4/1 V:V 1 ml) and the mixture heated to 100°C for 3 h. The mixture was then cooled to roomtemperature, diluted with AcOEt, washed twice with 5 M aq. HCl, brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by FCC (DCM/MeOH, 0-5%) to give 12 mg pure (S)-12-hydroxy-4,5,6,7-tetrahydrodiindeno[7,1-de:1′,7′-fg][1,3,2]dioxaphosphocine-12-oxide (20%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (dt, J = 14.8, 7.4 Hz, 4H), 7.04 (d, J = 7.7 Hz, 2H), 3.21-2.99 (m, 2H), 2.83 (dd, J = 16.0, 7.7 Hz, 2H), 2.27 (dd, J = 12.0, 6.3 Hz, 2H), 2.14-1.94 (m, 2H).13C NMR (100 MHz, $CDCl_3$): δ 146.5, 145.5, 139.3, 128.7, 122.9, 121.5, 59.3, 38.3, 30.6. 31P (162MHz, $CDCl_3$): δ -11.25.

S8: (R)-7,7′-bis(methoxymethoxy)-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene] 73



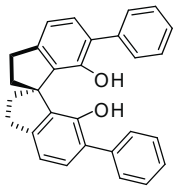
A solution of R-spinol (970 g, 3.8 mmol, 1 equiv) in THF (5ml) was slowly added to a suspension of NaH (60% in mineral oil, 828 mg, 19 mmol, 5 equiv) in THF (8ml) and the resulting mixture stirred for 3 h. MOMCl (0.72 ml, 9.5 mmol, 2.5 equiv) in THF (10ml) was added at 0°C and the reaction stirred at roomtemperature overnight. The reaction mixture was then diluted with AcOEt and the excess NaH quenched with a little water, washed with NH_4Cl, brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by FCC (PE/AcOET, 95/5) to give 1.1 g pure7,7′-bis(methoxymethoxy)-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene] (85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (t, J = 7.8 Hz, 2H), 6.89 (d, J = 7.5, 1 Hz, 2H), 6.74 (d, J = 8.1 Hz, 2H), 4.88 (d, J = 6.4 Hz, 2H), 4.82 (d, J = 6.4 Hz, 2H), 3.20-2.94 (m, 10H), 2.56-2.40 (m, 2H), 2.27-2.14 (m, 2H). 13C NMR (75 MHz, $CDCl_3$): δ 153.5, 145.7, 137.6, 127.6, 117.7, 111.3, 93.4, 59.5, 55.5, 39.2, 31.8

S9:(R)-6,6′-diiodo-7,7′-bis(methoxymethoxy)-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene][73]



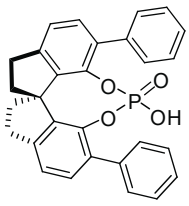
To a solution of (R)-7,7′-bis(methoxymethoxy)-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene] (1.1 g, 3.23 mmol, 1 equiv) and TMEDA (1.46 ml, 9.96 mmol, 3 equiv) in THF (32 ml, 0.1 M) cooled to -78 °C was added n-BuLi (1.4 M, 9 ml, 12.94 mmol, 4 equiv). The reaction mixture was then stirred 6 h at roomtemperature before being cooled to -78 °C again. I2 (3.28 g, 12.94 mmol, 4 equiv) in THF (20ml) was added and the reaction mixture stirred overnight at r.t. The reaction mixture was then diluted with DCM and washed with $NaHSO_3$, water and brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was then purified by FCC (PE/DCM, 90/10-70/30) to give 6,6′-diiodo-7,7′-bis(methoxymethoxy)-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene] (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, J = 8.0 Hz, 2 H), 6.78 (d, J = 8.0 Hz, 2H), 4.85 (d, J = 5.1 Hz, 2H), 4.63 (d, J = 5.1 Hz, 2H), 3.07-2.87 (m, 10 H), 2.58-2.36 (m, 2 H), 2.25-2.09 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2, 146.8, 143.5, 138.8, 122.6, 99.3, 89.0, 61.1, 57.0, 39.4, 31.0.

S10a:(R)-6,6′-diphenyl-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene]-7,7′-diol[73]



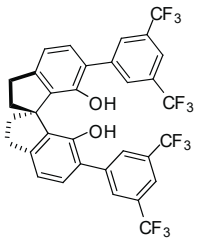
A solution of (R)-6,6′-diiodo-7,7′-bis(methoxymethoxy)-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene] (200 mg, 0.33 mmol, 1 equiv) and phenyl boronic acid (165 mg, 1.35 mmol, 4 equiv) in THF/MeOH (25:1 V/V, 6.6 ml, 0.05 M) was degassed once. Then K_2CO_3 (270 mg, 1.98 mmol, 6 equiv) in water (1ml) and $Pd(PPh_3)_4$ (52 mg, 0.05 mmol, 15%) was added and the mixture degassed twice more. The reaction mixture was then heated to reflux for 24 h before being cooled to r.t, diluted with DCM and washed with water, brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was dissolved in dioxane (3 ml, 1M) and HCl (37%, 10% V/V) was added. The mixture was stirred under vigorous stirring at 80 °C for 2 h before being diluted with DCM, washed with aq. $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by FCC (PE/Et_2O, 95/5) to give 78 mg of pure (R)-6,6′-diphenyl-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene]-7,7′-diol (59% two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, J = 7.3 Hz, 4H), 7.41 (t, J = 7.5 Hz, 4H), 7.31 (t, J = 7.3 Hz, 2H), 7.20 (d, J = 7.6 Hz, 2H), 6.95 (d, J = 7.6 Hz, 2H), 5.07 (s, 2H), 3.22-2.97 (m, 4H), 2.54-2.28 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.6, 145.4, 137.6, 132.2, 130.7, 129.4, 128.7, 127.3, 127.1, 117.5, 58.6, 38.00, 31.3.

SPA 2: (R)-12-hydroxy-1,10-diphenyl-4,5,6,7-tetrahydrodiindeno[7,1-de:1′,7′-fg][1,3,2]dioxaphosphocine 12-oxide[73]



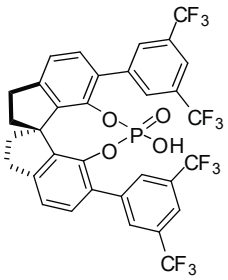
To a solution of (R)-6,6′-diphenyl-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene]-7,7′-diol (60 mg, 0.15 mmol, 1 equiv) in pyridine (0.5 ml, 0.3 M) was added $POCl_3$ (41 μl, 0.45 mmol, 3 equiv) and the mixture was heated to 80°C for 24 h. Subsequently the mixture was cooled to r.t and water (0.3 ml) was added and the mixture heated to 80°C for another 4 h. After cooling to r.t the mixture was acidified to pH 1 (aq. HCl 5M), diluted with DCM and washed with water and brine and concentrated under vacuum. The residue was purified by FCC (DCM/MeOH 0-5%) before being dissolved in DCM and washed twice with HCl (aq. 4M) then water before being concentrated under vacuum and co-evaporated with toluene. This gave 40 mg of (R)-12-hydroxy-1,10-diphenyl-4,5,6,7-tetrahydrodiindeno[7,1-de:1′,7′-fg][1,3,2]dioxaphosphocine 12-oxide (59% yield) ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$): δ 7.46-7.36 (m, 4H), 7.19 (ddd, *J* = 10.1, 5.9, 2.1 Hz, 6H), 7.16-7.05 (m, 4H), 3.03 (ddd, *J* = 17.2, 11.4, 6.7 Hz, 2H), 2.87-2.73 (m, 2H), 2.25 (dd, *J* = 12.0, 6.5 Hz, 2H), 2.11 (dd, *J* = 11.5, 8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3/CD_3OD$): δ 151.9, 148.9, 147.2, 144.7, 141.1, 136.8, 136.0, 134.39, 133.2, 129.1, 66.5, 45.2, 36.8. ^{31}P NMR (162 MHz, $CDCl_3/CD_3OD$): δ -10.80.

S10b:(R)-6,6′-bis(3,5-bis(trifluoromethyl)phenyl)-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene]-7,7′-diol[73]



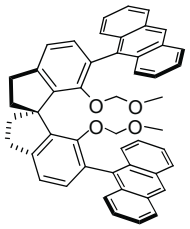
A solution of 6,6′-diiodo-7,7′-bis(methoxymethoxy)-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene] (200 mg, 0.33 mmol, 1 equiv) and 3,5-Bis(trifluoromethyl)phenylboronic acid (350 mg, 1.35 mmol, 4 equiv) in THF/MeOH (25:1 V/V, 6.6 ml, 0.05 M) was degassed once. Then K_2CO_3 (270 mg, 1.98 mmol, 6 equiv) in water (1ml) and $Pd(PPh_3)_4$ (52 mg, 0.05 mmol, 15%) was added and the mixture degassed twice more. The reaction mixture was then heated at reflux for 24 h before being cooled to roomtemperature, diluted with DCM and washed with water, brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was dissolved in dioxane (3 ml, 1M) and HCl (37%, 10% V/V) was added. The mixture was stirred under vigorous stirring at 80 °C for 2 h before being diluted with DCM, washed with aq. $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by FCC (PE/Et_2O, 95/5) to give 98 mg of pure (R)-6,6′-bis(3,5-bis(trifluoromethyl)phenyl)-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene]-7,7′-diol (44% two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 1.6 Hz, 4H), 7.88-7.67 (m, 2H), 7.30 (d, J = 7.7 Hz, 2H), 7.05 (d, J = 7.7 Hz, 2H), 4.93 (s, 2H), 3.15 (dt, J = 8.5, 4.7 Hz, 4H), 2.47 (ddd, J = 13.1, 6.6, 2.5 Hz, 2H), 2.37 (ddd, J = 13.1, 10.4, 8.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.0, 147.2, 139.8, 131.8, 131.6 (q, J = 33.1 Hz), 130.8, 129.6 (d, J = 3.4 Hz), 124.8, 123.5 (q, J = 272.6 Hz). 120.9 (quint, J = 3.1 Hz), 118.7, 58.1, 37.8, 31.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.88.

SPA 3: (R)-1,10-bis(3,5-bis(trifluoromethyl)phenyl)-12-hydroxy-4,5,6,7-tetrahydrodiindeno[7,1-de:1′,7′-fg][1,3,2]dioxaphosphocine 12-oxide[73]



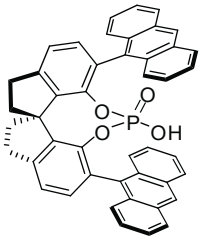
To a solution of (R)-6,6′-bis(3,5-bis(trifluoromethyl)phenyl)-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene]-7,7′-diol (98 mg, 0.145 mmol, 1 equiv) in pyridine (0.5 ml, 0.3 M) was added $POCl_3$ (40 μl, 0.44 mmol, 3 equiv) and the mixture was stirred for 24 h. A second dose of $POCl_3$ (40 μl, 0.44 mmol, 3 equiv) was added and the mixture stirred till full consumption of the starting material. After this water (0.3 ml) was added very carefully (strongly exothermic reaction) and the mixture was diluted with DCM and acidified to pH 1 (aq. HCl 5M), washed with water and brine and concentrated under vacuum. The residue was dissolved in THF (10 ml) and 1 ml of saturated Na_2CO_3 was added. The mixture was heated to 70 °C till full consumption of the intermediate (18h) before being returned to r.t, diluted with DCM and washed twice with HCl (aq. 4M), brine and concentrated under vacuum. The residue was purified by FCC (Toluene/DCM 0-100%) before being dissolved in DCM and washed twice with aq. HCl (aq. 4M) then water before being concentrated under vacuum and co-evaporated with toluene. This gave 96.6 mg of (R)-1,10-bis(3,5-bis(trifluoromethyl)phenyl)-12-hydroxy-4,5,6,7-tetrahydrodiindeno[7,1-de:1′,7′-fg][1,3,2]dioxaphosphocine 12-oxide (90% yield) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.65 (m, 4H), 7.46 (s, 2H), 7.26 (dd, *J* = 7.6, 1.3 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 2H), 3.24-3.10 (m, 2H), 2.99 (dd, *J* = 16.3, 7.8 Hz, 2H), 2.37 (dd, *J* = 12.1, 6.4 Hz, 2H), 2.29-2.16 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.2 (d, *J* = 2.3 Hz), 141.6 (d, *J* = 7.9 Hz), 140.6 (d, *J* = 3.5 Hz), 139.5, 132.2 (d, *J* = 3.8 Hz), 131.2 (q, *J* = 33.1 Hz), 130.7, 129.5, 123.3 (q, *J* = 272.7 Hz), 123.2, 120.6 (quint, *J* = 3.6 Hz), 59.9, 38.5, 30.5. ^{31}P NMR (162 MHz, $CDCl_3$): δ -10.60 ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.76.

S10c': (1R,6r,6's)-6,6'-di(anthracen-9-yl)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol[73]



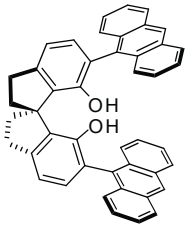
A solution of 6,6'-diiodo-7,7'-bis(methoxymethoxy)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene] (300 mg, 0.51 mmol, 1 equiv) and 9-anthracyl boronic acid (457 mg, 2.03 mmol, 4 equiv) and K_3PO_4 (861 mg, 4.06 mmol, 8 equiv) in DME (5.0 ml, 0.1 M) was degassed once via cycles of *freeze-pump-thaw*. $Pd(PPh_3)_4$ (54 mg, 0.051 mmol, 0.1 equiv) was added and the mixture degassed via the same method twice more. The reaction mixture was then heated to 85 °C for 48 h before being cooled to r.t, diluted with DCM and then washed with water, brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by FCC (Hexane/Toluene/iPrOH 94/5/1) to give 196 mg pure (1R,6r,6's)-6,6'-di(anthracen-9-yl)-7,7'-bis(methoxymethoxy)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene] (55% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (s, 2H), 8.10-8.02 (d, *J* = 7.5 Hz, 2H), 7.98 (t, *J* = 8.4 Hz, 4H), 7.61 (dd, *J* = 8.9, 1.1 Hz, 2H), 7.45 (dddd, *J* = 18.0, 8.0, 6.5, 1.4 Hz, 4H), 7.23-7.09 (m, 4H), 7.05 (d, *J* = 7.5 Hz, 2H), 6.21 (ddd, *J* = 8.8, 6.5, 1.2 Hz, 2H), 4.39 (d, *J* = 5.8 Hz, 2H), 3.84 (d, *J* = 5.8 Hz, 2H), 3.28 (ddd, *J* = 15.8, 10.7, 7.9 Hz, 2H), 3.20 -3.04 (m, 2H), 2.65 (td, *J* = 11.6, 11.1, 9.0 Hz, 2H), 2.52 (s, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.1, 145.5, 141.8, 134.5, 132.6, 131.6, 131.31, 130.7, 130.2, 128.7, 128.6, 127.8, 127.5, 127.0, 126.8, 126.1, 125.7, 125.5, 125.1, 119.9, 98.6, 60.1, 56.3, 39.0, 31.4.

S10c : (1R,6r,6's)-6,6'-di(anthracen-9-yl)-2,2',3,3'-tetrahydro 1,1'-spirobi[indene]-7,7'-diol[73]



A solution of (1R,6r,6's)-6,6'-di(anthracen-9-yl)-7,7'-bis(methoxymethoxy)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene] (196 mg, 0.28 mmol, 1 equiv) was dissolved in dioxane (3 ml, 0.1 M) and aq. HCl (37%, 10% V/V) was added. The mixture was stirred under vigorous stirring at 80 °C for 2 h. The mixture was then cooled to room temperature, diluted with DCM, washed with aq. $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by FCC (dry loaded on silica, PE/AcOEt, 7/3) to give 71 mg of pure (S)-6,6'-di(anthracen-9-yl)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol (41% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 2H), 8.12-8.03 (m, 2H), 8.00 (d, J = 8.5 Hz, 2H), 7.81 (dd, J = 8.7, 1.2 Hz, 2H), 7.48 (ddd, J = 8.3, 6.5, 1.3 Hz, 2H), 7.41 (ddd, J = 8.1, 6.6, 1.4 Hz, 2H), 7.33 (dd, J = 8.9, 1.1 Hz, 2H), 7.30-7.24 (m, 2H), 7.08 (d, J = 7.5 Hz, 2H), 7.00 (d, J = 7.5 Hz, 2H), 6.48 (ddd, J = 8.8, 6.5, 1.2 Hz, 2H), 4.59 (s, 2H), 3.33-3.20 (m, 2H), 3.15 (ddd, J = 16.0, 8.5, 2.3 Hz, 2H), 2.67-2.49 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 145.7, 133.3, 131.6, 131.5, 131.4, 131.0, 130.9, 130.7, 128.6, 128.1, 127.3, 126.5, 126.1, 125.8, 125.4, 125.2, 122.6, 116.9, 58.8, 38.3, 31.6.

SPA 4: (1r,5aR,10s,12S)-1,10-di(anthracen-9-yl)-12-hydroxy-4,5,6,7-tetrahydrodiindeno [7,1-de:1′,7′-fg][1,3,2]dioxaphosphocine 12-oxide[73]



To a solution of 6,6′-di(anthracen-9-yl)-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene]-7,7′-diol (71 mg, 0.12 mmol, 1 equiv) in pyridine (1.17 ml, 0.1 M) was added at 0°C $POCl_3$ (55µl, 0.59 mmol, 5 equiv) and the mixture was stirred at 80°C for 24 h after which a precipitate had formed. The reaction mixture was returned to r.t and dioxane (2 ml) was added followed by water (0.6 ml). The reaction mixture was then heated to 100°C for 48 h after which the precipitate had dissolved. The reaction mixture is then returned to r.t, diluted with DCM and washed with HCl (aq. 4M) and water before being concentrated under vacuum. The residue was purified by FCC (DCM, Acetone, AcOH 90/9/1) before being dissolved in DCM and washed twice with HCl (aq. 4M) then water before being concentrated under vacuum and co-evaporated with toluene. After 48h of drying under high vacuum 70 mg of (1r,5aR,10s,12S)-1,10-di(anthracen-9-yl)-12-hydroxy-4,5,6,7-tetrahydrodiindeno [7,1-de:1′,7′-fg][1,3,2]dioxaphosphocine 12-oxide (89% yield) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 2H), 7.84-7.69 (m, 4H), 7.70-7.58 (m, 2H), 7.38-7.26 (m, 6H), 7.28-7.17 (m, 4H), 7.13 (t, J = 7.7 Hz, 2H), 7.00 (t, J = 7.5 Hz, 2H), 3.45-3.23 (m, 2H), 3.23-2.86 (m, 2H), 2.57 (dd, J = 12.0, 6.3 Hz, 2H), 2.52-2.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 146.0, 144.1, 144.0, 140.3, 140.3, 133.3, 132.1, 131.3, 130.7, 130.6, 130.2, 130.2, 129.6, 128.5, 128.0, 128.0, 127.3, 126.4, 125.8, 124.6, 124.6, 122.3, 60.2, 38.9, 30.4. (Extra signals due to ^{31}P couplings depending on apodization factor) ^{31}P (121 MHz, $CDCl_3$) δ -11.77.

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Chapter 4

Enantioselective liquid liquid extraction utilizing VAPOL-, VANOL-, H8-BINOL- and TADDOL-based phosphoric acids

Introduction

Based upon the highly encouraging, record breaking results in enantioselective liquid liquid extractions, obtained when replacing the conventional BINOL derived backbone with the SPINOL derived backbone (chapter 3)[1], we envisioned that other chiral backbones present in the literature could also yield different, yet highly interesting effects on ELLE processes with phosphoric acid hosts. Their synthesis and subsequent application into ELLE of aminoalcohols and amino acids might prove to yield more industrially viable applications and shed light on the underlying chemical principles and dynamic interactions involved. One of the main challenges in the field of ELLE, which has become apparent in previous experiments, (Chapter 3, figure 8) is that slight changes in the structure of the guest have large consequences for the efficiency of the ELLE process. Obtaining a broader variety of hosts will not only allow for a tailor suited solution towards more guests, but also potentially circumvent other inconveniences present in the currently available pool of chiral phosphoric acid hosts. One of the major drawbacks regarding both the BINOL and SPINOL derived hosts is the lengthy synthesis routes involved, 7[2] and 14[1] steps respectively, preventing easy accessibility and availability at larger scales. Considering the pKa scale as calculated for all currently known phosphoric acids based on different chiral backbones[3], VAPOL, H8-BINOL and TADDOL derived hosts (Chapter 3, figure 1) appear as interesting candidates. All of these types of structures have the significant advantage of being commercially available or available through a relatively short synthetic route. In this chapter, the availability, efficiency and applicability of these three types of backbone in phosphoric acids for the ELLE of aminoalcohols and amino acids will be evaluated.

Were these new host types prove to be efficient and effective, it might allow ELLE to answer some of the modern day challenges that chemistry focusses on. Obtaining enantiopure compounds on a large scale for the agrochemical, pharmaceutical fine chemical or fragrance & flavor industries[4,5,6] for example. Whereas some chiral compounds can be obtained from natural (bio-)sources such as agriculture or fermentation,[7,8,9,10] large scale production *via* synthetic or separatory routes have proven more efficient in yielding the amounts, and more importantly, the variety needed.[11,12,13,14] While the synthetic route has provided much in terms of variety, it often struggles somewhat in providing the required amounts in a cost-efficient manner.[15,16] Alternatively, the separation of racemates offers far better scalability and cost-efficiency but suffers from lower versatility and technical issues such as problems with solids handling in the case of resolution by crystallization.[17,18,19,20,21] Attempts at expanding the versatility of separatory techniques have been made but

have encountered similar cost-effectiveness issues.[22,23,24,25] Enantioselective Liquid-Liquid Extraction (ELLE)[26] was investigated as an alternative method combining cost-efficiency, simplicity of handling, scalability and versatility. Since hosts and solvents can continuously be recycled, this is potentially a highly economical and environmentally friendly system. Currently, the main drawback of this method, which, to the best of our knowledge, prevents it from being industrially applicable, is a lack of highly enantioselective and robust chiral hosts ($\alpha_{op} > 1.5$). Known host categories,[27,28,29,30,31,32](crown ethers, amino acid derivatives, BINOL derivatives, Cu, Ln, Zn, Co, Ru complexes, tartrates, quinines or guanidinium derivatives) function, except for isolated examples, only at a proof of concept level. This can in part be attributed to a feeble understanding of the underlying principles behind these processes, hindering the design of more efficient selectors. The field of ELLE has therefore stagnated in recent years with only a few new results appearing such as the work of the groups of Schuur[33] and Tang[34] who have expanded upon these classical systems. Therefore achieving a deeper understanding of the chemical principles and physical properties behind this technique is vital if new, more selective hosts are to be developed for the ELLE of a wider range of compounds.

Since their discovery in 1993[35], both VAPOL and its derivative VANOL have served as highly efficient ligands in catalysis due to their unique vaulted structure.[36,37,38,39] Several highly efficient catalytic systems, in combination with a variety of metals as boron, aluminum and zirconium, or as stand-alone catalyst, have been reported over the years. Their synthesis on multigram scale being well described,[40] VAPOL and VANOL phosphoric acids (**PA1-2**) have the significant advantage of being readily available via commercial sources and therefore being easily applicable in ELLE on both laboratory and industrial scale.

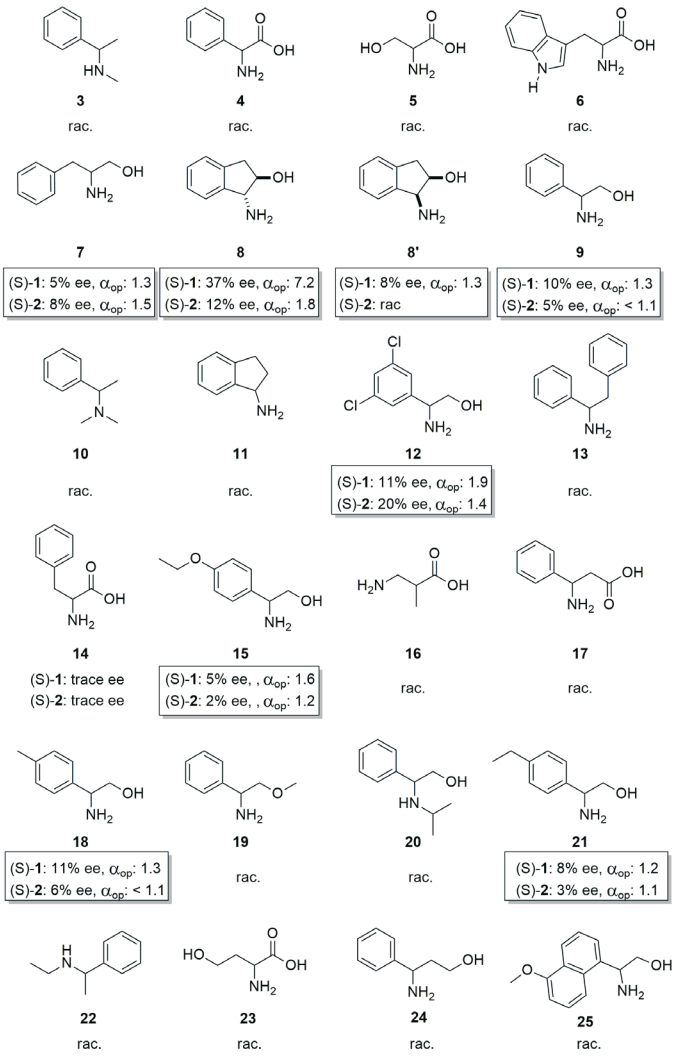
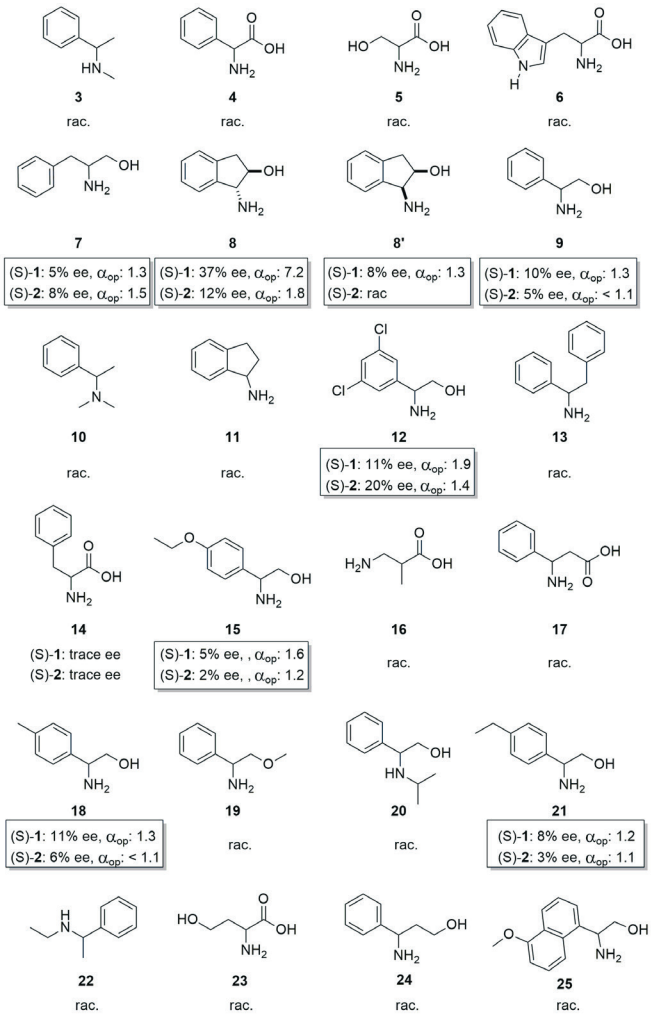


Figure 1. Phosphoric acid hosts used for Enantioselective Liquid-Liquid Extraction.

Results and Discussion

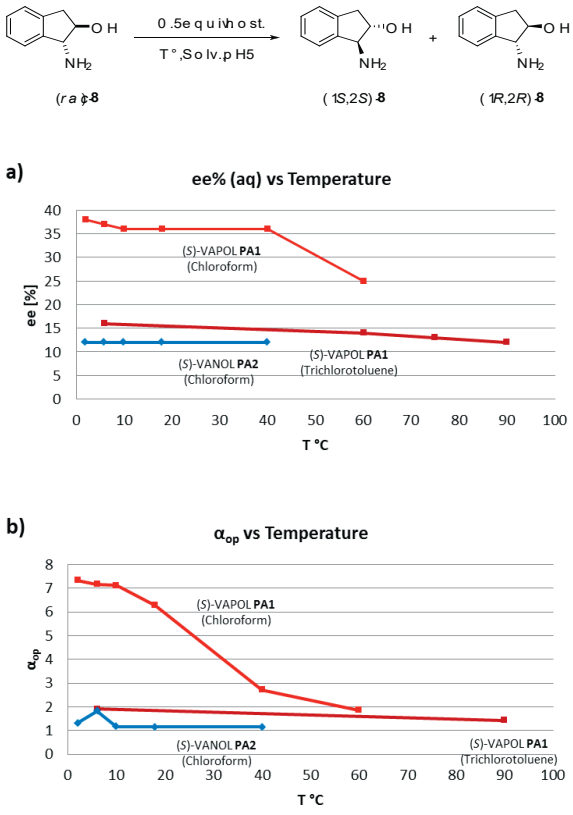
We began our investigations by screening a wide range of chiral guests to determine which classes could be extracted in an enantioselective manner with these hosts. Overall, high selectivities towards 1,2-aminoalcohols were observed, while amino acids or amines were extracted as racemates. (*S*)-VANOL **PA2** extracted phenylalaninol **7** with 8% ee and a good 1.5 α_{op} while (*S*)-VAPOL **PA1** extracted linear 1,2-aminoalcohols **9**, **12** and **15** with 10, 11 and 5% ee and an α_{op} of 1.3, 1.9 and 1.6, respectively (Scheme 1). Para-substituted 1,2-aminoalcohols **18** and **21** could be extracted with similar selectivities to unsubstituted **9** while O-methyl phenylglycinol **19** and N-isopropyl phenylglycinol **20** were extracted without any enrichment with both hosts underlining the importance of both the free amine and free alcohol moieties of the guest. The best results were obtained with cyclic 1,2-aminoalcohols. Indeed, when a racemic mixture of *trans*-1-amino-2-indanol (**8**), dissolved in a pH 5 phosphate buffer solution was placed in contact with a chloroform solution containing **PA1** and left to stir at 6 °C till equilibrated, (1*S*,2*S*)-*trans*-1-amino-2-indanol ((*S*)-**8**) was extracted preferentially with an impressive ee of 37%, and α_{op} of 7.2. The use of **PA2** resulted in 12% ee and 1.8 α_{op} under the same conditions. In the case of *cis*-1-amino-2-indanol (**8'**) good selectivity was also obtained (8%, 1.3 α_{op}). This level of selectivity has, to the best of our knowledge, never been achieved before for cyclic 1,2-aminoalcohols. Overall, while the selectivities obtained for this guest class may initially appear relatively low, they are actually highly interesting as ELLE can be performed in counter-current flow in a multi-staged set-up using a series of devices in which mixing and separation occurs, such as centrifugal contactor separators.[41] This allows the full separation of a racemate. The number of stages is determined by a_{OP}. In all cases the (S)-enantiomer of the host extracted preferentially the (S)-enantiomer of the amino alcohol.



Scheme 1. ELLE screening of chiral substrate classes with (S)-VAPOL **PA1** *and (S)-VANOL* **PA2**. *Conditions: 2 mM guest solution (H_2O, pH 5 phosphate buffer) vs 1 mM host solution ($CHCl_3$), 6 °C. Determination of the ee, distribution and α_{op} via chiral reverse phase HPLC of aqueous phase aliquots.*

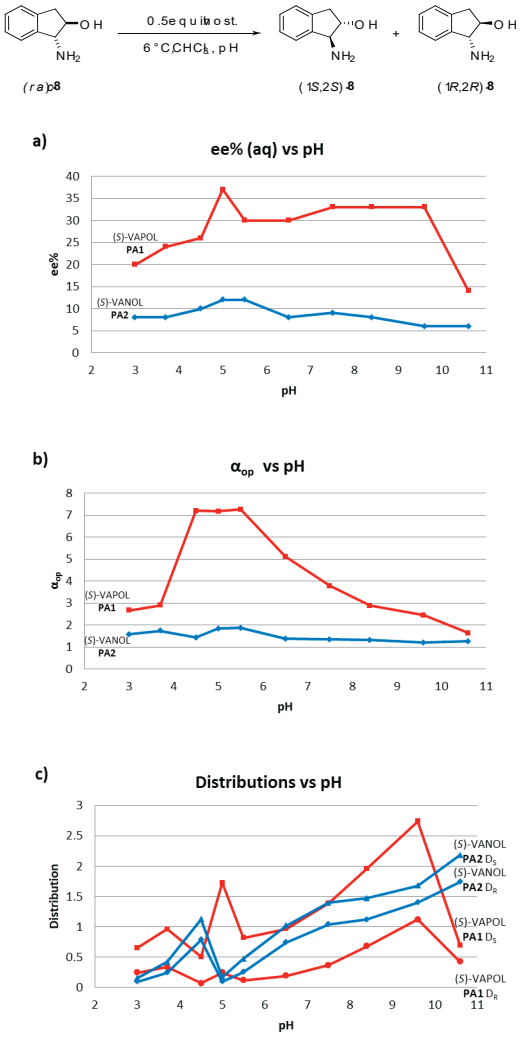
Encouraged by these results we studied the effect of the extraction parameters as temperature, solvent and pH are known to have marked effects on the efficiency of the process. Starting with temperature, we measured the selectivity of the ELLE of **8** over a 2-90 °C range. While an optimum was observed at 2 °C for (*S*)-VAPOL **PA1**, yielding impressively high selectivities with 38% ee and an α_{op} of 7.3, the process proved surprisingly robust towards changes in temperature with ee's remaining stable over the 2-40 °C range (38-36%, Scheme 2a) and only dropping significantly

above this point (25% ee at 60 °C). When the solvent was switched to trichlorotoluene, which is a less efficient solvent for the extraction but which allowed us to probe a wider temperature range, the ee dropped only by 4% when heating from 6 °C to 90 °C (16% and 12% ee, respectively). With **PA2** we found a similar robustness, with ee's remaining stable over the 2-40°C range. Operational selectivities also dropped less than expected (Scheme 2b), from 7.3 at 2 °C to 1.8 at 60 °C (2.7 at 40 °C) when using **PA1**, and dropping slightly from 1.8 at 6 °C to 1.2 at 40 °C when using **PA2**. This high temperature stability allows some design flexibility when adapting this ELLE process to large scale mixing separation devices, which could potentially be run at room temperature while retaining good α_{op} (6.3 at 18 °C) avoiding therefore the need for cooling and its inherent cost.



Scheme 2. Temperature screening for the ELLE of **8** *with* ***PA1*** *and* ***PA2.*** *Conditions: 2 mM guest solution (H_2O, pH 5 phosphate buffer) vs 1 mM host solution, 16h. Determination of the ee, distribution and α_{op} via reverse phase HPLC of aqueous phase aliquots.*

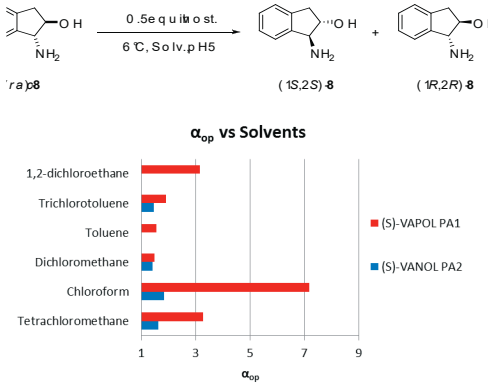
We then turned our attention to the pH dependency of the ELLE of **8** (Scheme 3). Both catalysts showed similar behaviors with an optimal pH around 5. Selectivities dropped significantly at more acidic or basic pH. Interestingly, in the case of **PA1**, the operational selectivity of the extraction proved remarkably stable in a ±0.5 pH unit window centered around pH 5 which is unusual for such a system[42] (Scheme 3a). Such a behavior renders the system more robust towards small local variations in pH. It should be noted that while α_{op} remains stable around pH 5 the distributions vary greatly (Scheme 3c) as the pH varies probably due to a combination of variations in complex stability and solubility. The effect of the host phase solvent was next studied (Scheme 4). Chloroform proved optimal for both hosts in terms of ee and α_{op}; other haloalkane based solvents resulted in lower selectivities while aromatic solvents, both halogenated and non-halogenated, gave relatively unfavorable results. With optimal conditions in hand we next investigated the scalability of the process. In addition to a good distribution and operational selectivity, the ability to dynamically recover the guest from the host is of vital importance. To measure this we employed a U-tube extractor, based on a modified design by Cram[43], which is a good procedure to establish the capability of the host to release the enriched guest into a receiving phase. In addition, it will demonstrate that the host can selectively transport the desired enantiomer in a catalytic fashion between the feeding and receiving phase with multiple turnovers allowing for the use of substoichiometric amounts of host. A blank extraction, run at pH 5 for 24 h in the absence of host, showed that no background leaching of guest from the feeding to the receiving phase occurred, indicating that all observed extraction would be due to transport by the host. When a U-Tube extractor composed of a 20 mM feeding phase and a 0.5mM host solution was run, an ee of 41% could be observed after 10 min in the receiving phase which remained stable over one hour. As the feeding phase became depleted in one enantiomer, the host increasingly transported the second enantiomer resulting in a slow erosion of the ee of the receiving phase, reaching 30% after two hours and dropping to 14% after four hours. At the end of the run 10 turnovers were reached. Overall these results clearly indicated that the enantioselective extraction process was catalytic and can be scaled up. We have previously established that large-scale racemate separation can be performed highly efficiently in counter-current flow using a number of centrifugal mixing separation devices[44,45,45] in series enhancing the ee at each step according to the Fenske equation. The high α_{op} observed would allow such a process to be run with as little as 5-6 stages with a final ee of up to 99% in the final stage as was shown in the case of 3,5-dinitrobenzoyl-(R),(S)-leucine.[46]



Scheme 3. pH screening for the ELLE of 8 with PA1 and PA2. Conditions: 2 mM guest solution (H_2O, phosphate buffer) vs 1 mM host solution ($CHCl_3$), 6 °C, 16h. Determination of the ee, distribution and α_{op} via reverse phase HPLC of aqueous phase aliquots.

To gain a better understanding of the origin of the remarkable selectivity in the extraction of *trans*-1-amino-2-indanol (**8**) using VAPOL phosphoric acid (**PA1**), DFT energy minimizations were carried out. The geometries of **PA1**⊃(S,S)-**8** and **PA1**⊃(*R,R*)-**8** were optimized at the B3LYP/6-31G++(d,p) level of theory, using an IEFPCM $CHCl_3$ solvation model (Figure 3).[43] The hydrogen bond lengths in the structure with (*S,S*)-**8** (N···O = 2.60 Å; O···O = 2.70 Å) are slightly shorter than those found in the structure with the (*R,R*)-enantiomer (N···O = 2.61 Å; O···O = 2.72 Å). Furthermore, where the (S,S)-guest nicely points outwards from the binding pocket

offered by the phosphoric acid, there appears to be some steric repulsion between the phenyl ring of the (R,R)-guest and the phenanthrene moiety of the host. The Gibbs free energy calculated for **PA1**⊃(*S*,*S*)-**8** is 3.8 kJ mol^{-1} lower than for **PA1**⊃(*R*,*R*)-**8**, which is in line with experimental observations [that is, selective extraction of the (S,S)-enantiomer, *vide supra*]. This steric interaction between the phenyl substituent of the guest and the phenanthrene moiety of the host is absent in the structures calculated for **PA2** (which would be an explanation for the lower ee in the extraction experiments.



Scheme 4. Solvent screening for the ELLE of 8 with PA1 and PA2. Conditions: 2 mM guest solution (H_2O, pH 5 phosphate buffer) vs 1 mM host solution, 6 °C. Determination of the ee, distribution and α_{op} via reverse phase HPLC of aqueous phase aliquots.

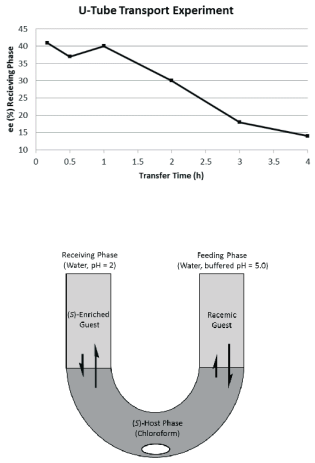


Figure 2. U-Tube model reactor. Conditions: Host phase: PA1 in chloroform (0.5 mM,10 ml). Feeding phase: 8 in H_2O (20.0 mM pH 5 phosphate buffer). Receiving phase: aq. HCl (5 ml, pH 2), 6°C Determination of the ee, distribution and a_{op} via reverse phase HPLC of aqueous phase aliquots.

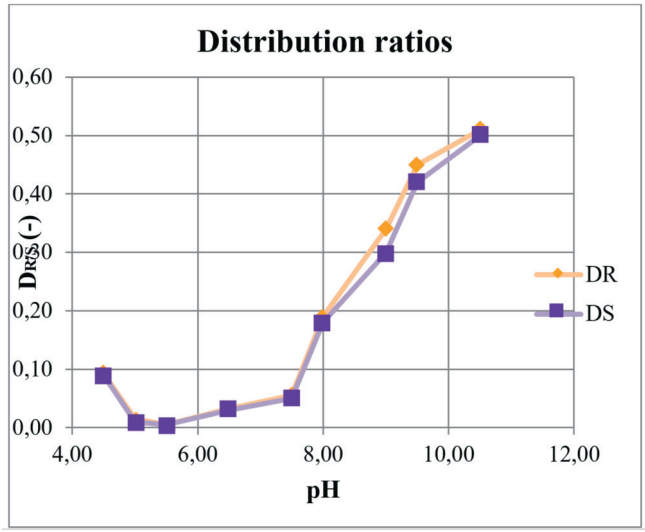


Figure 3. DFT energy minimized structures [B3LYP/6-31G++(d,p)] for the diastereomeric complexes PA1É(S,S)-8 (left) and PA1⊃(R,R)-8.

H8-BINOL derived chiral phosphoric acids and their application in ELLE

Having established and investigated the high efficiency of BINOL- (chapter 2), SPINOL (chapter 3),- VAPOL- and VANOL-based phosphoric acids as chiral hosts for enantioselective liquid liquid extraction of a range of 1,2-amino alcohols, the H8-BINOL and TADDOL derived phosphoric acids are left on the proposed shortlist in the introduction of this chapter.

Synthesis of the desired H8-BINOL derived hosts starts with the hydrogenation of commercially available chiral BINOL[47], to obtain 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol.[48] Subsequent aromatic nucleophilic substitution introduces halogen functionality on the 3- and 3′-positions, which are replaced by the desired aromatic functionalities employing a Suzuki reaction. Finally, one pot phosphorylation under basic conditions followed by hydrolysis leads to the desired H8-BINOL derived phosphoric acids ready to be employed in enantioselective liquid-liquid extractions.

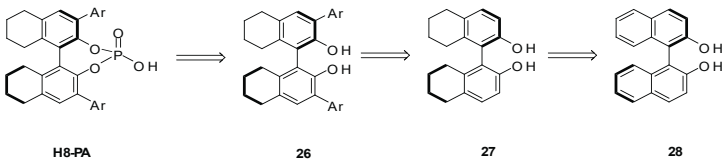
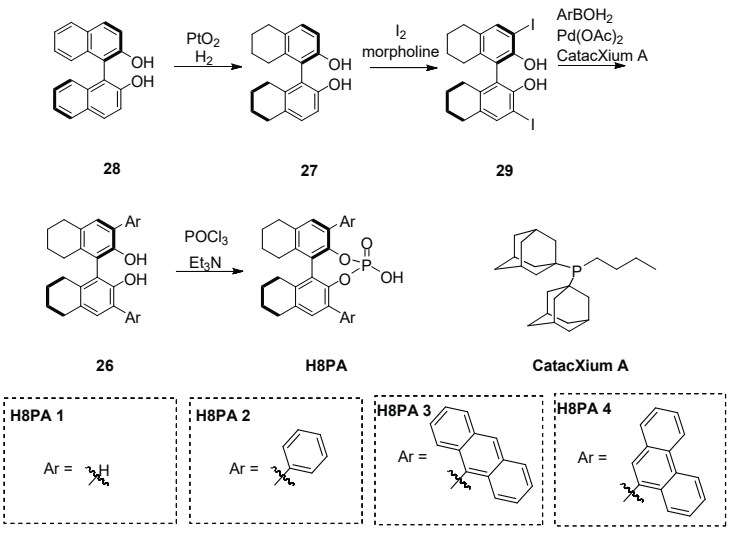


Figure 4. Rethrosynthetic scheme for the synthesis of H8-BINOL derived phosphoric acids.

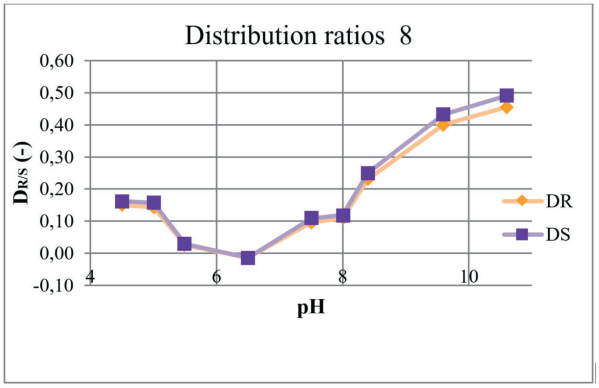
The lack of the highly reactive aromatic 6- and 6'-positions obviates the need for a protection and deprotection step. In addition, it avoids the relatively difficult to control selective lithiation of the 3- and 3'-positions (synthetic step 3, chapter 2). To allow for as much comparison as possible between the various C_2-symmetric chiral scaffolds in ELLE efficiency, aryl substituents were chosen to be similar as those described in the previous chapters for the BINOL- and SPINOL derived phosphoric acids. Moreover, the same location on the backbone has been substituted and their efficiency in ELLE will be tested against the same set of racemic amino acids, chiral amines and amino alcohols. The synthesis was performed according to a method described by Pausse *et al.* in 2009 with minor modifications.[49] These modifications were mainly applied for the purpose of obtaining the desired phosphoric acids, rather than the described thiophosphoric acids. The phosphorylation was performed according to previously reported methods.[50]



Scheme 5: Synthetic route towards H8-BINOL derived hosts. Reaction conditions: a) PtO_2, H_2, AcOH, r.t, 67%. b) I_2, morpholine, DCM, r.t, 95% c) K_2CO_3, $Pd[OAc]_2$, CataCXium A, $ArB(OH)_2$, DME, H_2O, 95°C, o.n., >80% d) $POCl_3$, Et_3N, dioxane, o.n. >77%.

Having obtained the various H8-BINOL derived scaffold phosphoric acids, their application in enantioselective liquid liquid extraction was investigated. Based on the successful interaction between phosphoric acids and amino alcohols in ELLE previously described (Chapter 1,2,3), application of the same library of racemic chiral compounds in phosphate buffer at pH =5.0, as given in Scheme 1, was employed. To our surprise, no enantioselectivity could be observed for any of the presented guests. Reactive extraction was found for all guests, however, with lack of enantiomeric

differentiation. The question remained if the right conditions were employed during initial batch extractions studies, to which point a pH screening for several of the previously highly successful chiral amino alcohols was performed. Batch extraction of a set of aqueous phases containing 1,2-amino indanol **8** at various pH in the presence of a DCM layer containing **HPA2** yielded the distribution curves for (S)- and (R)-**8**. When employing the other three H8-BINOL derived chiral phosphoric acids, similar distribution curves were obtained. This is because the extraction is host and pH dependent, but not backbone dependent, resulting in four identical distribution curves lacking enantioselectivity. In each case a minimum around pH= 5.5 and a gradual increase towards the higher pH ranges is observed. Similar testing was performed for amino alcohols **7**, **8**, **9** and **15**, in each case yielding reactive extraction, however no enantiodiscrimination.



Scheme 6: Distribution rates at several pH values for the extraction of 8 by H8PA2 as example for the extraction of 7,8,9 and 15 by H8PA1-4

Since a change in pH of the aqueous phase could not force the induction of the successful enantioselective liquid liquid extractions, temperature dependence was investigated. In most previously described situations a temperature optimum is found around 6 °C.[1,42,51] For most chiral amines targeted, solubility is drastically lowered at temperatures under 6 °C, forcing the amine to reside in the organic phase. The resulting boost in distribution is independent of the host, as it is solubility controlled,[42] and is therefore both enantiomers distribute equally, representing itself in a lower overall alpha value. At temperatures higher than 6 °C, a prominent (in the cases of BINOL and SPINOL)[1] or gradual (Vapol)[50] decrease in ee is observed, resulting in a lower alpha. Initial experiments regarding the H8-BINOL derived phosphoric acids were therefore executed at 6 °C. Repetition of the experiments at 2 °C and 18 °C in both cases resulted in similar observations, in which racemic

extraction occurs.

The relatively unexpected loss of enantioselectivity while switching from BINOL derived- to H8-BINOL derived phosphoric acids, prompted us to think about the structure activity relation. In a similar manner as for the SPINOL derived chiral phosphoric acids (Chapter 3) a hypothesis was proposed in which an interaction between the (BINOL/H8-BINOL) backbone of the host and the aromatic ring of the guest is responsible for enantiodiscrimination. Seeing as under standard ELLE conditions no enantiomeric discrimination can be observed, DFT calculations were employed to investigate the interactions between guest and 8H-BINOL derived hosts. Unfortunately no conclusive evidence could be drawn from these calculations towards the involvement of the backbone in a direct or indirect way.

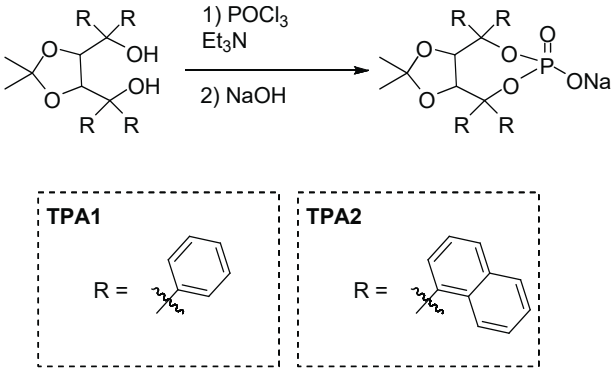
TADDOL derived phosphoric acids and their application in ELLE

The last well known class of chiral phosphoric acids present in literature is the TADDOL backbone based phosphoric acids.[3] Interestingly, while TADDOL derived phosphorous containing ligands, such as phosphoramidites, have been highly efficient in metal catalysis, the TADDOL derived phosphoric acids have only been used only sparingly.[52] This could be due to their relatively high pKa, as calculated by Yang *et al*,[3] in comparison to the binaphthyl backbones. Another reason can be found in the combination of a strong acidic component as a phosphoric acid, with an acid labile acetal moiety embedded in the TADDOL ligand.[51] Nevertheless, the application of TADDOL derived phosphoric acids was investigated by the group of Akiyama for enantioselective Mannich reactions. They reported good yields and ee's using a 5 mol% catalyst loading.[53] A more extensive investigation of this catalyst type for enantioselective Mannich reactions was reported recently.[54]

Based on this, the potential of TADDOL derived phosphoric acids in the enantioselective liquid liquid extraction of amino acids and amino alcohols could be high. Moreover, testing and screening this host type will most probably provide interesting information towards the importance of the pKa of the phosphoric acid moiety in ELLE. Thereby perhaps providing more structure activity relationship data, which might have a positive influence on the further application and optimization of all chiral phosphoric acids in ELLE.

The synthesis of such TADDOL based phosphoric acids is straightforward, and can be performed according to procedures reported by Pichota *et al*.[55], although we used slight modifications. Starting from the commercially available diol, phosphorylation and subsequent hydrolysis under basic conditions furnishes the desired chiral phosphoric acid in a mere two steps. Whereas with the previously mentioned chiral

phosphoric acid hosts the hydrolysis could be performed under acidic conditions allowing for a one pot reaction (or sometimes even during workup),[1] a strict absence of acidic media has to be maintained in the case of the TADDOL backbone which necessitates the separation of the phosphorylation and hydrolysis steps. The obtained sodium-host salt is stable for a period of at least a month after isolation and purification, given proper storage conditions.



Scheme 5: Synthetic route towards TADDOL derived hosts. Reaction conditions: a) $POCl_3$, Et_3N, dioxane, 16 h, 70%. b) THF, NaOH, H_2O, 10h, 66%.

Additional control experiments were performed in which the stability of the acidic moiety present in the TADDOL backbone is tested under standard ELLE conditions (pH=5.0, dual layer system, 6°C) without the presence of a racemate/guest. No significant hydrolysis was observed over a period of 24 h, rendering the host stable enough to perform ELLE and allowing to proceed with initial batch library experiments.

When applying TADDOL derived chiral phosphoric acids in ELLE, in particular against the same library of chiral amines and amino acids as depicted in Scheme 1 of this chapter, similar results were obtained as with the H8-BINOL derived phosphoric acids. Unfortunately, only reactive extraction could be observed. The lack of enantiodiscrimination could arise from the absence of a key sterical or electronic interaction to fulfill the 3 point rule of chirality.[56] In line with the research performed for the H8-BINOL derived phosphoric acid hosts, for the most promising amino-alcohols (**7**,**8**,**9** and **15**) the influence of the pH of the aqueous phase was tested. Results of **9** are shown in Figure 3 below, and highly similar results were obtained for amines **7**,**8** and **15**.The lack of enantiodiscrimination across the pH range tested prevents the use of these two TPA (the most common TADDOL derived chiral phosphoric acids in literature) hosts in ELLE for the resolution of chiral amines.

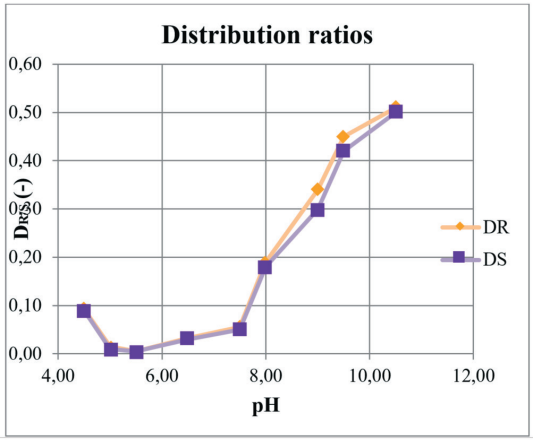


Figure 3 : Distribution rates at several pH values for the extraction of 8 by TPA1 as example for the extraction of 7,8,9 and 15 by TPA1-2

Conclusions

In summary, we have investigated the efficiency of VAPOL-, VANOL-, H8-BINOL and TADDOL-based phosphoric acids as chiral hosts for the enantioselective liquid-liquid extraction of a range of chiral 1,2-aminoalcohols. VAPOL- and VANOL-based phosphoric acid proved to be good selectors for several 1,2-aminoalcohols, offering a particular cost-efficient process for their resolution due to the relatively easy synthetic availability of these phosphoric acids and the high selectivity reached. In particular, (*S*)-VANOL **PA2** allows for the resolution of phenylalaninol (**7**) while (*S*)-VAPOL **PA1** proved particularly efficient for the ELLE of *trans*-1-amino-2-indanol (**8**) yielding an ee of 37% and impressive operational selectivity of 7.2. DFT calculations were applied to shine light on the origin of the remarkable selectivity, and show a clear preference for binding of one of the enantiomers. The extraction process proved also to be highly robust, tolerating small variations in optimal conditions with little or no impact on its efficiency. The U-tube experiments show the catalytic nature of the extraction process as well as the feasibility of an efficient back-extraction. In view of the high operational selectivity, this process could be easily scaled up using as little as 5-6 stages. The application of H8-BINOL and TADDOL-based phosphoric acids showed a lack of enantiomeric discrimination. In both cases, all synthesized derivatives showed reactive extraction under standard ELLE conditions. The investigation of the influence of pH on these systems showed no improvement towards enantioselective binding, raising several questions towards the key supramolecular interactions and 3D structures of the host-guest systems. The use of common analysis techniques

(NMR, HPLC), crystallization and DFT calculations could not provide the answers to the hypotheses proposed.

Future perspective on the application of chiral phosphoric acids

Combining all obtained information on chiral phosphoric acids in ELLE, reported in the previous four chapters, we now possess a much larger range of information on the efficient extraction of chiral amines and amino alcohols. The investigation of the many parameters influencing ELLE of chiral amines using chiral phosphoric acid hosts allows us to draw several preliminary conclusions, however it also raises a number of questions. First it allows us to efficiently extract amino alcohols under more than just standard ELLE conditions, at industrially viable levels. Secondly, this allows us to form a hypothesis towards the mode of action of extraction and the role of the C_2-symmetric chiral scaffolds tested. This has been described in depth in Chapter 3.

Nevertheless, these hypotheses remain tentative as many observations remain difficult to explain and the divergences between the several backbones in terms of steric and electronic properties makes generalizationsdifficult.[1,42,50]

For example, when looking at the relatively small differences between the BINOL and 8H-BINOL C_2-symmetric chiral scaffold, a conclusion regarding the high importance of the second aromatic ring in the backbone could easily be made. This however, would disregard the difference in pKa of the phosphoric acids, the difference in electronic properties of the 'primary aromatic backbone ring' and the fact that the SPINOL backbone also lacks a secondary aromatic ring (however it is able to differentiate between enantiomers). (this chapter)

Similarly, small differences between the size and quadrupole moment of 3,3'-groups on the BINOL derived scaffolds lead to highly significant differences in extraction efficiency. In some cases these effects completely dominating the ability of the host to perform chiral discrimination (Chapter 2). This however cannot be extended to the SPINOL backbone, where only small differences in enantiomeric excess are observed for the various 3,3'-substituents. This could indicate the difference in positioning and therefore the different role the large aromatic substitutions play in the formation of a suitable cavity for the chiral amine to bind. The surprising role of the 3,3'-substituents is once more highlighted by the peculiar SPINOL-anthracene host behavior in toluene, in which the enantiomeric preference is completely inverted. Use of DFT calculations to investigate this role did not lead to meaningful results

Therefore further research aiming to elucidate the exact guest-host interacting is required to make a valid conclusion as to why such small differences in the backbone

of the chiral phosphoric acid host have such a devastating effect on the outcome and efficiency of enantioselective liquid liquid extraction of 1,2-amino alcohols and amino acids.

Experimental Section

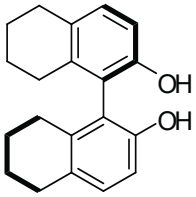
General information

Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gels 60, 0.25 mm. Conversions of the reactions were determined by TLC unless otherwise stated. Components were visualized by UV and potassium permanganate staining. Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). ^{1}H- and ^{13}C-NMR were recorded on a Varian AMX400 (400 and 101 MHz, respectively) or a Varian VXR300 (300 and 75 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. All reactions were carried out under nitrogen or argon atmosphere in either oven dried round bottom flasks (gram scale or above) or oven dried sealed tubes (sub-gram scale) using standard Schlenk techniques. Diethyl ether, tetrahydrofuran, dichloromethane and toluene were used from the solvent purification system (MBRAUN SPS systems, MB-SPS-800). All catalysts, ligands, reagents and other solvents were purchased from commercial sources and used as received without further purification unless otherwise stated, except organo-lithium reagents which were titrated before use using diphenylacetic acid. When needed, degassing of solvents was performed via the freeze, pump, thaw technique. RP-HPLC measurements were performed on a Shimadzu SIL-20A with a CTO-20AC column oven and LC-20AD pumps on a CROWNPAK® CR(-) chiral column (Daicel, Japan) equipped with a guard column. Calibration curves were prepared in the concentration range employed for the determination of the distribution. Uncertainties were typically lower than 2.0%. General HPLC conditions for enantiomeric separation of aryl-1,2- and aryl-2,1-amino alcohols: Perchloric acid solutions (pH =1,5 or pH =1) flow = 1.0 ml/min were used as eluent, with exception of serine (**5**), phenylalanine (**14**), homoserine (**23**), 3-amino-3-phenyl-1-propanol (**24**) where flow of 0,5 ml/min was applied. Column temperature was set at 20°C, with exception of 3-aminoisobutyric acid (**22**), where 0°C was applied. All data is in accordance with literature, unless otherwise stated.

General procedure for standard ELLE extraction experiments

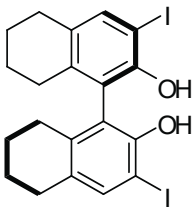
To a vial with a stirring bar, a solution of the racemic guest (0.4 ml, 2.0 mM) dissolved in a phosphate buffer solution (buffer strength 0.1 M, indicated pH) was added to a solution of the host in $CHCl_3$ (0.4 ml, 1.0 mM). After capping the vial, the mixture was cooled to the indicated temperature and stirred at 900 rpm for 16 h. The phases were allowed to separate over a period of 2 min. The aqueous phase was removed and an aliquot was injected into a reverse phase HPLC for determination of the ee, distribution and α_{op}. All extraction experiments were carried out *in triplo* and with a simultaneous blank reaction (concentration of host = 0.0 mM).

Hydrogenation of R-BINOL[48]



(R)-BINOL (5.328 g, 18.6 mmol, 1 equiv) and PtO2 (0.48 g, 2.1 mmol, 0.11 equiv) in AcOH (160 mL) was added to a 500 ml flask under H2 (balloon, 1 atm) and the mixture was stirred at room temperature for 3 d. The mixture was then filtered through celite which was washed with chloroform (270 mL). The organic phase was washed successively with H2O and sat. aq. $NaHCO_3$ then dried (Na_2SO_4) filtered and concentrated in vacuo. The crude product was purified by flash column chromatography and obtained as a white solid in 96% yield (5.3 g). ^{1}H NMR (400 MHz $CDCl_3$-d) δ 7.07 (d, J = 8.3 Hz, 2H) 6.83 (d, J = 8.3 Hz, 2H), 4.54 (bs, 2H), 2.75 (t, J = 6.3 Hz, 4H), 2.29 (dt, J = 17.4, 6.3 Hz, 2H), 2.16 (dt, J = 17.4, 6.3 Hz, 2H) 1.73 (m, 8H).

Iodination of *R*-H_8-BINOL[26]

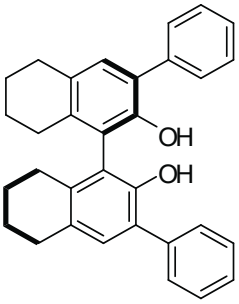


To a solution of (R)-H_8-BINOL (2g, 6.8 mmol, 1 equiv) in CH_2Cl_2 (60 mL) were added successively at room temperature, morpholine (3.6 mL, 41 mmol, 6 equiv) and I_2 (3.45 g, 13.6 mmol, 2 equiv). The mixture was stirred for 5 h and turned progressively red. Then CH_2Cl_2 (50 mL) and aq. HCl (1 N, 50 mL) were added. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed successively with a saturated aqueous sodium thiosulfate solution (3x50 mL) and brine, then dried over Na_2SO_4 and concentrated in *vacuo*. The obtained solid was used without further purification. ^{1}H NMR (400 MHz $CDCl_3$-*d)* δ 7.51 (s, 2H) 4.97 (s, 2H) 2.72 (t, J = 6.1 Hz, 4H) 2.26 (dt, J = 17.5, 6.1 Hz, 2H) 2.09 (dt, J = 17.5, 6.1 Hz, 2H) 1.69 (m, 8H)

General procedure for Suzuki cross-coupling

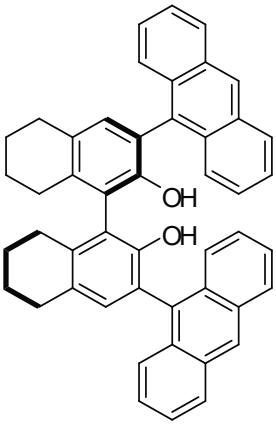
A sealed tube was charged with $Pd(OAc)_2$ (2 mg, 2 mol%) and $(adamantly)_2$-butylphosphine (4 mg, 2.5 mol%) and placed under inert athmosphere. A solution of iodated H_8-BINOL (200 mg, 0.44 mmol, 1 equiv) and 3 equiv of the corresponding boronic acid, dissolved in DME and 1M K_2CO_3 solution (2 mL) was added. The mixture was heated up to 95 °C for 1-15 h. After cooling down the organic phase was separated, diluted with CH_2Cl_2, and washed with sat. aq. NH_4Cl solution and H_2O. The organic layer was dried over Na_2SO_4 and solvent was evaporated in *vacuo*. The obtained solid residue was purified by column chromatography (eluent hexane/ CH_2Cl_2).

3,3′-diphenyl-5,5′,6,6′,7,7′,8,8′-octahydro-[1,1′-binaphthalene]-2,2′-diol[48]



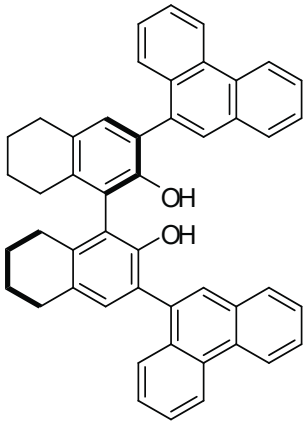
The material was obtained as a white solid. (82%, 155 mg) ^{1}H NMR (400 MHz $CDCl_3$-d) δ 7.61 (m, 4H) 7.44 (t, J = 7.1 Hz, 4H), 7.34 (m, 2H), 7.17 (s, 2H), 4.92 (bs, 2H), 2.82 (t, J = 6.2 Hz, 4H) 2.42 (dt, J = 17.4, 6.2 Hz, 2H) 2.27 (dt, J = 17.4, 6.2 Hz, 2H) 1.77 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$-d) δ 150.7, 140.6, 139.2, 134.4, 132.9, 131.9, 130.1, 129.8, 128.7, 122.8, 31.9, 29.9, 25.8.

3,3′-di(anthracen-9-yl)-5,5′,6,6′,7,7′,8,8′-octahydro-[1,1′-binaphthalene]-2,2′-diol48



The material was obtained as a white solid. (51%, 76 mg) ^{1}H NMR (400 MHz $CDCl_3$-*d)* δ 8.80 (m, 4H) 7.38-8.03 (m, 14H) 7.24 (m, 2H) 4.88 (m, 2H) 2.90 (t, J = 5.5 Hz, 4H) 2.46-2.78 (m, 4H) 1.91 (m, 8H) ^{13}C NMR ($CDCl_3$-*d)* δ 150.0, 136.3, 136.0, 135.8, 131.4, 130.9, 130.6, 129.9, 129.5, 128.5, 128.0, 127.8, 127.6, 127.0, 126.7, 126.4, 125.0, 123.6, 123.2, 122.6, 28.8, 26.9, 23.0, 22.9.

3,3′-di(phenanthren-9-yl)-5,5′,6,6′,7,7′,8,8′-octahydro-[1,1′-binaphthalene]-2,2′-diol[48]

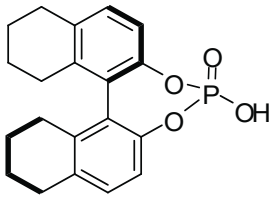


The material was obtained as a white solid. (62%, 102 mg) ^{1}H NMR (400 MHz $CDCl_3$-*d)* δ 8.54 (s, 2H) 8.10 (m, 2H) 8.05 (d, J = 8.4 Hz, 2H) 7.89 (d, J = 7.9 Hz, 2H) 7.75 (dd, J = 8.8, 1.2 Hz, 2H) 7.52 (m, 4H) 7.44 (ddd, *J* = 8.1, 6.5, 1.1 Hz, 2H) 7.32 (ddd, *J* = 8.7, 6.5, 1.3 Hz, 2H) 7.13 (s, 2H) 4.66 (s, 2H) 2.88 (t, J = 6.0 Hz, 4H) 2.76 (dt, *J* = 17.3, 6.2 Hz, 2H) 2.67 (dt, J = 17.5, 5.9 Hz, 2H) 1.94 (tt, *J* = 8.4, 4.4 Hz, 8H) ^{13}C NMR ($CDCl_3$-*d)* δ 147.1, 136.7, 132.5, 131.5, 130.5, 128.6, 127.6, 127.1, 127.0, 125.6, 122.3, 122.1, 29.0, 26.9, 22.7, 22.6

General procedure for phosphorylation

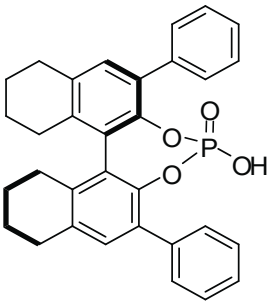
A dry Schlenk flask was charged with the diol (1 equiv) and brought under N_2 atmosphere. The solid was solubilized in dioxane 5 ml and the solution was cooled to 0°C. Subsequently NEt_3 (5 equiv) and $POCl_3$ (3 equiv) were added. The reaction mixture was left stirring overnight at 95°C. After quenching with 1 ml H_2O, the mixture was left stirring for another 10 min. The solution was then acidified using 6 N aq. HCl to pH = 1. The mixture was heated to 50 °C for 2 h, cooled down, and extracted with toluene. The organic layer was washed with H_2O and brine before drying on Na_2SO_4 and removing the solvent *in vacuo*. The compound was then purified by FCC using hexane/DCM as eluent.

4-*hydroxy*-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide[48]



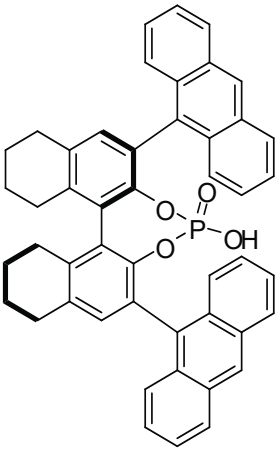
The material was obtained as a white solid. (Quantitative yield, 114 mg) ^{1}H NMR (400 MHz $CDCl_3$-*d)* δ 7.11 (m, 4H) 2.80 (dd, J = 15.5, 8.7 Hz, 4H) 2.67 (ddd, J = 16.4, 8.9, 4.6 Hz, 2H), 2.28 (dt, *J* = 16.6, 5.7 Hz, 2H) 1.79 (m, 6H) 1.55 (dt, *J* = 39.0, 8.4, 5.6 Hz, 2H); ^{31}P NMR (162 MHz, $CDCl_3$-*d*) δ 0.7 (s)

4-hydroxy-2,6-diphenyl-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide[48]



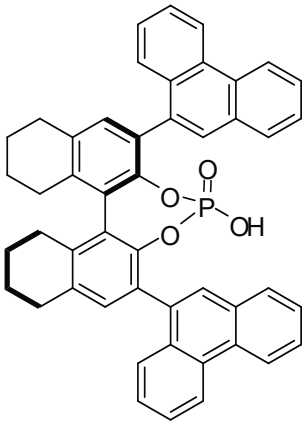
The material was obtained as a white solid. (42%, 54 mg) ^{1}H NMR (400 MHz $CDCl_3$-*d)* δ 7.60 (m, 4H) 7.42 (m, 4H) 7.33 (d, J = 7.3 Hz, 2H) 7.15 (s, 2H) 2.81 (t, J = 6.2 Hz, 4H) 2.41 (dt, J = 17.2, 6.2 Hz, 2H) 2.26 (dt, J = 17.3, 6.3 Hz, 2H) 1.76 (m, 8H); ^{13}C NMR ($CDCl_3$-*d*) δ 143.2, 137.1, 136.5,134.4, 134.3, 131.0, 130.9, 130.8, 129.3, 128.1, 127.2, 127.1, 28.5, 27.3, 22.1, 22.0 ^{31}P NMR (162 MHz, $CDCl_3$-*d*) δ 4.3 (s)

2,6-di(anthracen-9-yl)-4-hydroxy-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide (rotamers)[48]



The material was obtained as a white solid. (54%, 34 mg) ^{1}H NMR (400 MHz $CDCl_3$-*d)* δ 8.73 (m, 4H) 7.80-8.02 (m, 4H) 7.43-7.76 (m, 10H) 7.27 (m, 2H) 2.96 (ddd, *J* = 19.2, 9.4, 5.6 Hz, 6H) 2.61 (ddd, *J* = 17.5, 5.7 Hz, 2H) 1.94 (m, 8H) ; ^{13}C NMR ($CDCl_3$-*d*) δ 144.4, 144.2, 144.0, 137.2, 136.8, 134.6, 134.0, 133.8, 132.7, 132.2, 131.7, 131.0, 130.7, 130.6, 130.2, 129.8, 129.7, 129.5, 129.4, 128.6, 128.5, 127.5, 127.3, 126.8, 126.8, 126.5, 126.4, 126.1, 125.8, 123.0, 122.6, 28.6, 27.5, 22.3, 22.2 (contains rotamers) ^{31}P NMR (162 MHz, $CDCl_3$-*d*) δ 4.05, 3.99 (contains rotamers)

4-hydroxy-2,6-di(phenanthren-9-yl)-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine 4-oxide[48]



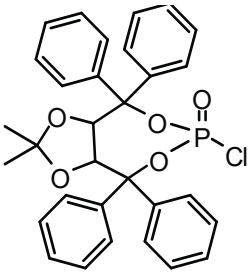
The material was obtained as a white solid. (51%, 49 mg) ^{1}H NMR (400 MHz $CDCl_3$-*d)* δ 8.50 (s, 2H) 8.04 (m, 2H) 7.99 (m, 2H) 7.91 (m, 2H) 7.69 (ddd, J = 21.4, 7.9, 1.2 Hz, 2H) 7.20-7.49 (m, 10H) 3.11 (m, 2H) 3.00 (m, 4H), 2.75 (ddd, *J* = 16.6, 7.1, 4.8 Hz, 2H), 2.03 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$-*d*) δ 147.5, 147.4, 146.8, 146.7, 141.1, 139.4, 138.9, 137.1, 134.4, 130.7, 130.5, 130.3, 130.0, 129.6, 128.9, 128.5, 128.0, 127.8, 127.5, 32.0, 31.0, 25.4; ^{31}P NMR (162 MHz, $CDCl_3$-*d*) δ 3.52 (s)

General procedure phosphorylation TADDOL[28]

To a solution of TADDOL (0.5 g, 1.07 mmol, 1 equiv) in THF (6 mL) was added *n*-BuLi (1.34 mL, 2.14 mmol, 2 equiv) at – 78 °C. The mixture was warmed to rt and stirred for 1h, then again cooled to – 78 °C before addition of phosphorus oxychloride (0.13 mL, 1.39 mmol, 1.3 equiv). The mixture was stirred for 3h at – 78 °C, the reaction was quenched with a sat. aq. $NaHCO_3$ solution and extracted with toluene. Then the solvent was evaporated in *vacuo* and the solid residue was purified by column chromatography (eluent CH_2Cl_2/ MeOH) to afford an almost white solid product.

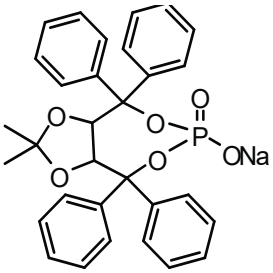
To a solution of 6-chloro-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide (217.2 mg, 0.4 mmol, 1 equiv) in THF (8.7 mL) were added H_2O (4.3 mL) and NaOH (40 mg, 0.92 mmol, 2.5 equiv). After stirring for 10h at rt the solvent was removed under reduced pressure, and then the residue was dissolved in AcOEt. The solution was filtered, then the solvent was evaporated in *vacuo* and the solid residue was purified by column chromatography (eluent CH_2Cl_2/ MeOH) to afford the white product.

6-chloro-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide[52]



The material was obtained as a almost white solid. (549 mg, 70%) ^{1}H NMR (400 MHz $CDCl_3$-*d*) δ 7.61 (td, *J* = 8.1, 1.6 Hz, 4H), 7.24 – 7.45 (m, 16H), 5.40 (d, J = 7.9, 1H), 5.35 (d, J = 7.9, 1H), 0.65 (s, 3H), 0.59 (s, 3H) ; ^{31}P NMR (162 MHz, $CDCl_3$-*d*) δ -12.81 (s)

Sodium (3aR,8aR)-Tetrahydro-2,2-dimethyl-4,4,8,8-tetraphenyl-1,3-dioxolo[4,5-e][1,3,2]dioxaphos-phepin-6-olate 6-Oxide[52]



The material was obtained as a white solid. (246 mg, 66%) ^{1}H NMR (400 MHz, CD_3OD-*d*) δ 7.51 – 7.59 (m, *J* = 8.0, 3.9, 2.1 Hz, 8H), 7.15 – 7.24 (m, 12H), 5.31 (s, 2H), 0.68 (s, 6H); ^{31}P NMR (162 MHz, CD_3OD-*d*) δ -11.58 (s)

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Chapter 5

Catalytic Cross-Coupling Reactions: Fast, Greener and Scalable Direct Coupling of Organolithium Compounds using minimal amounts of solvents

Introduction

One of the more notoriously difficult parts in the synthesis of all previously described chiral phosphoric acids containing a symmetric C2-axis is the introduction of the 3- and 3'-aryl substituents via a Suzuki reaction (Chapter 2, 3, 4). Being crucial to the formation of the chiral cavity around the phosphoric acid group, the aryl substituents play an important role in the selectivity of the host. Several alternatives to the Suzuki reaction have been established in the class of Pd-catalysed C-C bond forming reactions, however, all have their corresponding challenges. In a typical Pd-catalysed C-C bond forming reaction, a strictly inert reaction atmosphere, elevated temperatures and long reaction times are often required, while toxic waste is produced. In the next two chapters however, an attractive alternative was developed, overcoming a significant portion of these challenges.

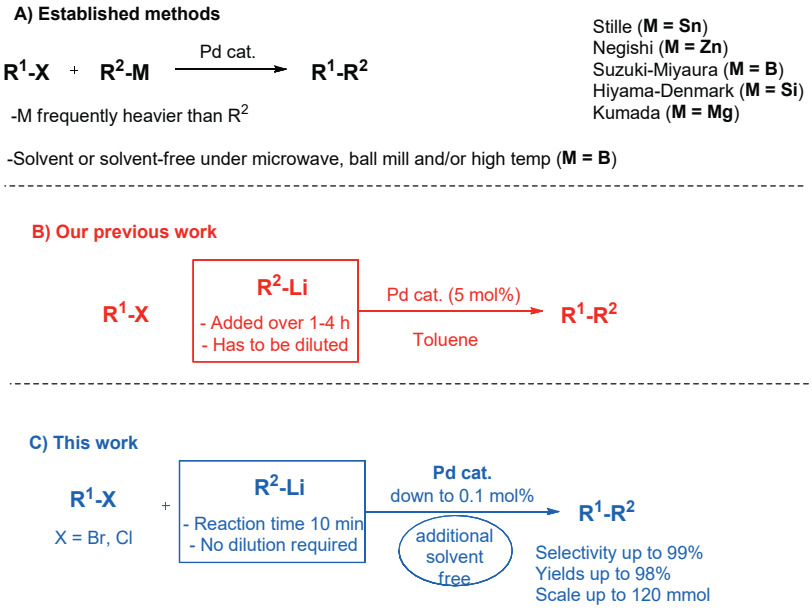
The development of greener, more efficient and simple reaction methodologies sets a priority for the synthetic chemistry community both in industry as well as in academia.[1] Solvents are mainly responsible for the environmental impact of synthetic procedures in fine chemicals and pharmaceuticals, being generally the largest contributors to the magnitude of the E factor [E = organic waste (kg)/ product (kg)]; a value introduced by Sheldon et al. in 2007 to measure the "greenness" of a chemical process.[2,3] Thus, reduction or elimination of solvents from organic reactions is of major concern in chemical process development.[4-5,6,7] Higher energy use, toxicity, safety hazards and massive waste treatment are direct implications of the use of large volumes of solvents that negatively affect both costs and environmental impact. Inspired by the 12 principles of Green Chemistry,[8] the development of sustainable production is committed to reduce or, possibly, prevent the use of traditional solvents that still, as today, represent the major share of chemical waste production in the fine chemical industry (up to 80%).

An ideal solution to the abovementioned issues is to completely exclude the solvent from the reaction medium. These so called solvent-free conditions often lead to additional improvements also in other critical parameters such as the catalytic loading (generally lower)[9,10,11,12,13], the speed of the reaction (generally higher)[14,15,16,17], and the volume/output ratio.[18,19]

A particular challenging class of transformations in this respect are the widely used transition metal-catalysed reactions. Despite the central role played by Pd-catalysed cross-coupling reactions of organometallic compounds with organo-(pseudo)halides,

both in industrial[20,21,22] and academic laboratories,[23-24,25,26] the corresponding solvent-free variants have been scarcely reported. Although boron compounds have been engaged in solvent-free cross-coupling reactions, thus far the use of microwaves,[27,28] ball mill[29,30] and/or high temperatures are required (Scheme 1A).

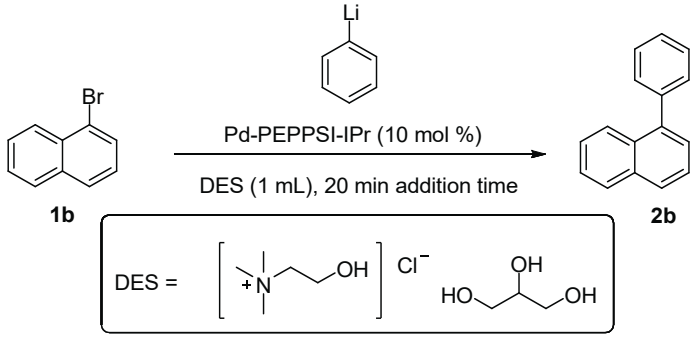
Based upon the pioneering work of Murahasi[31,32], our group has recently described methods for the palladium-catalysed direct cross-coupling of highly reactive organolithium reagents[33,34,35] (among the most versatile and widely used reagents in organic synthesis) with organic halides under mild conditions.[36-37,38,39,40,41,42,43,4431] The extreme reactivity of organometallic reagents like organolithium compounds[33] commonly dictates highly controlled conditions like low temperatures, dilution, slow addition, etc. to achieve high conversion and selectivity in their chemical transformations. In the case of Pd-catalysed cross-coupling reactions directly applying organolithium compounds, the use of toluene as a solvent and slow addition of a previously diluted solution of organolithium reagent are key factors in order to obtain high selectivity and good yields, while avoiding the notorious lithium-halogen exchange and homocoupling side reactions (Scheme 1B).[45,]



Scheme 1. A) *Established methods for Pd-catalysed cross-coupling reactions.* **B)** *Catalytic cross coupling with organolithium compounds.* **C)** *A fast, highly scalable and additional solvent free direct cross-coupling of organolithium compounds.*

However, the use of these reagents drastically reduces the amount of byproducts generated with the light and non-toxic lithium halide being the only stoichiometric waste. Inspired by the report of the group of García-Álvarez[46] on the use of deep eutectic solvents (DES, mostly obtained by mixing a quaternary ammonium salt as choline chloride with a hydrogen-bond donor such as glycerol or water) for the 1,2-addition of Grignard and organolithium reagents to ketones, we set out to explore the Pd-catalysed cross-coupling reaction of organolithium compounds and organic halides employing these fascinating solvents. Despite the high reactivity of organolithium compounds toward protic solvents, we were delighted to find that the reaction between an excess of PhLi (2-10 eq) as 2.0 M solution in dibutylether and 1-bromonaphthalene using 10 mol% of Pd catalyst in a type III DES(Choline Chloride in H_2O) proceeded with good selectivity although in low yield (28-53% conversion, see Table 1). We hypothesized that probably small droplets of substrate containing high concentration of catalyst were formed and that the reaction was taking place directly in the organic phase rather than in the DES phase. However, due to quenching of the organolithium reagent by the solvent, the conversions obtained were low. We questioned whether the innate reactivity of organolithium compounds could be turned into an inherent advantage offering the possibility to develop a low solvent Pd-catalysed cross-coupling protocol which proceeds within minutes, without the support of any additional device (microwave, ball mills, etc), with low catalytic loading and at ambient temperature without the use of strictly inert conditions. Despite the formidable challenge presented by the quest to control selectivity when mixing solutions of organolithium reagents with neat organohalides, due to the possibility for numerous competing reactions, we show here that the Pd-catalysed cross-coupling of highly polar organometallic compounds dissolved in the minimal amount of solvent, which are added directly to the solid substrate and catalyst affords the desired coupled product with excellent selectivities within 10 min and in many cases with E factors as low as 1.

Table 1 *Cross-coupling reactions in DES*



entry	PhLi (equiv.)	Magnetic stirring speed	Reaction time after addition	Conversion
1	2 eq	1200 rpm	5 min	30%
2	10 eq	1200 rpm	5 min	53%
3	2 eq	300 rpm	2 h	28%

Results and Discussion

Reaction conditions: preliminary studies and optimization

We set out to investigate the reaction between 4-methoxybromobenzene **1a**, a reluctant aryl bromide in coupling reactions,[47] and commercially available phenyllithium as 2.0 M solution in dibutylether, since successful conditions for the coupling of these two substrates would most probably apply also to a wide variety of other coupling partners (Table 2). All the reactions were carried out by adding the organolithium compound (without further dilution) to a neat stirred mixture of catalyst and organic halide over 10 min at room temperature. Moreover, we employed a 1 mmol scale to illustrate the synthetic utility of the method. Reactions using the *in situ* prepared palladium complex Pd/XPhos, (generated by mixing $Pd_2(dba)_3$ with XPhos)[48] previously reported to be effective for other Pd-catalysed cross coupling reactions with aryllithium reagents[25,26], afforded the cross coupling product within 10 min although in the presence of significant amounts of the undesired homocoupling

product (Table 2, entry 1). By employing Pd-PEPPSI-IPent catalyst,[49] the selectivity was raised to 90% at the expense of the homocoupling product (Table 2, entry 2). Nonetheless, we were delighted to find that the commercially available, air and temperature stable Pd-PEPPSI-IPr catalyst, which is seven times cheaper than Pd-PEPPSI-IPent,[50] afforded full conversion and nearly perfect selectivity (>95%, 84% isolated yield) toward the coupled product **2a** at rt in less than 10 min, avoiding the formation of dehalogenation or homocoupling side products **3** and **4** (Table 2, entry 3). Importantly, the high selectivity was maintained while lowering the catalyst loading to 1.5 mol% (Table 2, entry 4). With an efficient catalyst for Csp^2-Csp^2 cross-coupling in hand, we then turned our attention to the challenging Csp^3-Csp^2 low solvent cross-coupling with alkyllithium compounds. The direct use of commercially available *n*-BuLi, one of the most reactive organometallic reagents, in combination with Pd-PEPPSI-IPr led to the desired product **2v** although with slightly diminished selectivity (Table 2, entry 5). Further screening of catalysts showed that the use of commercially available Pd[P(*t*Bu)$_3$]$_2$[51] restored the selectivity (> 95%) toward the coupled product **2v** with excellent (82 %) isolated yield (Table 2, entry 6). Importantly, when this reaction was performed using an extremely low catalyst loading (0.1 mol %), product **2v** was still obtained with high conversion and good selectivity (Entry 7).

Table 2 *Screening of different Ligands*

Entry[a]	R	[Pd]	[Pd] (x mol %)	2a:3:4 [b]
1	Ph	$Pd_2(dba)_3$/XPhos	3	85:3:12
2	Ph	Pd-PEPPSI-IPent	3	90:2:8
3	Ph	Pd-PEPPSI-IPr	3	>95:-:-
4	Ph	Pd-PEPPSI-IPr	1.5	>95:-:-[c]
5	*n*-Bu	Pd-PEPPSI-IPr	1.5	88:2:10
6	*n*-Bu	Pd[P(*t*-Bu)$_3$]$_2$	1.5	**2v**, >95:-:-[d]
7	*n*-Bu	Pd[P(*t*-Bu)$_3$]$_2$	0.1	**2v**, 86:9:5[e]

[a]Conditions: The commercial organolithium reagent (1.2 mmol in corresponding commercial concentration) was added to a mixture of **1a** *(1 mmol) and palladium catalyst over 10 min.* [b] **2a:3:4** *ratio's determined by GC analysis. dba = dibenzylideneacetone.* [c]*84% yield.* [d]*82% yield.* [e] *91% conversion.*

Scope and applicability

To our delight the optimized conditions proved to be general and could be applied successfully to the low solvent cross-coupling of a variety of aryllithium (**2a-2u**) and the even more reactive alkyllithium reagents (**2v-2af**), in all cases affording the products with high selectivity within minutes (Table 3). The remarkably fast cross-coupling methodology gave also excellent results in combination with non-commercially available aryllithium reagents obtained through common preparative procedures such as lithium/halogen exchange (**2f-2h**) and *ortho*-directed lithiation. Illustrative is the case of the highly hindered bis-*ortho*-substituted 2,6-dimethoxy-phenyllithium, used in the synthesis of compounds **2i**-**2k,** that was prepared by direct metalation of 1,3-dimethoxybenzene using THF. In all cases, the organolithium reagents were prepared using the minimal amount of ethereal solvent to maintain them soluble. Despite the higher reactivity and basicity of alkyllithium reagents when compared with (hetero)aryllithium compounds, we were delighted to find high selectivities and yields also for a variety of Csp^3-Csp^2 cross coupling products. This includes the use of different alkyllithium compounds as *n*-BuLi, *n*-HexLi as well as the smallest MeLi with electron-rich and electron-poor arylbromides (Table 3, **2v**-**2ad**). The bifunctional C(sp^3)-(trimethylsilyl)methyllithium reagent[28] also couples with excellent selectivity providing synthetically versatile benzylsilanes **2ae** and **2af**. A limitation so far for this protocol employing the Pd[P(*t*-Bu)$_3$]$_2$ based catalytic system is that use of secondary alkyllithium reagents such as *i*-PrLi and *s*-BuLi leads to the formation of dehalogenation products.

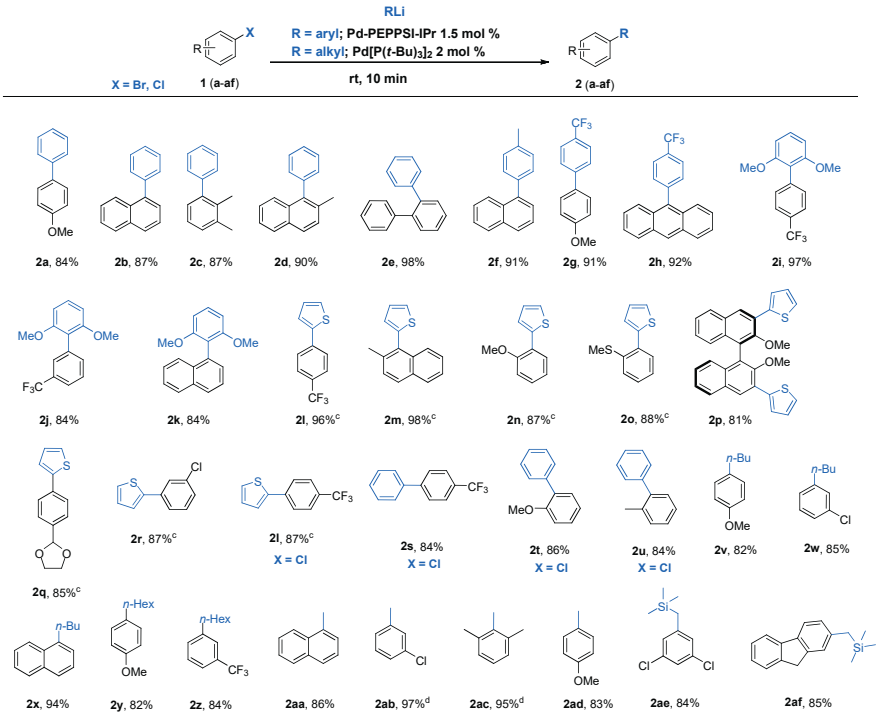
Despite the conditions of highly concentrated reaction partners, various observations highlight how the reaction proceeds exclusively under catalyst control. Thus, the reaction of 1-bromonaphthalene **1b** resulted, with both aryl- and alkyllithium, in the corresponding coupled products (**2b, 2k, 2x** and **2aa**) without the formation of regioisomers indicating that benzyne intermediates via 1,2-elimination are not formed. Apart from liquid substrates even solid bromofluorene **1af** was successfully employed, despite the acidity of the benzylic protons (pK_a = 22). The reaction of *n*-BuLi and MeLi with *p*-chloro-bromobenzene occurs selectively with no detectable chloride displacement (Table 3, compounds **2w** and **2ab**).

Sterically hindered bromides **1c**-**1e**, known for being more reluctant substrates in the synthesis of biaryls[23], were also successfully coupled at room temperature in 10 min indicating that the transmetallation step takes place rapidly, under these conditions, inducing a fast coupling process.

The dramatic effect of the low solvent conditions in enhancing the reaction-rate was demonstrated in the coupling of commercially available 2-thienyllithium which, according to our previous observations, required the addition of stoichiometric amounts of tetramethylethylenediamine (TMEDA) as activating agent and elevated temperatures (40 °C) to react.[22] Under additional solvent-free conditions 2-thienyllithium reacted smoothly at room temperature within 10 min, in high selectivity and yield, without the use of any additive (**2l**-**2r**). We have recently shown that the cross-coupling of 2-alkoxy-substituted arylbromides with organolithium is plagued by fast bromine-lithium exchange induced by the ortho-directing alkoxy unit. The use of the corresponding aryl chlorides, inherently less prone to halogen/lithium exchange, is thus mandatory to afford selectively the product and prevent side products formation.[27] However, to our surprise, under our additional solvent-free protocol, aryl bromides **1n**, **1o** and 3,3'-dibromo-BINOL **1p**, could all be coupled successfully with 2-thienyllithium in high selectivity (>95%) and with excellent yield avoiding the notorious bromine-halogen exchange (Table 3). To emphasize the versatility of the new method, it has to be noted that the only previous reported synthesis of BINOL derivate **2p** required the preparation of the corresponding bis-trifluoroboronate BINOL derivate and further reaction with 2-bromothiophene under microwave conditions.[52] The use of acetal-protected aldehyde **1q** was also tolerated without the cleavage of the protecting group. As in the case of alkyllithium compounds 1-bromo-3-chlorobenzene **1r** reacted with 2-thienyllithium using Pd-PEPPSI-IPr catalyst selectively, leaving the chloride untouched. Nevertheless the electron-poor aryl chloride **1l** reacted readily with 2-thienyllithium, and electron-rich chlorides-**1t** and **1u** were also easily coupled under the optimized conditions using more reactive PhLi at room temperature (Table 3).

A major issue often associated with solvent-free reactions is the homogeneity of the reaction medium, in particular with solid starting materials. However, the methodology presented here provides high selectivity and yields when solid substrates such as **1h**, **1p**, **1q**, **1ae** and **1af** were used in combination with concentrated solutions of aryllithium and $TMSCH_2Li$ compounds. We hereby note that the solids are stirred for a small amount of time prior to the addition of the concentrated organolithium solution, approximately 1 min, to ensure dispersion of the solid catalyst in the solid starting material.

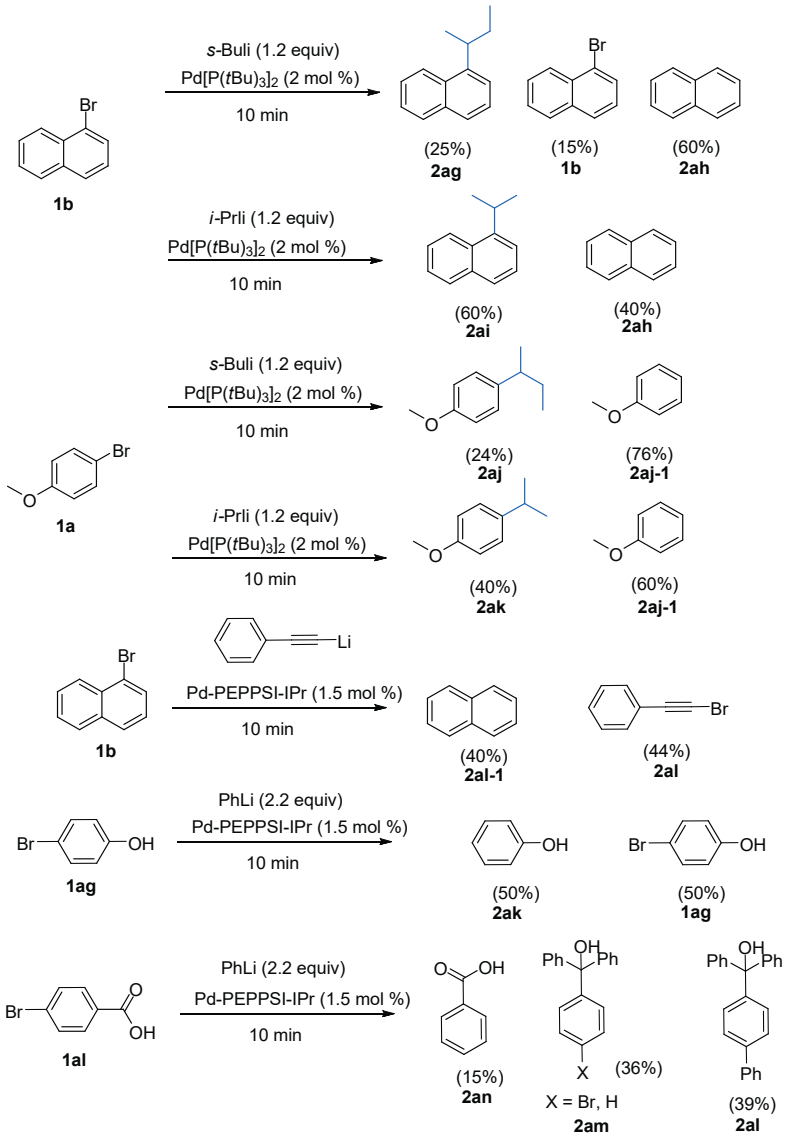
Table 3. *Pd-Catalysed cross-coupling of organolithium reagents with aryl halides under low solvent conditions*[a,b].



[a]*Conditions: RLi (1.2 mmol) was added to a mixture of organic bromide (1 mmol) and catalyst over 10 min. X = Br unless otherwise noted (2l,12,2t,2u X=Cl). Selectivity 2:3,4 >95%. Compounds* **2** *were extracted with* Et_2O *or AcOEt, after quenching the reaction mixture with minimum amount of sat. aq.* NH_4Cl. [b] *All yields given are isolated yields.* [c]*3 mol % of catalyst was employed for the reaction with 2-thienyllithium.* [d]*GC yield: product was not isolated due to volatility issues.*

The highly reactive nature of organolithium reagents, in combination with the implicitly high concentration of the low solvent reaction conditions presented in this chapter comes, however, with some obvious limitations. In the cases where the halogenated substrate is a solid, proper stirring becomes crucial towards obtaining full conversion. Lack of sufficient stirring yields inconsistent results regarding conversion of the reaction. In these cases, even the use of *n*-HexLi- and *n*-BuLi yields substantial reduction of the halogenated starting material. The use of highly sterically hindered alkyl lithium reagents under these conditions often yields a combination of product and dehalogened substrate (Table 4, substrate **1a**, **1b**). Finally, the presence of unprotected OH functionalities leads to side reactions in the form of deprotonation or 1,2-addition (in the case of acid functionalities, **1ah**).

Table 4. *Pd-Catalysed cross-coupling of organolithium reagents; limitations*

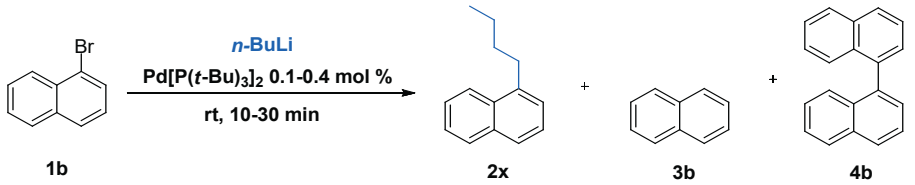


[a]Conditions: RLi (1.2 mmol, 1.6M) was added to a mixture of organic bromide (1 mmol) and catalyst over 10 min. Compounds 2 were extracted with Et2O or AcOEt, after quenching the reaction mixture with minimum amount of sat. aq. NH4Cl. All yields given in brackets are GC-conversion: product was not isolated due to low conversion.

Scalability of the low solvent Pd-Catalysed direct Cross-Coupling of organolithium reagents

In organic chemistry, problems in the scaling up of batch reactions have been known to arise from various issues including inefficient mixing and lack of heat transfer. To test if this novel method is suitable to be performed on larger-scale, the cross-coupling between *n*-BuLi and 1-bromonaphthalene **1b** was tested on multigram scale with catalyst loading as low as 0.1 mol %. We were pleased to find that the scale of the reaction had little effect on the selectivity although the presence of a small amount of dehalogenated side product was observed (Table 5). It is noteworthy that the cross-coupling was found to maintain its effectiveness even at 120 mmol scale employing 0.4 mol % of catalyst providing exceptional E factors as low as 0.8 (Table 5, entry 3). It should be emphasized that typical E factors in the range of 5-100 are seen in transformations producing fine-chemicals and pharmaceuticals.[2] Importantly, after the addition of the organolithium compound, the crude product was quenched, washed with water, and dried, giving the desired product in reagent grade quality within 60 min, including all the operations.

Table 5 *Catalyst loading effect for the cross-coupling of 1-bromonaphthalene with n-BuLi*

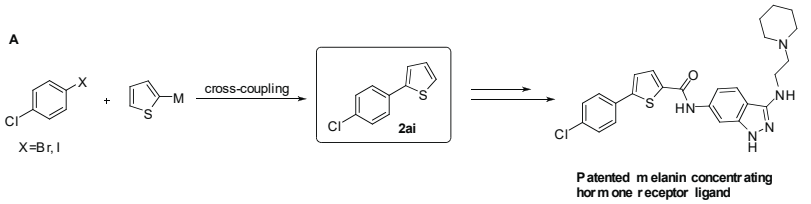


Entry	ArBr	[Pd]	Reaction time (min)
1	5 mmol (1.03 g)	0.4 mol % (11 mg)	20
2	10 mmol (2.05 g)	0.1 mol % (7 mg)	20
3	120 mmol (27 g)	0.4 mol % (250 mg)	30

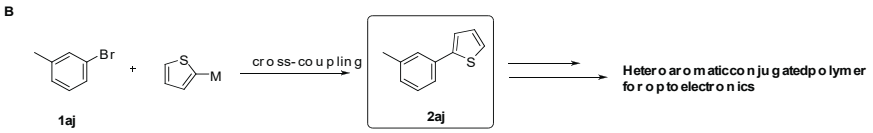
[a]*Conditions: n-BuLi (as X1.6 M solution in hexane) was added to a mixture of* **1b** *and* $Pd[P(t\text{-}Bu)_3]_2$ *over 20-30 min.*
[b]**2x:3b:4b** *ratios determined by GC analysis and* ^1H *NMR.* [c]**2x***: 19.9 g, 90% isolated yield.*

Potential of the methodology in synthetic application

To demonstrate the advantages of the new method, we have compared it with some established cross-coupling methodologies currently used in the production of two typical building blocks for pharmaceuticals and conjugated polymers for light emitting devices. The first example deals with the preparation of a key intermediate (2ai) for the synthesis of a patented melanin concentrating hormone (MCHs) receptor ligand (Scheme 2) involved in the treatment of eating disorders, weight gain, obesity, depression and anxiety. The reaction between 1-bromo-4-chlorobenzene 1ai and 2-thienyllithium under the optimized reaction conditions provided the cross-coupling product 2ai in high yield and selectivity within 10 min at RT (E factor: 4.7). In sharp contrast, the reported procedure (E factor: 41) involves the corresponding thienylboronic acid, needs a mixture of DME/H_2O heated at reflux for 4 h, 2 eq of base and requires the corresponding highly reactive aryl iodide. The second example illustrates the synthesis of a heteroaromatic monomer employed in the preparation of polymeric materials for optoelectronic devices. Coupling between 2-thienyllithium and 3-methyl-1-bromobenzene 1aj gives access to the desired compound 2aj, at room temperature, in very good yield within 10 min and with an E factor 5 times lower than in the reported synthetic methodology (110 °C, 10 h in toluene using an organotin compounds with a molecular weight 4 times higher that 2-thienyllithium). In the last example, in addition to the remarkable differences in reaction time (10 min vs. 600 min) and temperature (20 °C vs 110 °C), the use of additional solvent-free cross-coupling of 2-thienyllithium also avoids potentially toxic tin wastes and their often difficult removal, and prevents the use of strictly inert atmosphere required for the coupling of the corresponding tin reagent.



LITERATURE	THIS WORK
M: $B(OH)_2$ (MW: 44.8)	M: Li (AW: 6.94)
X = I	X = Br
$Pd(PPh_3)_2$ 5 mol%, Na_2CO_3 2.1 eq	Pd-PEPPSI-IPr 3 mol%
DME/H_2O 1:1, reflux.	Low solvent, room temperature
Reaction time: 4 h	Reaction time: 10 min
Yield: 80%	Yield: 94%
E factor: 41	E factor: 4.7



LITERATURE	THIS WORK
M: Li (AW: 6.94) (1.1 eq)	M: $SnBu_3$ (MW: 290.06) (1 eq)
Pd-PEPPSI-IPr 3 mol%	$Pd(PPh_3)_4$ (1.8 mol%).
Additional solvent free, room temperature, under air	Toluene, 110 °C under Argon
Reaction time: 10 min	Reaction time: 10 h
Yield: 84%	Yield: 95%
E factor: 8.3	E factor: 43

Scheme 2. Comparison between established methods and the present cross coupling protocol with organolithium reagents in the synthesis of key intermediates for a melanin concentrating hormone receptor ligand (A) and conjugated polymer for optoelectronic devices (B).

Conclusions

We have discovered that, in sharp contrast to all common reaction protocols using highly reactive organometallics like organolithium compounds, the Pd-catalysed cross coupling of arylbromides and alkyl- or aryllithium reagents under low solvent conditions proceeds exceptionally fast and selective. Based on this finding we have developed general low solvent methodology for the Pd-catalysed direct cross-coupling of organolithium compounds with organic halides, under ambient conditions providing high yields and excellent selectivities. Fast reaction times (10 min), lower catalyst loading (down to 0.1 mol %), high scalability, operational simplicity (see methods) and the possibility to avoid the use of a strictly inert atmosphere, of syringe pumps and of additives such as TMEDA are key feature of this methodology. Compared to reported Pd-catalysed cross-coupling, this methodology is particularly attractive due to the strongly reduced environmental impact i.e. outstanding volume-time-output ratio, limited amount and low toxicity of the waste and 5 to 10 fold reduction in E-factor. The use of stable and commercially available catalysts, commercial or readily available and inexpensive organolithium reagents and the applicability to a wide variety of organic bromides are additional factors that contribute to the prospect of these C-C bond formations in the art of synthesis.

General methods

Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by UV and cerium/molybdenum or potassium permanganate staining. Progress and conversion of the reaction were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). ^{1}H- and ^{13}C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. All reactions were carried out under a nitrogen atmosphere. THF and Et_2O were dried and distilled over sodium. $Pd[P(t\text{-}Bu)_3]_2$, was purchased from Strem, $Pd_2(dba)_3$, XPhos, Pd-PEPPSI-*i*Pr and Pd-PEPPSI-*i*Pent were purchased from Aldrich and used without further purification. *n*-BuLi (1.6 M solution in hexane) was purchased from Acros. PhLi (1.8 M solution in dibutylether), MeLi (1.6 M in diethylether), $TMSCH_2Li$ (1.0 M in pentane), *n*-HexLi (2.3 M in hexane), 2-thienylLi (1.0 M in THF/hexane), and the compounds used as precursor for the preparation of lithium reagents, namely 1-bromo-2,6-dimethoxy-benzene, 1-bromo-4-methylbenzene and 1-bromo-4-(trifluoromethyl) benzene were purchased from Aldrich. All the bromides were commercially available and were purchased from Aldrich, TCI Europe N.V. and Acros Organics. *p*-tolyllithium, (4-(trifluoromethyl)phenyl)lithium and (2,6-dimethoxyphenyl) lithium were prepared according to described procedures.[22,23,25,53] E factors were calculated according to the procedure reported by Lipshutz *et al.*[3]

General procedure (A) for the cross-coupling with (hetero)aryllithium reagents

The corresponding commercially available or homemade (hetero)aryllithium reagent as an 2.0 M solution in hexane was added over a stirred mixture of substrate (1 mmol) and Pd-PEPPSI-*i*Pr (1.5 mol %, 10.5 mg) at room temperature for 10 min. After the addition was completed a saturated solution of aqueous NH_4Cl was added and the mixture was extracted with Et_2O. The organic phases were combined and dried with anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude product that was then filtered over a silica gel plug.

General procedure (B) for the cross-coupling with (hetero)aryllithium reagents

The corresponding commercially available or homemade thionyllithium reagent as 1.0 M solution inTHF/hexane was added over a stirred mixture of substrate (1 mmol) and Pd-PEPPSI-*i*Pr (3 mol %, 20 mg) at room temperature for 10 min. After the addition was completed a saturated solution of aqueous NH_4Cl was added and the mixture was extracted with Et_2O. The organic phases were combined and dried with anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude product that was then filtered over a silica gel plug.

General procedure (C) for the cross-coupling with alkyllithium reagents

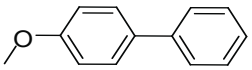
The corresponding commercially available alkyllithium reagent as 1.6 M solution in hexane was added over a stirred mixture of substrate (1 mmol) and $Pd[P(t\text{-}Bu)_3]_2$ (2 mol%, 10 mg) at room temperature for 10 min. After the addition was completed a saturated solution of aqueous NH_4Cl was added and the mixture was extracted with Et_2O. The organic phases were combined and dried with anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude product that was then filtered over a silica gel plug.

Reactions carried out in 120 mmol scale

Commercially available *n*-BuLi (100 mL, 1.6 M solution in hexane) was added via cannula over a mixture of substrate (120 mmol, 27 g) and $Pd[P(t\text{-}Bu)_3]_2$ (0.4 mol%, 250 mg) at room temperature for 30 min, keeping the temperature between 20-25 °C with the use of an additional water bath. After the addition was completed, water was slowly added and the mixture was extracted with Et_2O. The organic phase were combined and dried with anhydrous Na_2SO_4 and solvent was removed under reduced pressure affording the final product in reagent grade quality.

Note 1: The transformations described here have been performed under N_2 atmosphere. However, we have repeated the synthesis (e.g. compound **2m**) keeping the Schlenk flask open to the air and a similar selectivity (>99%) and isolated yield (95%) was obtained.

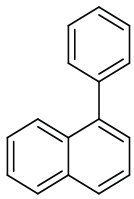
Spectral data of compounds 2a-2ah:4-Methoxybiphenyl (2a): [41]



CAS Registry Number: 613-37-6.
Synthesized using catalytic system A with 1-bromo-4-methoxybenzene (1 mmol, 187 mg) and 798 μL of PhLi as 2.0 M sol. in dibutylether.

Catalytic system A: Reaction carried out at room temperature. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 155 mg, 84% yield. White solid; M.p. = 88-89 ºC; ^1H NMR (300 MHz, $CDCl_3$): δ 7.55-7.28 (m, 7H), 6.96 (d, 2H, J = 9.1 Hz), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 140.9, 133.9, 128.8, 128.3, 126.8, 126.7, 114.3, 55.4 MS (m/z, %): 184 (M+ , 100), 169 (M+ -15, 44), 141 (37), 139 (10), 115 (30).

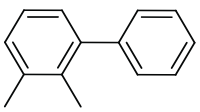
1-Phenylnaphthalene (2b):[54]



CAS Registry Number: 605-02-7
Synthesized using catalytic system A with 1-bromonaphthalene (1 mmol, 207 mg) and 798 μL of PhLi as 2.0 M sol. in dibutylether.

Catalytic system A: Reaction carried out at room temperature. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/Et_2O 100:1), 178 mg, 87% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 7.90-7.81 (m, 3H), 7.51-7.36 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.9, 140.4, 134.0, 131.8, 130.2, 128.4, 127.7, 127.3, 127.0, 126.1, 125.9, 125.5. HRMS (APCI+, *m/z*): calc. C16H12 (M+): 204.0939. Found: 204.0933.

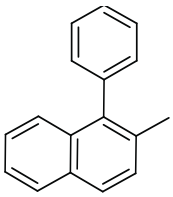
2,3-Dimethyl-1,1'-biphenyl (2c):[55]



CAS Registry Number: 3864-18-4
Synthesized using catalytic system A 1-bromo-2,3-dimethylbenzene (1 mmol, 185 mg) and 798 μL of PhLi as 2.0 M sol. in dibutylether.

Catalytic system A: Reaction carried out at room temperature. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/Et_2O 100:1), 159 mg, 87% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH3), 2.32 (s, 3H, CH3), 7.20 (d, J = 8.0 Hz, 1H, Ar), 7.29-7.34 (m, 2H, Ar), 7.37-7.43 (m, 3H, Ar), 7.56-7.58 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 19.9, 124.5, 126.9, 127.0, 128.4, 128.6, 130.0, 135.7, 136.9, 138.8, 141.2.

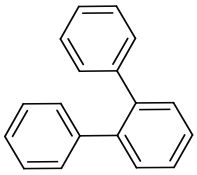
2-Methyl-1-phenylnaphthalene (2d):[56]



CAS Registry Number: 29304-63-0

Catalytic system A: Synthesized using catalytic system A with 1-bromo-2-methylnaphthalene (1 mmol, 221 mg) and 798 μL of PhLi as 2.0 M sol. in dibutylether. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 196 mg, 90% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.50-7.45 (m, 2H), 7.43-7.36 (m, 4H), 7.32-7.24 (m, 3H), 2.22 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 139.8, 138.1, 133.1, 132.9, 131.9, 130.1, 128.6, 128.4, 127.7, 127.2, 127.0, 126.1, 125.8, 124.7, 20.8.

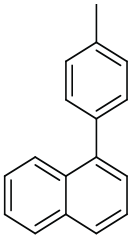
1,1′:2′,1″-Terphenyl (2e):[57]



CAS Registry Number: 84-15-1

Catalytic system A: Synthesized using catalytic system A with 2-bromo-1:1′-biphenyl (1 mmol, 233 mg) and 798 μL of PhLi as 2.0 M sol. in dibutylether. Colorless oil obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 225 mg, 98% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 7.46–7.33 (m, 4 H), 7.22–7.01 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.5, 140.5, 130.6, 129.9, 127.8, 127.4, 126.4.

1-(p-Tolyl)naphthalene (2f):[6]

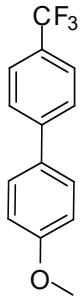


CAS Registry Number: 27331-34-6

Catalytic system A: Synthesized using catalytic system A with 1-bromonaphthalene (1 mmol, 207 mg) and 2394 μL of *p*-tolyllithium (0.6 M solution in diethylether).

White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 198 mg, 91% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.96-7.81 (m, 3H), 7.54-7.36 (m, 6H), 7.29 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 137.9, 137.0, 133.9, 131.8, 130.1, 129.1, 128.4, 127.6, 127.0, 126.2, 126.1, 125.8, 125.5, 21.3.

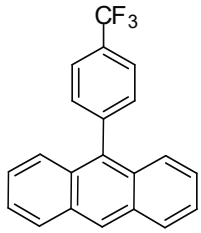
4-Methoxy-4'-(trifluoromethyl)-1,1'-biphenylphenyl (2g):[8]



CAS Registry Number: 10355-12-1

Catalytic system A: Synthesized using catalytic system A with 1-bromo-4-methoxybenzene (1 mmol, 187 mg) and 2394 μL of *p*-trifluoromethylphenyllithium (0.6 M solution in diethylether). Off white solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 229 mg, 91% yield. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.70-7.62 (br s, 4H), 7.55(md, J = 9.1 Hz, 2H), 7.01 (md, J = 9.1 Hz, 2H), 3.87 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 159.8, 144.3, 132.0, 128.7 (q, J = 32.4 Hz), 128.5, 127.2, 125.6 (q, J = 3.8 Hz), 124.7 (q, J = 272.2 Hz), 114.4, 55.4. ^{19}F-NMR (282 MHz, $CDCl_3$): -62.73

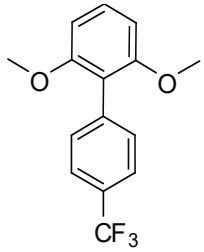
9-(4-(Trifluoromethyl)phenyl)anthracene (2h):[58]



CAS Registry Number: 386-23-2

Catalytic system A: Synthesized using catalytic system A with 9-bromoanthracene (1 mmol, 257 mg) and 2394 μL of *p*-trifluoromethylphenyllithium (0.6 M solution in diethylether). Yellow solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 305 mg, 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.04 (d, *J* = 7.7 Hz, 2H), 7.84 (d, *J* = 7.8 Hz, 2H), 7.57–7.53 (m, 4H), 7.27–7.21 (m, 2H), 7.13 (ddd, *J* = 8.7,6.5, 1.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.83, 135.11, 131.68, 131.26, 129.92, 128.46, 127.25, 126.67, 126.19, 125.79, 125.40, 125.23.

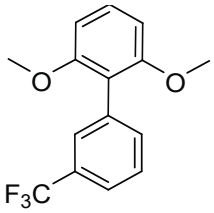
2,6-Dimethoxy-4'-(trifluoromethyl)-1,1'-biphenylphenyl (2i):[59]



CAS Registry Number: 603112-21-6

Catalytic system A: Synthesized using catalytic system A with 1-bromo-4-(trifluoromethyl)benzene (1 mmol, 225 mg) and 2394 μL of 2,3-dimethoxy-phenyllithium (0.6 M solution in diethylether). White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 274 mg, 97% yield. ^{1}H NMR (200 MHz, $CHCl_3$): δ 3.76 (s, 6H), 6.68 (d, J = 8.3 Hz, 2H), 7.38 (t, J = 8.3 Hz, 1H), 7.48 (d, J= 8.0 Hz, 2H), 7.66 (d, 3 J= 8.3 Hz, 2H);^{13}C NMR (75 MHz, $CHCl_3$): δ 55.8, 104.2, 118.0, 124.5, 124.5 (q, J=270 Hz), 127.9, 129.4, 131.4, 138.1, 157.5

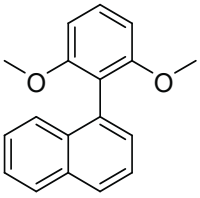
2,6-Dimethoxy-3′-(trifluoromethyl)-1,1′-biphenylphenyl (2j):[60]



CAS Registry Number: 603112-20-5

Catalytic system A: Synthesized using catalytic system A with 1-bromo-3-(trifluoromethyl)benzene (1 mmol, 225 mg) and 2394 μL of 2,3-dimethoxy-phenyllithium (0.6 M solution in diethylether). White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 237 mg, 84% yield. ^1H NMR (200 MHz, $CHCl_3$): δ 3.81 (s, 6H), 6.73 (d, J= 8.3 Hz, 2H), 7.34 (t, J=8.4 Hz, 1H), 7.51 - 7.78 (m, 4H); ^{13}C NMR (75 MHz, $CHCl_3$): δ 56.3, 104.6, 118.3, 124.0, 125.0 (q, J= 270 Hz), 128.5, 129.8, 130.0, 130.7, 134.9, 135.3, 157.9

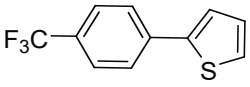
1-(2,6-Dimethoxyphenyl)naphthalene (2k):[29]



CAS Registry Number: 173300-93-1

Catalytic system A: Synthesized using catalytic system A with 1-bromonaphthalene (1 mmol, 207 mg) and 2394 μL of of 2,3-dimethoxy-phenyllithium (0.6 M solution in diethylether). White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 222 mg, 84% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (m, 2H), 7.58 (dd, J = 8.2, 7.0 Hz, 1H), 7.55-7.34 (m, 5H), 6.75 (d, J = 8.2 Hz, 2H), 3.66 (s, 6H). ^{13}C NMR (101MHz, $CDCl_3$): δ 158.4, 133.5, 132.7, 132.6, 129.1, 128.2, 128.0, 127.4, 126.0, 125.5, 125.4, 125.34, 117.6, 104.1, 55.9.

2-(4-(Trifluoromethyl)phenyl)thiophene (2l):[63]

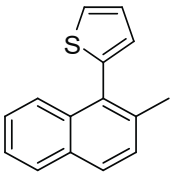


CAS Registry Number: 115933-15-8.

Catalytic system B: Synthesized using catalytic systems B with 1-bromo-4-(trifluoromethyl)benzene (1 mmol, 225 mg) and 1200 μL of 2-thienyllithium. White solid obtained after column chromatography (SiO_2, *n*-pentane/ EtOAc 100:1), 219 mg, 96% yield.

^1H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 8.3 Hz, 2 H), 7.65 (d, J = 8.2 Hz, 2 H), 7.54 (s, 1 H), 7.45-7.39 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.02, 139.31, 129.19 (q, J F = 32.5 Hz), 126.96, 126.72, 126.29, 125.93 (q, J F = 3.8 Hz), 124.38 (q, J F = 270.0 Hz), 121.96. ^{19}F NMR (471 MHz, $CDCl_3$): δ -62.44

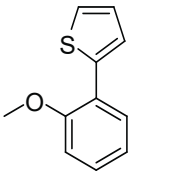
1-(2-Methylnaphthalen-1-yl)thiophene (2m):[61]



CAS Registry Number: 1064187-66-1

Catalytic system B: Synthesized using catalytic system B with 2-methyl-1-bromonaphthalene (1 mmol, 221 mg) and 1200 μL of 2-thienyllithium as 1.0 M sol. in THF/hexane. Colorless oil obtained after filtration over a silica plug (SiO_2, *n*-pentane), 220 mg, 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.311 (s, 3H), 6.94 (dd, J) 3.4 Hz, 1.2 Hz, 1H), 7.15 (dd, J) 5.1 Hz, 3.4 Hz, 1H), 7.31-7.37 (m, 3H), 7.41 (dd, J) 5.1 Hz, 1.2 Hz, 1H), 7.58-7.61 (m, 1H), 7.74 (d, J) 8.0 Hz, 1H), 7.77 (dd, J) 6.0 Hz, 2.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 125.6, 126.5, 126.9, 127.8, 128.3, 128.4, 128.8, 129.0, 130.9, 132.5, 134.8, 136.6, 140.7

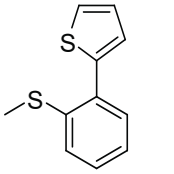
2-(2-Methoxyphenyl)thiophene (2n):[62]



CAS Registry Number: 17595-92-5

Catalytic system B: Synthesized using catalytic system B with 1-bromo-2-methoxybenzene (1 mmol, 187 mg) and 1200 μL of 2-thienyllithium as 1.0 M sol. in THF/hexane. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 165 mg, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (dd, J = 7.8 and 1.1 Hz, 1H), 7.50 (dd, J = 3.7 and 1.1 Hz, 1H), 7.32 (dd, J = 5.3 and 1.1 Hz, 1H), 7.26 (dt, J = 7.8 and 1.1 Hz, 1H), 7.09 (dd, J = 5.3 and 3.7 Hz, 1H), 7.00 (t, J = 7.8 Hz, 2H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 155.53, 139.41, 128.53, 128.30, 126.72, 125.35, 125.29, 123.27, 120.86, 111.54, 55.47.

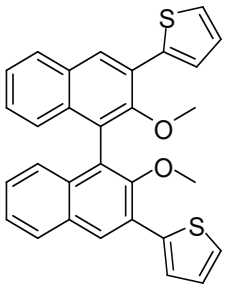
2-(2-(Methylthio)phenyl)thiophene (2o):



Synthesized using catalytic system B with (2-bromophenyl)(methyl) sulfane (1 mmol, 202 mg) and 1200 μL of 2-thienyllithium as 1.0 M sol. in THF/hexane. Yellow oil obtained after column chromatography (SiO_2, *n*-pentane/EtOAc 100:1), 88% yield.

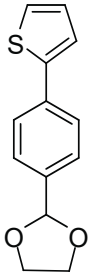
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (q, *J* = 5.9, 5.1 Hz, 2H), 7.41 – 7.29 (m, 3H), 7.24 (t, *J* = 7.1 Hz, 1H), 7.20 – 7.14 (m, 1H), 2.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.29, 138.07, 133.24, 130.95, 128.43, 127.58, 127.09, 125.90, 125.61, 124.76, 16.17.

2,2′-(2,2′-Dimethoxy-[1,1′-binaphthalene]-3,3′-diyl)dithiophene (2p):



Synthesized using catalytic system B with 3,3′-dibromo-2,2′-dimethoxy-1,1′-binaphthalene (1 mmol, 472 mg) and 2400 µL of 2-thienyllithium as 1.0 M sol. in THF/hexane. Yellow solid obtained after column chromatography (SiO_2, *n*-pentane/EtOAc 100:1), 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 2H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 3.5 Hz, 2H), 7.40 (q, *J* = 4.9, 4.3 Hz, 4H), 7.24 (t, *J* = 7.1 Hz, 3H), 7.16 (dd, *J* = 9.7, 6.1 Hz, 4H), 3.34 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.32, 139.55, 133.48, 130.71, 128.72, 128.06, 127.96, 127.23, 126.48, 126.31, 126.26, 125.86, 125.72, 125.29, 60.49. HRMS (APCI+, *m*/*z*): calculated for $C_{30}H_{23}O_2S_2$ [M+H$^+$]: 479.11395; found: 479.11182.

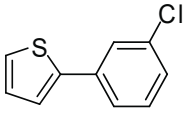
2-(4-(Thiophen-2-yl)phenyl)-1,3-dioxolane (2q):[16]



CAS Registry Number: 81707-47-3

Catalytic system B: Synthesized using catalytic system B with 2-bromo-4-phenyl)-1,3-dioxolane (1 mmol, 229 mg) and 1200 µL of 2-thienyllithium as 1.0 M sol. in THF/hexane. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 197 mg, 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 – 7.56 (m, 2H), 7.47 (dd, *J* = 8.3, 2.4 Hz, 2H), 7.39 – 7.20 (m, 2H), 7.07 (dd, *J* = 5.2, 3.4 Hz, 1H), 4.21 – 3.95 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.02, 128.00, 126.99, 125.87, 125.04, 123.38, 103.42, 65.29

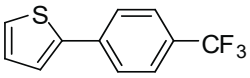
2-(3-Chlorophenyl)thiophene (2r):[63]



CAS Registry Number: 59156-10-4

Catalytic system B: Synthesized using catalytic system B with 1-bromo-3-chlorobenzene (1 mmol, 191 mg) and 1200 µL of 2-thienyllithium as 1.0 M sol. in THF/hexane. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 169 mg, 87% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.00-7.59 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.69, 136.08, 134.71, 130.08, 128.11, 125.82, 124.31, 123.72

2-(4-(Trifluoromethyl)phenyl)thiophene (2l):[43]

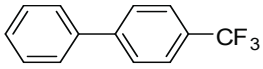


CAS Registry Number: 115933-15-8

Catalytic system B: Synthesized using catalytic system B with 1-chloro-4-(trifluoromethyl)benzene (1 mmol, 180 mg) and 1200 μL of 2-thienyllithium as 1.0 M sol. in THF/hexane. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 198 mg, 87% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.73 (m, 2 H), 7.61-7.65 (m, 2 H), 7.40 (dd, J = 3.6 Hz, J = 1.1 Hz, 1 H), 7.37 (dd, 3 J = 5.1 Hz, 4 J = 1.1 Hz, 1 H), 7.12 (dd, J = 5.1 Hz, J = 3.6 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 142.7, S-5 137.9, 129.3 (q, 1 JCF = 32.5 Hz), 128.5, 126.4, 126.1, 126.0 (q, J = 3.8 Hz), 124.6; ^{19}F NMR (471 MHz, $CDCl_3$): δ –62.5.

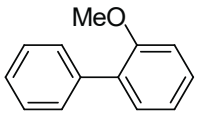
4-(Trifluoromethyl)-1,1′-biphenyl (2s):[64]



CAS Registry Number: 398-36-7

Catalytic system A: Synthesized using catalytic system A with 1-chloro-4-(trifluoromethyl)benzene (1 mmol, 180 mg) and 798 μL of PhLi as 2.0 M sol. in dibutylether. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 187 mg, 84% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 4 H), 7.61 (d, J = 7.3 Hz, 2 H), 7.48 (t, J = 7.6 Hz, 2 H), 7.42 (t, J = 7.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.87, 139.92, 129.48 (q, J = 32.5 Hz), 129.13, 128.32, 127.56, 127.42, 125.83 (q, J = 3.8 Hz), 124.46 (q, J = 270.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ -62.39.

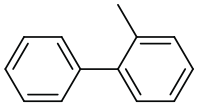
2-(Methoxy)-1,1′-biphenyl (2t):[65]



CAS Registry Number: 86-26-0

Catalytic system A: Synthesized using catalytic system A with 1-chloro-2-methoxybenzene (1 mmol, 142 mg) and 798 μL of PhLi as 2.0 M sol. in dibutylether. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 155 mg, 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80, 6.83- 7.20 (m, 2 H), 7.26-7.58 (m, 7H); ^{1}H NMR (75 MHz, $CDCl_3$): δ 56.2, 121.7, 125.6, 127.9, 128.7, 128.7, 128.9, 129.4, 136.5, 157.8

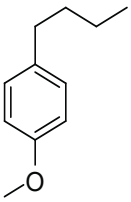
2-(Methyl)-1,1'-biphenyl (2u):[66]



CAS Registry Number: 643-58-3

Catalytic system A: Synthesized using catalytic system A with 2-chloro-toluene (1 mmol, 126 mg) and 798 μL of PhLi as 2.0 M sol. in dibutylether. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 141 mg, 84% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3 H), 7.18-7.39 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 125.3, 127.6, 128.2, 128.4, 128.5, 129.3, 129.7, 133.7, 136.5, 137.2

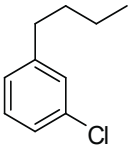
1-Butyl-4-methoxybenzene (2v).[13]



CAS Registry Number: 18272-84-9

Catalytic system C: Synthesized using catalytic systems C with 1-bromo-4-methoxybenzene (1 mmol, 187 mg) and 750 μL of *n*-butyllithium 1.6 M in hexane. Colorless oil obtained after filtration over a silica plug (SiO_2, *n*-pentane), 135 mg, 82% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, J = 7.6 Hz, 3 H), 1.34 (sext., J = 7.6 Hz, 2 H), 1.58 (quint., J = 7.6 Hz, 2 H), 2.56 (t, J = 7.6 Hz, 2 H), 3.79 (s, 3 H), 6.83 (d, J = 8.7 Hz, 2 H), 7.11 (d, J = 8.7 Hz, 2 H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 135.1, 129.6, 113.2, 55.4, 35.2, 31.4, 22.7, 14.1

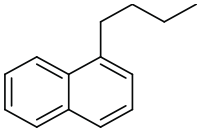
1-Butyl-3-chlorobenzene (2w).[67]



CAS Registry Number: 15499-28-2

Catalytic system C: Synthesized using catalytic systems C with 1-bromo-3-chlorobenzene (1 mmol, 191 mg) and 750 μL of *n*-butyllithium 1.6 M in hexane. Colorless oil obtained after filtration over a silica plug (SiO_2, *n*-pentane), 144 mg, 85% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, J = 7.6 Hz, 3 H), 1.34 (sext., J = 7.6 Hz, 2 H), 1.58 (quint., J = 7.6 Hz, 2 H), 2.56 (t, J = 7.6 Hz, 2 H), 6.83 (d, J = 8.7 Hz, 2 H), 7.11 (d, J = 8.7 Hz, 2 H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.1, 129.4, 127.9, 126.6, 125.7, 35.4, 33.2, 22.7, 13.8

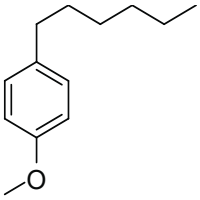
1-Butylnaphthalene (2x).22



CAS Registry Number: 1634-09-9.

Catalytic system C: Synthesized using catalytic systems C with 1-bromo-naphthalene (1 mmol, 207 mg) and 750 μL of *n*-butyllithium 1.6 M in hexane. Colorless oil obtained after filtration over a silica plug (SiO_2, *n*-pentane), 173 mg, 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05-8.02 (m, 1H), 7.83-7.81 (m, 1H), 7.70-7.67 m, 1H), 7.48-7.44 (m, 2H), 7.37-7.35 (m, 1H), 7.31-7.29 (m, 1H), 3.05 (t, J = 7.8 Hz, 2H), 1.75-1.65 (m, 2H), 1.50-1.41 (m, 2H), 0.96 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3, 134.2, 132.3, 129.1, 126.7, 126.2, 125.9, 125.8, 125.7, 124.2, 33.4, 33.2, 23.0, 14.4

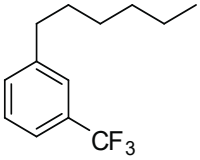
1-Hexyl-4-methoxybenzene (2y).[22]



CAS Registry Number: 81693-80-3.

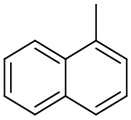
Catalytic system C: Synthesized using catalytic systems C with 1-bromo-4-methoxybenzene (1 mmol, 187 mg) and 520 μL of *n*-hexyllithium 2.3 M in hexane. Colorless oil obtained after filtration over a silica plug (SiO_2, *n*-pentane), 157 mg, 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, J = 7.8 Hz, 2H), 6.80 (d, J = 7.8 Hz, 2H), 3.76 (s, 3H), 2.54 (t, J = 7.6 Hz, 2H), 1.61–1.48 (m, 2H), 1.35–1.16 (m, 6H), 0.86 (t, J = 6.5 Hz, 3H). 13C NMR (75 MHz, $CDCl_3$): δ 157.5, 135.0, 129.2, 113.6, 55.2, 35.0, 31.7, 29.7, 28.9, 22.6, 14.1

1-Hexyl-3-(trifluoromethyl)benzene (2z).



Catalytic system C: Synthesized using catalytic systems C with 1-bromo-3-(trifluoromethyl)benzene (1 mmol, 225 mg) and 520 μL of *n*-hexyllithium 2.3 M in hexane. Colorless oil obtained after column chromatography (SiO_2, *n*-pentane/EtOAc 100:1), 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.32 (m, 4H), 2,66 (t, *J* = 7.8 Hz, 2H), 1.63 (m, 2H), 1.34 (m, 6H), (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.44, 143.72, 131.74, 128.55, 124.99, 122.40, 35.76, 31.61, 31.23, 28.87, 22.54, 14.03. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.5. HRMS (APCI+, *m*/*z*): calculated for $C_{13}H_{18}F_3$ [M+H$^+$]: 231.13606; found: 231.13713.

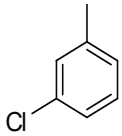
1-Methyl-naphthalene (2aa).[68]



CAS Registry Number: 90-12-0.

Catalytic system C: Synthesized using catalytic systems C with 1-bromonaphthalene (1 mmol, 207 mg) and 750 μL of methyllithium 1.6 M in diethylether. Colorless oil obtained after filtration over a silica plug (SiO_2, *n*-pentane), 122 mg, 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.67 (s, 3H), 7.29-7.44 (m, 2H), 7.46-7.53 (m, 2H), 7.68-7.71 (m, 1H), 7.82-7.85 (m, 1H), 7.97-8.00 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 19.4, 124.1, 125.5, 125.6, 125.7, 126.3, 126.5, 128.5, 132.6, 133.5, 134.2

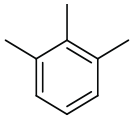
1-Chloro-3-methylbenzene (2ab).[69]



CAS Registry Number: 108-41-8.

Catalytic system C: Synthesized using catalytic systems C with 1-bromo-3-chlorobenzene (1 mmol, 191 mg) and 750 μL of methyllithium 1.6 M in diethylether. Colorless oil obtained after filtration over a silica plug (SiO_2, *n*-pentane), 106 mg, 84% yield.

1,2,3-trimethylbenzene (2ac).



CAS Registry Number: 526-73-8.

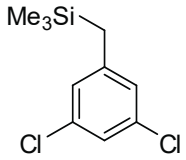
Catalytic system C: Synthesized using catalytic systems C with 1,3-dimethyl-2-bromobenzene (1 mmol, 185 mg) and 750 μL of methyllithium 1.6 M in diethylether.

1-Hexyl-3-(trifluoromethyl)benzene (2z).

Catalytic system C: Synthesized using catalytic

systems C with 1-bromo-3-(trifluoromethyl)benzene (1 mmol, 225 mg) and 520 μL of n-hexyllithium 2.3 M in hexane. Colorless oil obtained after column chromatography (SiO2, n-pentane/EtOAc 100:1), 84% yield. 1H NMR (400 MHz, CDCl3): δ 7.46-7.32 (m, 4H), 2,66 (t, J = 7.8 Hz, 2H), 1.63 (m, 2H), 1.34 (m, 6H), (t, J = 6.6 Hz, 3H).
^{13}C NMR (100 MHz, CDCl3): δ 187.44, 143.72, 131.74, 128.55, 124.99, 122.40, 35.76, 31.61, 31.23, 28.87, 22.54, 14.03. 19F NMR (376 MHz, $CDCl_3$): δ -62.5. HRMS (APCI+, m/z): calculated for C13H18F3 [M+H+]:231.13606; found: 231.13713.

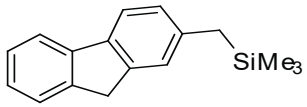
(3,5-Dichlorobenzyl)trimethylsilane (2ae).[22]



CAS Registry Number: 69380-94-5.

Catalytic system C: Synthesized using catalytic systems C with 1-bromo-3,5-dichlorobenzene (1 mmol, 225 mg) and 1200 μL of (trimethylsilyl)methyllithium 1.0 M in pentane. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 196 mg, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (t, J = 1.9 Hz, 1H), 6.87 (d, J = 1.9 Hz, 2H), 2.04 (s, 2H), 0.01 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.5, 134.6, 126.4, 124.3, 27.2, -1.8.

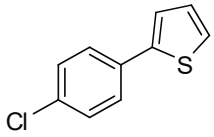
((9*H*-Fluoren-2-yl)methyl)trimethylsilane (2af). [26]



CAS Registry Number: 1694669-89-0

Catalytic system C: Synthesized using catalytic systems C with 2-bromo-9*H*-fluorene (1 mmol, 245 mg) and 1200 μL of (trimethylsilyl)methyllithium 1.0 M in pentane. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 214 mg, 85% yield. ^{1}H NMR (400 MHz, C_7D_8): δ 7.57 (d, J = 7.5 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 7.4 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.98 (s, 1H), 6.91 (d, J = 7.8 Hz, 1H), 3.49 (s, 2H), 2.02 (s, 2H), -0.01 (s, 9H). ^{13}C NMR (101 MHz, C_7D_8): δ 143.9, 143.2, 142.5, 139.2, 138.5, 126.9, 126.2, 125.3, 125.1, 124.8, 119.9, 119.6, 36.9, 27.3, - 1.8

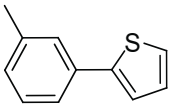
2-(4-chlorophenyl)thiophene (2ag).[71]



CAS Registry Number: 40133-23-1

Catalytic system B: Synthesized using catalytic systems B with 1-bromo-4-chlorobenzene (1 mmol, 191 mg) and 1200 μL of 2-thienyllithium as 1.0 M sol. in THF/hexane. Off white solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 155 mg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.55–7.51 (m, 2H), 7.37–7.23 (m, 4H), 7.10–7.05 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 143.1, 133.2, 133.0, 129.0, 128.2, 127.1, 125.2, 123.4

2-(*m*-tolyl)thiophene (2ah).[72]



CAS Registry Number: 85553-43-1

Catalytic system B: Synthesized using catalytic systems B with 1-bromo-3-methylbenzene (1 mmol, 171 mg) and 1200 μL of 2-thienyllithium as 1.0 M sol. in THF/hexane. Collorless oil obtained after filtration over a silica plug (SiO_2, *n*-pentane), 146 mg, 84% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.02-7.45 (m, 7H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.53, 138.46, 134.25, 128.73, 127.89, 126.64, 124.58, 123.06, 21.51

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Chapter 6

Fast, Efficient One-Pot Pd-Catalysed Cross-Coupling of (Hetero)Arenes

Introduction

Biaryl structures are key components in catalysts, natural products, pharmaceuticals, polymers and many other important classes of chemicals.[1,2] The development of efficient syntheses of biaryls has therefore drawn major attention by the chemical community over the past decades.[3,4,5,6] Among the various methods explored, the transition metal catalysed cross-coupling of two aryl groups (Figure 1A) has proven to be among the most efficient and versatile strategies available and new developments continuously emerge expanding the scope of this approach.[7,8,9,10,11,12,13,14] One of the major remaining challenges is the development of complementary methods which are not only highly efficient but also economically viable and environmentally friendly. Indeed, many of the above mentioned well-established methods require the use of heat, stoichiometric amounts of additional reagents and/or additives as well as dilute conditions, which negatively impact the reaction outcome in terms of environmental cost. One of the solutions to overcome some of the above mentioned issues was the development of low solvent coupling reactions.[15] This resulted in significant improvements not only reducing the waste created but also, in many cases, of other parameters such as catalytic loading, reaction speed and scalability. Inspired, in part, by the 12 principles of green chemistry[16] our group has been interested in the development of novel more sustainable cross-coupling methods which resulted in procedures for the palladium-catalyzed direct cross-coupling of highly reactive organolithium reagents with organic halides, ethers and triflates based on the pioneering work of Murahashi (Figure 1B).[17,18,19,20,21,22,23,24,25,26,27,28,29] The use of organolithium reagents[30,31] instead of classical coupling partners such as Stille,[32] Kumada[33] or Suzuki-Miyaura[34] reagents resulted in a significant improvement in atom efficiency, employing mild conditions, while maintaining high yields. These strategies have proven versatile alternatives to classical methods and have been recently applied to total synthesis of biologically active compounds.[35] In addition, these couplings often reach full conversion much faster than the previously mentioned methods, an improvement that has also been the focus of much research recently.[36,37] A second step towards higher efficiency was achieved very recently by our group by demonstrating that the direct coupling of organolithium compounds to aryl halides could also be achieved using minimal solvent,[38] which reduced the overall waste of the reaction significantly. However remaining issues included the need to separately prepare the organolithium reagent, limited availability of coupling partners, and relatively low functional group tolerance. The need to prepare the organolithium partner separately was considered the most important target. This two-step process was responsible for most of the generated waste, for

significantly lowering the scope of substrates, in many cases simply due to the poor solubility of the resulting organolithium reagent, and also because the reactivity of the organolithium results in the degradation of several common functional groups. In our search to address these issues, we furthered our investigation into the unique properties of these cross-coupling reactions and herein we report the development of a novel, without additional solvent, direct palladium catalyzed cross-coupling of a wide range of distinct (hetero)arenes mediated by organolithium reagents (Figure 1C). This simple and straightforward one-pot procedure affords a wide variety of biaryl products, including advanced intermediates, with excellent yields in record coupling times. Moreover the need for inert conditions and the separate formation of the organolithium partner were eliminated.

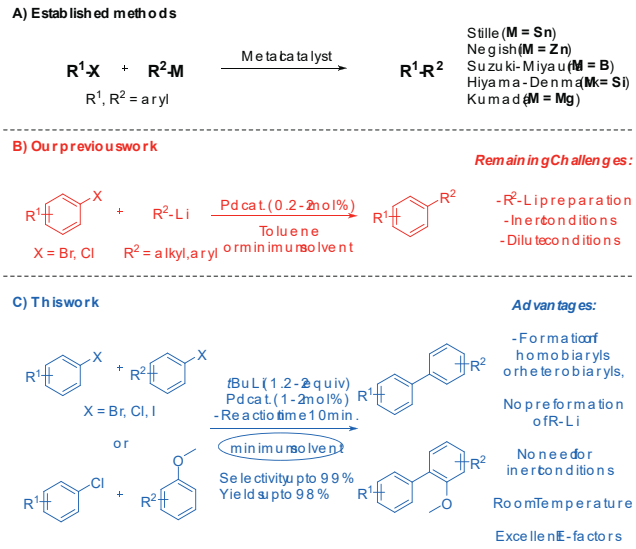
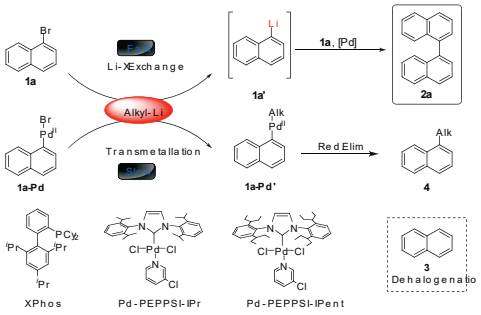


Figure 1: A) Established methods for metal catalysed cross-coupling reactions. B) Catalytic cross-couplings with organolithium compounds. C) Fast and efficient one-pot Pd-catalysed cross-coupling of distinct (Hetero)Arenes.

Results and discussion

In, as far as we are aware, preliminary studies the Pd-catalysed one pot homocoupling of 1-bromonaphthalene (**1a**) mediated by an alkyl lithium to obtain binaphthalene was examined (**2a, Scheme 1**). We reasoned it would be possible to bypass the need for the separate formation of the aryl lithium partner due to the differences in kinetics between the different possible coupling and lithium-halogen exchange reactions. It was anticipated that with the use of either *t*-Buli, *s*-BuLi or EtLi, the cross

coupling between an aryl bromide (**1a**) and *in situ* formed aryl lithium (**1a'**, leading to **2a**) would occur before side reactions i.e. dehalogenation (leading to **3**) or cross coupling between the aryl bromide and the alkyl lithium (leading to **4**). This meant that upon addition of the alkyl lithium to the aryl bromide, lithium halogen exchange would selectively occur to form an aryl lithium intermediate which is immediately consumed in the coupling step avoiding any buildup of the organolithium species (which would lead to **3** upon quenching) bypassing many of the issues in previous reported methods using organolithium reagents[7a] while retaining high levels of selectivity. While the use of EtLi and *s*-BuLi, in combination with various palladium catalysts, saw little to no formation of the desired homocoupled product (Table 1, entries 1-7), we were delighted to observe that when *t*-BuLi in heptane[39] was added over a period of 10 min onto neat 1-bromonaphthalene in the presence of 1 mol% $Pd[P(t\text{-}Bu)_3]_2$ or Pd-PEPPSI-IPent[40] about 50% conversion to **2a** occurred (entries 9-10). While no formation of **4** could be observed under these conditions, a significant amount of starting aryl bromide remained. Switching to cheaper Pd-PEPPSI-IPr as catalyst (entry 11) saw a slight increase in selectivity but no notable change in conversion which allowed us to opt for the cheaper of the two. We reasoned that the active form of the catalyst might be oxygen generated nanoparticles as we recently demonstrated to be the case in organolithium based transformations[xxviii] and that switching from an inert atmosphere to dry air would promote the formation of the active catalyst and enhance the conversion further. We were pleased to see that under these conditions, conversion to **2a** enhanced to 76% (entry 12) with no proportional increase in side products. Further investigations showed that we could also reduce the amount of catalyst to 1 mol% and of *t*-BuLi from two to 0.7 equivalents (as 0.5 equiv. are in theory needed, this actually represents a slight excess of *t*-BuLi, entry 14). We propose this is only possible due to the fact that the consumption of *t*-BuLi in the lithium-halogen exchange is faster than the elimination of *t*-BuBr.[41,42] Overall this resulted in an 80% isolated yield of **2a**.



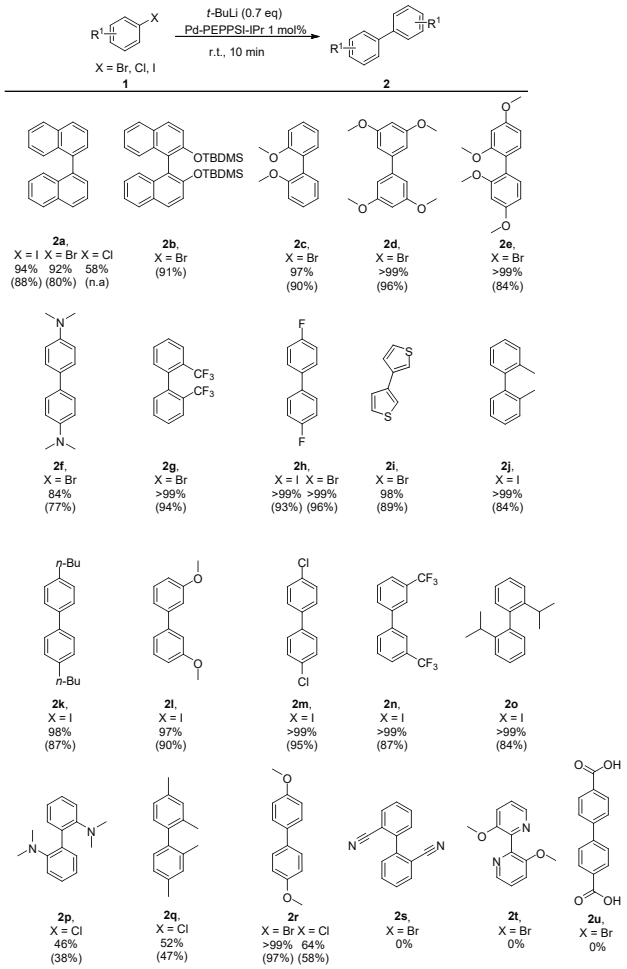
Scheme 1: Possible cross coupling and lithium halogen exchange reactions.

Entry[a]	RLi (equiv.)	[Pd] (x mol %)	1a:2a:3:4 [b]
1	Et (2)	Pd-PEPPSI-IPent (2)	67:**0**:5:28
2	Et (2)	Pd-PEPPSI-IPr (2)	41:**3**:25:30
3	Et (2)	$Pd[P(t\text{-}Bu)_3]_2$ (2)	65:**0**:6:29
4	*s*-Bu (2)	Pd/C (5)	57:**0**:24:0
5	*s*-Bu (2)	Pd-PEPPSI-IPent (2)	57:**14**:13:15
6	*s*-Bu (2)	Pd-PEPPSI-IPr (2)	57:**6**:3:33
7	*s*-Bu (2)	$Pd[P(t\text{-}Bu)_3]_2$ (2)	54:**17**:4:25
8	*t*-Bu (2)	XPhos/Pd_2dba_3 (1)	66:**0**:34:0
9	*t*-Bu (2)	$Pd[P(t\text{-}Bu)_3]_2$ (2)	36:**47**:18:0
10	*t*-Bu (2)	Pd-PEPPSI- IPent (2)	35:**51**:14:0
11	*t*-Bu (2)	Pd-PEPPSI-IPr (2)	32:**55**:13:0
12 [c]	*t*-Bu (2)	Pd-PEPPSI-IPr (2)	5:**76**:19:0
13[c]	*t*-Bu (0.7)	Pd-PEPPSI-IPr (0.1)	8:**81**:11:0
14[c]	*t*-Bu (0.7)	Pd-PEPPSI-IPr (1)	0:**92**:8:0

Table 1 : Optimisation of the formation of **2a** *over* **3** *and* **4***: a) All experiments were carried out by stirring the starting material and catalyst under inert atmosphere, followed by the dropwise addition of the commercially available organolithium reagent in heptane over a period of 10 min at room temperature. b) Ratios determined by GC-MS c) inert atmosphere was replaced by dry air.*

These conditions proved general and could be applied to a wide range of substrates providing the homocoupled products selectively and in high yields (Scheme 2). Sterically demanding substrates such as TBDMS protected 2-bromonaphthol (**1b**) and 2-bromoanisole (**1c**) similarly gave excellent yields (91%, 90%). Electron rich 3,5- and 2,4-dimethoxybromobenzene (**1d**-**e**), who might suffer from a loss in selectivity due to the added possibility of *ortho*-lithiation, or 4-bromodimethylaniline (**1f**) also gave good to excellent yields of the homocoupled biphenyl products (**2d**-**f**, 77-96%). Aryl bromides bearing electron withdrawing groups or heteroaryl bromides also function well under these conditions (**2g-i**, 89-96%). Employing aryl

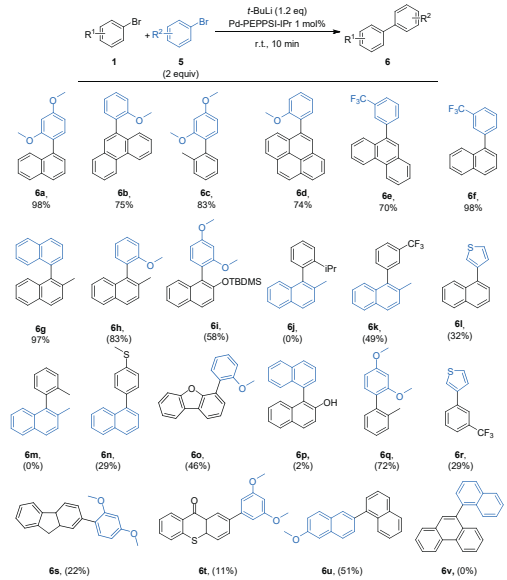
iodides instead of aryl bromides (**2a'**, **2h'**, **2j**-**m**) showed no significant difference in terms of conversion or selectivity, all giving excellent yields of the corresponding homocoupled biphenyl products (**2a**, **2h**, **2j**-**o**, 84-95%). Compound **2m** especially was highly interesting as the reaction proved chemoselective for the iodine vs the chloride. In the case of aryl chlorides (**2a''**, **2p**-**r**), however, lower conversions were obtained (46-64%). The cause of this, as far as our experimental observations go, is due to a slower lithium-halogen exchange resulting in two issues. First the *t*-BuLi mediated elimination of *t*-BuX (X = Br or Cl) becomes more favored leading to loss of reagent, second the anticipated palladium nanoparticles have time to aggregate into palladium black which is inactive. As expected, the high reactivity of organolithium reagents is incompatible with several functional groups, which undergo a variety of side reactions such as reduction/addition (**2s, 2t**) or 1,2-addition (**2u**). In cases where a side reaction is found to be faster than the coupling, lower conversion is observed. A major difference, in comparison to the same reaction under diluted conditions, is the lack of reactivity of pyridine based substrates. Whereas, previously, when using toluene as solvent, pyridine based substrates reacted with high efficiency, this reactivity is lost under the present low solvent conditions. We hypothesize that the increased concentration leads to a more effective binding between the substrate and palladium catalyst, thereby poisoning its reactivity (**2t**).



Scheme 2: Scope of the homocoupling reaction. All experiments were carried out by stirring the starting material and catalyst under dry air, followed by the dropwise addition of the t-BuLi in heptanes over a period of 10 min at room temperature. Conversions determined by GCMS. Isolated yields indicated between parentheses.

Subsequently the possibility of heterocoupling of two distinct aryl halides under the optimized conditions was explored (Scheme 3). We envisioned, in view of the efficiency of the homo coupling step and the previously obtained results as reported in chapter 6, that even a slight difference in the rate of lithium-halogen exchange between both aryl halides would be sufficient to result in high selectivities for the heterocoupled product vs the homocoupled product. Indeed when 1-bromo-2,4-dimethoxybenzene (**5a**), which benefits from an ortho-directing group effect for the lithium-halogen exchange, was reacted with **1a,** an approximately 8:2 ratio in favor of the heterocoupled product vs the homocoupled products was observed. Simply

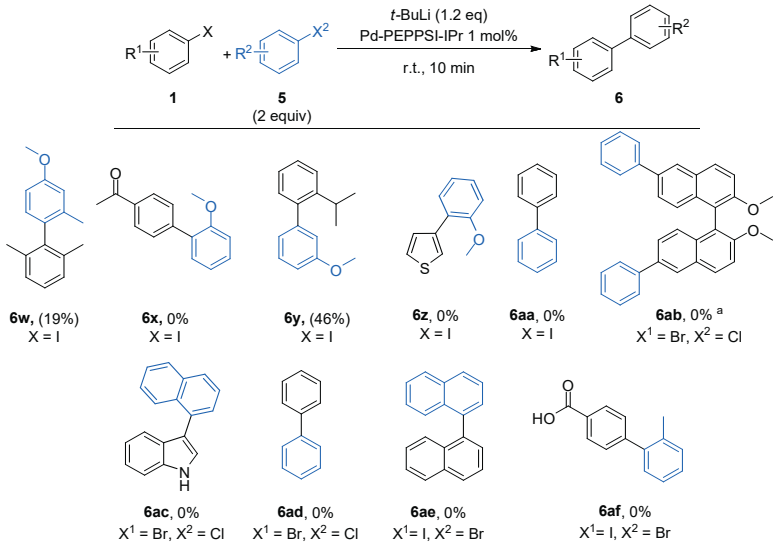
increasing the amount of **5a** and *t*-BuLi resulted in near full conversion of **1a** to the heterocoupled product with 98% isolated yield. The heterocoupling of various aryl bromides possessing *o*-methoxy directing groups with non-directed aryl bromides, including ones with extended π-systems and sterically highly encumbered substrates, also gave high yields of the desired heterocoupled products (**6b-d**, 74-98%). To our surprise a directing group was not a strict requirement and substrates with different electronic (**6e-f,** 70-98%) or steric (**6g,** 97%) properties also resulted in very high selectivites for the heterocoupled products. However, predicting which combination will lead to the cross-coupled product in high yields is challenging. Determining which substrate combination will possess the required difference in rates of their respective lithium-halogen exchange and subsequent homocoupling versus cross coupling rate can, at this point, only be performed experimentally. In some cases, the presence of increased amounts of sterical hindrance around the reactive center appears to hinder the coupling sufficiently (**6j, 6m, 6s, 6t, 6v**). In other cases, undesired coordination of certain functional groups with either the palladium catalyst or the lithium reagent is considered to be the cause of low reactivity and therefore lower yields (**6n, 6o, 6t**). In the cases of **6i** and **6s** side reactions were observed. Finally, starting materials capable of extremely rapid homocoupling reactions performed less well in cross-coupling reactions, due to the highly favorable dimerization (**6l, 6r**).



Scheme 3: Scope of the cross coupling reaction of two distinct aryl halides. All experiments were carried out by stirring **1**, **5** *and 1 mol% Pd-PEPPSI-iPr under dry air, followed by the dropwise addition of the t-BuLi in heptanes over a period of 10 min at room temperature. Indicated yields are after isolation, conversions in parentheses are determined by GCMS.*

We next turned our attention to the possibility of cross coupling aryl groups bearing different halogens. In view of the previous results, we believed this might be possible as significant differences in rate of lithium halogen exchange exists in those starting materials. (Scheme 3)

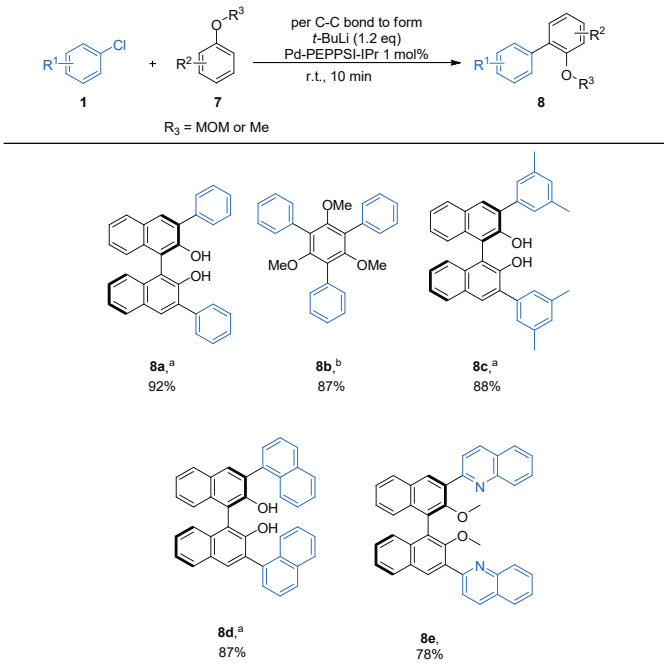
Application of iodinated starting materials in hetero cross-coupling, however, proved their unsuitability under the applied conditions (**6w-6aa**). Because of low yield, the compounds in Scheme 4 were not isolated. Conversion was determined via GC measurements. Suppressing the undesired homo-coupling side reaction, in these cases, requires further research. Cross-coupling between bromo- and chloro- or bromo- and iodo- bearing aryls (**6ab-6af**) yielded the homo-coupled product, resulting from reaction of the starting material bearing the most reactive halogen with itself. (with exception of **6af**, which yielded the 1,2-addition product). In all performed experiments (**6ab-6af**) not a trace of desired product could be observed.



Scheme 4: Scope of the cross coupling reaction of two distinct aryl halides. All experiments were carried out by stirring **1**, **5** *and 1 mol% Pd-PEPPSI-iPr under dry air, followed by the dropwise addition of the t-BuLi in heptanes over a period of 10 min at room temperature. Indicated yields are after isolation, conversions in parentheses are determined by GCMS. When only conversion in parenthases is given, product was not isolated. [a]4 equiv of* **5**, *2.4 equiv of t-BuLi and 2 mol% catalyst are applied.*

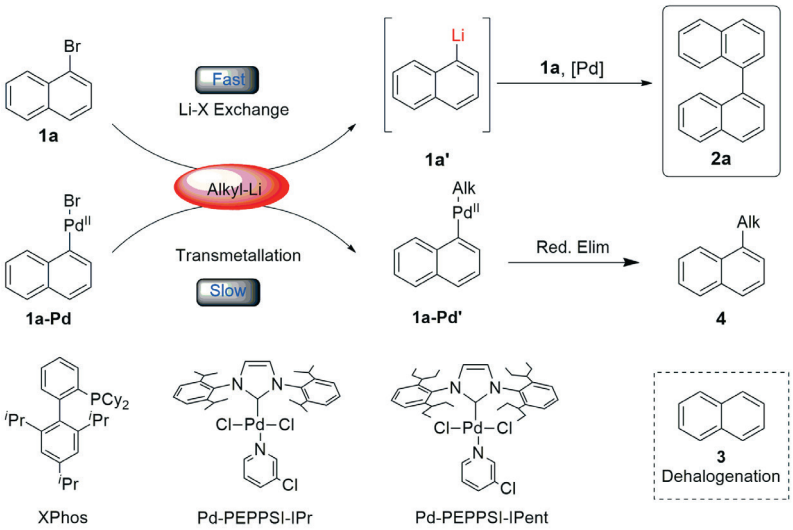
Based on observations made during studies on the homocoupling i.e. that ortho-lithiation[43] could occur faster than lithium-halogen exchange at aryl chlorides and that steric hindrance was well tolerated, we further explored the heterocoupling between aryl chlorides and anisole derivatives (Scheme 5). Remarkably, under the

optimized conditions, MOM-protected BINOL (**7a**) or 1,3,5-trimethoxybenzene react smoothly (10 min, room temperature, no additional solvent) with chlorobenzene in excellent yields and selectivities to form the corresponding 3- and 3'- disubstituted polyaromatic compounds (**8a**-**b**, 87-92%) The formation of **8a** is particularly interesting as it opens the way for the efficient synthesis of various scaffolds often used as precursors to chiral phosphoric acids or phosphoramidites that are used in asymmetric catalysis. Based on these results the scope was expanded to multiple other known, frequently used, chiral BINOL derivates (**8c**-**e**) which were obtained in a highly efficient manner (78-88% yields)[44]. The efficiency of our methodology is demonstrated in the successful formation of compound **8b**. Being only made once before, this substrate is the results of three, subsequent, increasingly difficult cross-couplings. Using this methodology, the obtained yield of **8b** is twice as high as previously reported.[71] The methoxy groups still present in the product potentially allow for even further introduction of aryl groups, using a nickel-carbene complex, as previously described by our group, creating highly intriguing molecular structures.[26]



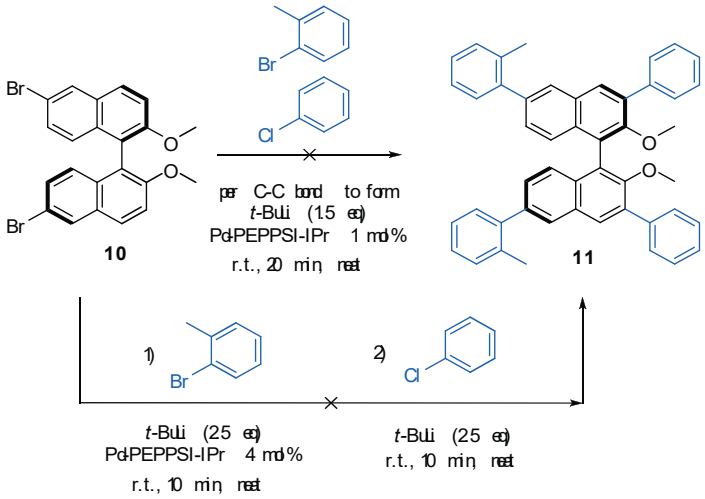
Scheme 5: Cross coupling reaction of aryl chlorides to anisole derivatives. All experiments were carried out by stirring **1**, **7** *and 1 mol% Pd-PEPPSI-iPr under dry air, followed by the dropwise addition of the t-BuLi in heptanes over a period of 10 min at room temperature. a) An acidic workup was performed after the coupling to remove the MOM group and facilitate purification b) reaction mixture was stirred for 1 h. Indicated yields are after isolation.*

A brief comparison of the method as employed in scheme 5 *versus* one of the representative classical pathways for the formation of **8a** is shown in Scheme 6. While the reported synthesis of **8a** involves a two-step pathway requiring long reaction times with moderate yields,[45] our method furnished **8a** in a fraction of that time in excellent yields, starting directly from BINOL dimethylether **7a** and the chlorobenzene. This overall highlights the remarkable selectivity, efficiency and advantages of this process over existing methods.



Scheme 6: Comparison of methods for the synthesis of 8a.

Combination of the aforementioned methodologies presented in this chapter, was envisioned to potentially furnish a 6,6′-3,3′-quatro aryl substituted BINOL scaffold **11**. Based upon both a cross-coupling between two bromide substrates (for 6,6′-substitution) in combination with or followed by a subsequent one pot ortho-lithiation and second cross coupling (for 3,3′-substitution) was investigated (Scheme 7). Using 6,6′-brominated methoxy protected BINOL substrate **10** as starting material, we envisioned the introduction of all aryl substituents in one pot, opening up quick access towards several highly functionalized BINOL derivatives. Initially all reagents were placed together, however full reduction of substrate **10** was observed. Subsequent attempts relying on a stepwise approach, in which first a cross-coupling was attempted according to Scheme 3 (general procedure B) followed by an ortho lithiation based coupling (scheme 7) did also not result in desired compound **11** either.



Scheme 7: Attempts towards combination of methodologies presented in this chapter.

Conclusions

In summary, we have developed a highly efficient method for the homocoupling of aryl halides and the heterocoupling of aryl halides to either aryl bromides or arenes bearing a directing group for ortho-lithiation. Taking advantage of the remarkable affinity of Pd-PEPPSI-IPr for catalysing the cross-coupling of aryl halides and organolithium reagents and carefully controlling the formation of the latter, we achieved high yields and selectivity for these reactions while eliminating the need for strict inert conditions, temperature control or for the separate formation of one of the coupling partners. The presented method provides a very fast, exceptionally mild, highly selective, versatile and convenient way to access many important biaryl and polyaromatic structures. This is especially demonstrated by short reaction times, the capability of forming highly hindered biaryl systems, as well as widely used intermediates.

Experimental Section

General methods:

Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by UV and cerium/molybdenum or potassium permanganate staining. Progress and conversion of the reaction were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). ^{1}H- ^{19}F- and ^{13}C-NMR were recorded on a Varian AMX400 (400, 376 and 100.59 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for 1H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. All reactions were carried out under a dry air atmosphere. $Pd[P(t\text{-}Bu)_3]_2$, was purchased from Strem, $Pd_2(dba)_3$, XPhos, Pd-PEPPSI-*i*Pr and Pd-PEPPSI-*i*Pent were purchased from Aldrich and used without further purification. t-BuLi (2.2-3.2 M solution in heptane) was purchased from Aldrich and titrated before use *via* the diphenylacetic acid method.[46] All reagents were commercially available and were purchased from Aldrich, TCI Europe N.V. and Acros Organics except for 1-Chloro-2,4,6-triisopropylbenzene which was made according to known literature procedures.[xl]
Reaction vessels were purged beforehand with dry air from cylinders purchased at Linde Gas.

General Note on Safety

The outstanding performance of lithium reagents is a direct result of their high reactivity.[47] Safe and proper handling via care and attention are therefore a must. Throughout literature many comprehensive descriptions on the proper handling of lithium reagents have been reported.[xlii] Especially in the presence of oxygen, enhanced reactivity is expected by formation of oxides. The safe use of lithium reagents in the presence of air and water has been reported by Hevia *et al*.[xlii]

General procedure for the homocoupling of aryl halides (A)

The corresponding aryl halide (1 mmol, 1 equiv.) and Pd-PEPPSI-*i*Pr (7 mg, 1.0 mol %) were added to a Schlenk flask under a dry air atmosphere. *t*-BuLi (0.7 equiv., 2.2-3.2 M in heptane) was added at room temperature to the stirred mixture over a period of 10 min with a syringe pump. After the addition was completed, a saturated solution of aqueous NH_4Cl was added and the mixture was extracted with Et_2O. The organic phases were combined, dried over anhydrous Na_2SO_4 and residual solvents removed under vacuum. Filtration over a silica gel plug (conditions for each compound indicated below) of the residue afforded the desired homocoupled product.

General procedure for the cross-coupling of aryl bromides (B)

The corresponding aryl bromide (1 mmol, 1 equiv.), the aryl bromine prone to lithium- halogen exchange (2 mmol, 2 equiv.) and Pd-PEPPSI-*i*Pr (7 mg, 1.0 mol %) were added to a Schlenk flask under a dry air atmosphere. *t*-BuLi solution (1.2 equiv., 2.2-3.2 M in heptane) was added at room temperature to the stirred mixture over a period of 10 min with a syringe pump. After the addition was completed, a saturated solution of aqueous NH_4Cl was added and the mixture was extracted with Et_2O. The organic phases were combined, dried over anhydrous Na_2SO_4 and residual solvents removed under vacuum. Filtration over a silica gel plug (conditions for each compound indicated below) of the residue afforded the desired heterocoupled product.

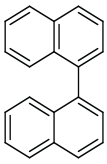
General procedure for the cross-coupling of aryl chlorides to anisole derivatives via ortho-lithiation (C)

The corresponding anisole derivative (1 mmol, 1 equiv.) was added to a stirred Schlenk flask under a dry air atmosphere followed by the aryl chloride, (1.5 mmol per reactive center, 1.5 equiv. per reactive center) and Pd-PEPPSI-*i*Pr (7 mg per reactive center, 1.0 mol% per reactive center). *t*-BuLi (1.2 equiv. per reactive centre, 2.2-3.2 M in heptane) was added at room temperature to the stirred mixture over a period of 10 min with a syringe pump. After the addition was completed, a saturated solution of aqueous NH_4Cl was added and the mixture was extracted with Et_2O. The organic phases were combined, dried over anhydrous Na_2SO_4 and residual solvents removed under vacuum. Filtration over a silica gel plug (conditions for each compound

indicated below) of the residue or recrystallization from cyclohexanes afforded the desired heterocoupled product.

For the synthesis of the following compounds general procedure A was used

binaphthalene (2a)[48]



CAS Registry Number: 604-53-5

From 1-bromonaphthalene (1 mmol, 207 mg) and 298 µL of *t*-BuLi in heptane.

Brown solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 102 mg, 80% yield.

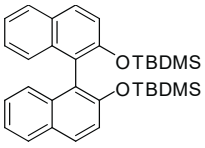
From 1-iodonaphthalene (1 mmol, 254 mg) and 298 µL of *t*-BuLi in heptane.

Brown solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 112 mg, 88% yield.

From 1-chloronaphthalene (1 mmol, 162 mg) and 298 µL of *t*-BuLi.

Observed 58% conversion by GC-MS, product not isolated. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (dd, *J* = 8.2, 3.5 Hz, 4H), 7.64 – 7.56 (t, 2H), 7.49 (dd, *J* = 12.7, 6.9 Hz, 4H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.29 (dd, *J* = 14.3, 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.61, 133.68, 133.01, 128.30, 128.04, 127.99, 126.72, 126.13, 125.96, 125.53.

2,2′-bis((tert-butyldimethylsilyl)oxy)-1,1′-binaphthalene (2b)[49]

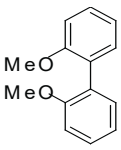


CAS Registry Number: 1618090-36-0

From ((1-bromonaphthalen-2-yl)oxy)(tert-butyl)dimethylsilane (1 mmol, 337 mg) and 298 µL of *t*-BuLi in heptane.

Yellow oil obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:0-5), 175 mg, 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dt, *J* = 17.8, 8.3 Hz, 4H), 7.66 (t, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.26 (s, 2H), 7.19 – 7.07 (m, 2H), 1.09 (s, 18H), 0.31 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.93, 135.13, 129.77, 129.75, 128.09, 127.14, 126.58, 124.21, 122.55, 115.38, 26.23, 18.76, -3.83.

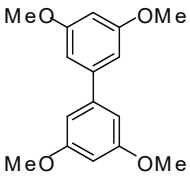
2,2′-dimethoxybiphenyl (2c)[50]



CAS Registry Number: 4877-93-4

From 2-bromoanisole (1 mmol, 187 mg) and 298 µL of *t*-BuLi in heptane. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 96 mg, 90% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (td, *J* = 8.2, 1.7 Hz, 2H), 7.25 (dd, *J* = 7.1, 2.0 Hz, 2H), 7.03 – 6.96 (m, 4H), 3.78 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.01, 131.44, 128.57, 127.80, 120.32, 111.08, 55.68.

3,3′,5,5′-tetramethoxybiphenyl (2d)[xxiii]

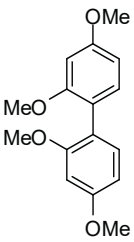


CAS Registry Number: 108840-33-1

From 1-bromo-3,5-dimethoxybenzene (1 mmol, 216 mg) and 298 µL of *t*-BuLi in heptane.

White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 132 mg, 96% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, *J* = 2.3 Hz, 4H), 6.47 (t, *J* = 2.3 Hz, 2H), 3.84 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.61, 146.11, 108.18, 102.14, 58.09.

2,2′,4,4′-tetramethoxybiphenyl (2e)[51]

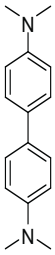


CAS Registry Number: 3153-72-8

From 1-bromo-2,4-dimethoxybenzene (1 mmol, 216 mg) and 298 µL of *t*-BuLi in heptane.

White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:0-5), 115 mg, 84% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.0 Hz, 2H), 6.62 (d, *J* = 8.1 Hz, 4H), 3.90 (s, 6H), 3.83 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.12, 158.16, 132.03, 120.17, 104.16, 98.90, 55.69, 55.38.

$N^4,N^4,N^{4'},N^{4'}$-tetramethyl-[1,1'biphenyl]-4,4'-diamine (2f)[52]

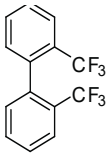


CAS Registry Number: 366-29-0

From 4-bromodimethylaniline (1 mmol, 200 mg) and 298 µL of *t*-BuLi in heptane.

White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:0-5), 92 mg, 77% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.8 Hz, 4H), 6.82 (d, *J* = 8.6 Hz, 4H), 2.99 (s, 12H). ^{13}C NMR (101 MHz, $CDCL_3$): δ 151.92, 132.52, 129.62, 115.75, 43.46, 33.59.

2,2'-bis(trifluoromethyl)biphenyl (2g) [27]

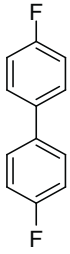


CAS Registry Number: 567-15-7

From 2-bromobenzotrifluoride (1 mmol, 225 mg) and 298 µL of *t*-BuLi in heptane.

White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 136 mg, 94% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.59 – 7.48 (m, 2H), 7.32 (d, *J* = 6.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.15, 134.19, 133.31, 130.75, 128.61 (q, *J* C-F = 274.0 Hz), 127.95, 125.23. ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.14.

4,4'-difluorobiphenyl (2h)[53]



CAS Registry Number: 398-23-2

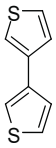
From 1-bromo-4-fluorobenzene (1 mmol, 175 mg) and 298 µL of *t*-BuLi in heptane.

Clear oil obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 91 mg, 96% yield.

From 1-fluoro-4-iodobenzene (1 mmol, 222 mg) and 298 µL of *t*-BuLi in heptane.

Clear oil obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 177 mg, 93% yield.^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 8.8, 5.3 Hz, 4H), 7.12 (t, *J* = 8.7 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.06 (d, *J* C-F = 246.5 Hz), 139.04 (d, *J* = 3.3Hz), 131.21 (d, *J* = 8.1Hz), 118.32 (d, *J* = 21.5Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -115.76.

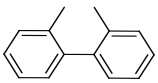
3,3′-bithiophene (2i)[54]



CAS Registry Number: 3172-56-3

From 3-bromothiophene (1 mmol, 163 mg) and 298 μL of *t*-BuLi in heptane. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 73 mg, 89% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (dd, *J* = 2.7, 1.5 Hz, 2H), 7.37 – 7.33 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.24, 126.36, 126.08, 119.79.

2,2′-Dimethylbiphenyl (2j)[55]

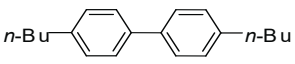


CAS Registry Number: 605-39-0.

From 2-iodo-toluene (1 mmol, 218 mg) and 298 μL of *t*-BuLi in heptane.

Clear oil obtained after filtration over a silica plug (SiO_2, *n*-pentane), 81 mg, 89% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.20 (m, 6H), 7.12 (d, *J* = 7.3 Hz, 2H), 2.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.58, 135.79, 129.78, 129.26, 127.12, 125.51, 19.80.

3,3′-bis(trifluoromethyl)biphenyl (2k)[56]

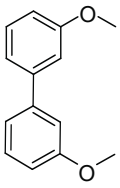


CAS Registry Number: 7641-81-8

From 1-butyl-4-iodobenzene (1 mmol, 260 mg) and 298 μL of *t*-BuLi in heptane.

Colourless solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 116 mg, 87% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.0 Hz, 4H), 7.28 – 7.19 (m, 4H), 2.68 – 2.59 (m, 4H), 1.62 (q, *J* = 8.0 Hz, 4H), 1.39 (q, *J* = 7.4 Hz, 4H), 0.94 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.99, 128.72, 126.77, 35.27, 33.63, 22.40, 13.96

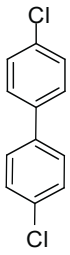
3,3′-dimethoxybiphenyl (2l)[57]



CAS Registry Number: 6161-50-8

From 3-iodoanisole (1 mmol, 234 mg) and 298 μL of *t*-BuLi in heptane. Clear oil obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 96 mg, 90% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (t, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.17 – 7.13 (m, 2H), 6.92 (d, *J* = 8.2 Hz, 2H), 3.88 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.91, 143.99, 142.64, 129.73, 119.71, 112.96, 55.30.

4,4'-dichlorobiphenyl (2m):[58]

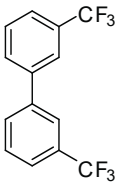


CAS Registry Number: 2050-68-2

From 1-chloro-4-iodobenzene (1 mmol, 238 mg) and 298 μL of *t*-BuLi in heptane.

Clear oil obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 106 mg, 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.6 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.07, 136.40, 131.69, 130.86.

3,3'-bis(trifluoromethyl)biphenyl (2n)[59]

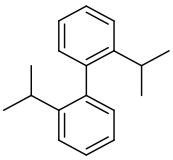


CAS Registry Number: 580-82-5

From 3-(trifluoromethyl)-iodobenzene (1 mmol, 272 mg) and 298 μL of *t*-BuLi in heptane.

Clear oil obtained after filtration over a silica plug (SiO_2, *n*-pentane/Et_2O 100:1), 126 mg, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 2H), 7.77 (d, *J* = 7.7 Hz, 2H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.60 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.22, 134.64, 133.97, (q, J = 7.5 Hz), 127.43(q, J C-F = 272.3 Hz), 126.71, (q, *J* C-F = 3.8 Hz), 104.99. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.76.

2,2'-diisopropylbiphenyl (2o)[60]

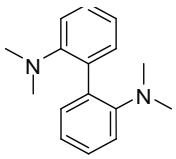


CAS Registry Number: 36919-88-7

From 1-iodo-2-isopropylbenzene (1 mmol, 246 mg) and 298 μL of *t*-BuLi in heptane.

White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 100 mg, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.37 (m, 4H), 7.28 – 7.22 (m, 2H), 7.15 (d, *J* = 7.5 Hz, 2H), 2.78 (p, *J* = 6.9 Hz, 2H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.15 (dd, *J* = 6.9, 1.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.46, 142.86, 132.43, 130.24, 127.92, 127.73, 32.51, 27.53, 25.78.

$N^2,N^2,N^{2'},N^{2'}$-tetramethyl-[1,1′-biphenyl]-2,2′-diamine (2p)[61]

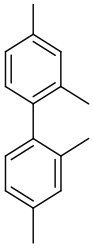


CAS Registry Number: 20627-78-5

From 2-chlorodimethylaniline (1 mmol, 156 mg) and 298 μL of *t*-BuLi in heptane.

White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 46 mg, 38% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 1H), 7.14 (t, *J* = 8.4 Hz, 2H), 6.68 (dd, *J* = 4.4, 2.3 Hz, 3H), 6.59 (dd, *J* = 8.5, 2.3 Hz, 2H), 2.95 (b, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.14, 137.62, 131.70, 118.82, 114.85, 113.12, 43.02.

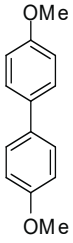
2,2′,4,4′-tetramethylbiphenyl (2q)[62]



CAS Registry Number: 3976-36-1

From 4-chloro-*m*-xylene (1 mmol, 141 mg) and 298 μL of *t*-BuLi in heptane. Colourless solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 50 mg, 47% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 7.12 – 6.91 (m, 6H), 2.36 (s, 6H), 2.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.29, 139.16, 138.42, 133.17, 132.08, 128.84, 23.77, 22.45.

4,4′-dimethoxybiphenyl (2r)[63]



CAS Registry Number: 2132-80-1

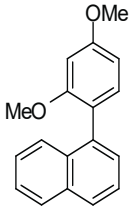
From 4-bromoanisole (1 mmol, 187 mg) and 298 μL of *t*-BuLi in heptane. Colourless solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 104 mg, 97% yield.

From 4-chloroanisole (1 mmol, 142 mg) and 298 μL of *t*-BuLi in heptane. Colourless solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/ Et_2O 100:1), 62 mg, 58% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.8 Hz, 4H), 6.97 (d, *J* = 8.8 Hz, 4H), 3.85 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.34, 136.13, 130.37, 116.81, 57.99.

Spectral data of Heterocoupled Compounds (from two aryl bromides):

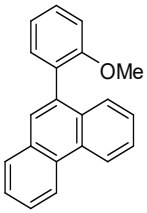
For the synthesis of the following compounds general procedure B was used

1-(2,4-dimethoxyphenyl)naphthalene (6a):



From 1-bromo-2,4-dimethoxybenzene (1 mmol, 246 mg), 1-bromonaphthalene (2 mmol, 508 mg) and 514 µL of *t*-BuLi in heptane. White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/Et_2O 100:1), 259 mg, 98% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, *J* = 14.0, 8.2 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.51 (tt, *J* = 14.5, 7.4 Hz, 3H), 7.31 (d, *J* = 8.2 Hz, 1H), 6.76 – 6.68 (m, 2H), 3.96 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.38, 160.98, 139.58, 136.29, 135.28, 135.03, 130.87, 130.35, 130.22, 129.28, 128.33, 128.26, 128.15, 125.00, 107.08, 101.57, 58.25, 58.16. HRMS (ESI+, *m*/*z*): calculated for $C_{18}H_{17}O_2$ [M+H$^+$]: 265.1223; found: 265.1169.

9-(2-methoxyphenyl)phenanthrene (6b):[64]

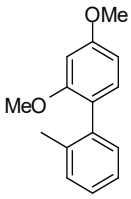


CAS Registry Number: 569674-06-2

From 9-bromophenanthrene (1 mmol, 257 mg), 2-bromoanisole (2 mmol, 374 mg) and 514 µL of *t*-BuLi in heptane.

White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 213 mg, 62% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.81 (dd, *J* = 13.8, 8.2 Hz, 2H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.79 (s, 1H), 7.76 – 7.64 (m, 4H), 7.62 – 7.50 (m, 2H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 6.9 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 3.75 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.23, 138.64, 134.60, 134.51, 134.24, 133.00, 132.93, 132.39, 131.91, 131.40, 130.57, 129.94, 129.36, 129.20, 129.03, 128.99, 125.47, 125.32, 123.46, 113.71, 58.27.

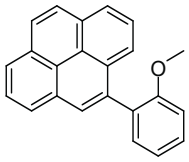
2,4-dimethoxy-2'-methyl-1,1'-biphenyl (6c)



From 2-bromotoluene (1 mmol, 171 mg), 1-bromo-2,4-dimethoxybenzene (2 mmol, 492 mg) and 514 µL of *t*-BuLi in heptane.

White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane), 169 mg, 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.13 (m, 4H), 7.06 (d, *J* = 8.9 Hz, 1H), 6.56 (d, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 3.75 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.88, 160.22, 141.05, 139.81, 133.93, 133.00, 132.20, 129.76, 128.06, 126.31, 106.73, 101.18, 58.06, 58.04, 22.62. HRMS (APCI+, *m*/*z*): calculated for $C_{15}H_{17}O_2$ [M+H$^+$]: 229.1223; found: 229.1162

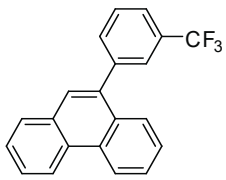
4-(3-methoxyphenyl)pyrene (6d)



From 4-bromopyrene (1 mmol, 281 mg), 2-bromoanisole (2 mmol, 374 mg) and 514 µL of *t*-BuLi in heptane.

Green solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/acetone 100:1), 304 mg, 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 7.4 Hz, 3H), 8.12 (s, 2H), 8.04 (d, *J* = 6.8 Hz, 2H), 7.93 (d, *J* = 6.0 Hz, 2H), 7.57 – 7.46 (m, 2H), 7.22 – 7.11 (m, 2H), 3.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.71, 136.69, 132.05, 131.36, 131.23, 131.05, 130.79, 129.78, 129.34, 128.23, 127.70, 127.20, 126.02, 125.68, 125.18, 125.01, 124.87, 124.20, 120.87, 111.20, 55.67. HRMS (ESI+, *m*/*z*): calculated for $C_{23}H_{17}O$ [M+H$^+$]: 309.1274; found: 308.2276.

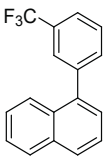
9-(3-(trifluoromethyl)phenyl)phenanthrene (6e)



From 9-bromophenanthrene (1 mmol, 257 mg), 3-bromobenzotrifluoride (2 mmol, 550 mg) and 514 µL of *t*-BuLi in heptane.

Colourless liquid obtained after filtration over a silica plug (SiO_2, *n*-pentane/acetone 100:1), 226 mg, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, *J* = 8.8 Hz, 1H), 8.75 (d, *J* = 8.7 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.77 – 7.55 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.25, 139.85, 136.10, 133.97, 133.35, 133.32, 132.83, 131.44 (q, *J* C-F = 273.3 Hz), 129.70, 129.67, 129.58, 129.46, 129.39, 129.22, 129.05, 128.24, 126.90, 126.87, 125.74, 125.32, 125.25.^{19}F NMR (376 MHz, $CDCl_3$): δ -62.39. HRMS (ESI+, *m*/*z*): calculated for $C_{21}H_{14}F_3$ [M+H$^+$]: 323.1042; found: 324.2226.

1-(3-(trifluoromethyl)phenyl)naphthalene (6f)[65]

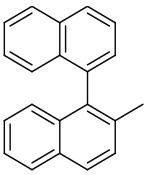


CAS Registry Number: 194874-05-0

From 1-bromonaphthalene (1 mmol, 254 mg), 3-bromobenzotrifluoride (2 mmol, 550 mg) and 514 μL of *t*-BuLi in heptane.

Colourless oil obtained after filtration over a silica plug (SiO_2, *n*-pentane), 269 mg, 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, *J* = 8.5 Hz, 1H), 7.99 (s, 1H), 7.95 – 7.82 (m, 3H), 7.79 – 7.50 (m, 5H), 7.38 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.20, 137.34, 134.71, 134.29, 133.97, (q, *J* C-F = 273.9 Hz), 132.20, 131.01, 130.63, 130.03, 129.80, 129.39, 128.87, 127.46, 127.42, 127.39, 127.35, 126.71, 126.67, 126.63, 126.59, 125.54, 25.55. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.48.

2-methyl-1,1'-binaphthalene (6g).[66]



CAS Registry Number: 69363-30-0

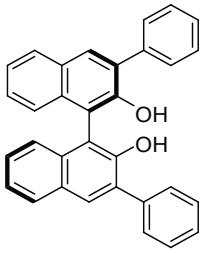
Synthesized using catalytic system B with 1-bromo-2-methylnaphthalene (1 mmol, 221 mg), 1-bromonaphthalene (2 mmol, 508 mg) and 514 μL of *t*-BuLi in heptane.

Colourless oil obtained after filtration over a silica plug (SiO_2, *n*-pentane), 260 mg, 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.5 Hz, 1H), 8.27 – 8.23 (m, 1H), 7.89 – 7.81 (m, 2H), 7.83 – 7.76 (m, 2H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.65 – 7.50 (m, 3H), 7.52 – 7.43 (m, 1H), 7.39 – 7.28 (m, 2H), 2.64 (s, 3H). ^{13}C NMR (101 MHz, CD_2Cl_2): δ 136.85, 135.57, 133.97, 133.48, 132.95, 130.84, 129.59, 129.26, 128.99, 128.87, 128.26, 128.21, 128.03, 127.88, 127.61, 127.08, 126.80, 126.58, 125.05, 123.83, 25.14

Spectral data of Heterocoupled Compounds (from an aryl chloride and anisole derivatives):

For the synthesis of the following compounds general procedure C was used (The bottle of t-BuLi was titrated at 3,1M in heptane)

3,3′-diphenyl-[1,1′-binaphthalene]-2,2′-diol (8a).[67]

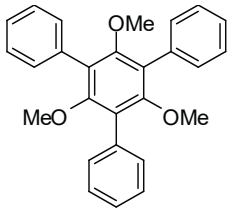


CAS Registry Number: 75640-70-9

From 2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (1 mmol, 374 mg), chlorobenzene (3 mmol, 338 mg) and 790 μL of *t*-BuLi in heptane.

White solid obtained after recrystallization from cyclohexane, 403 mg, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 2H), 7.93 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 7.2 Hz, 4H), 7.50 (t, *J* = 7.5 Hz, 4H), 7.41 (q, *J* = 7.1 Hz, 4H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 5.36 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.79, 140.12, 135.62, 134.05, 133.33, 132.26, 132.11, 131.14, 131.11, 130.43, 130.00, 126.99, 126.94, 115.07.

1,3,5-trimethoxy-2,4,6-triphenyl (8b).[68]

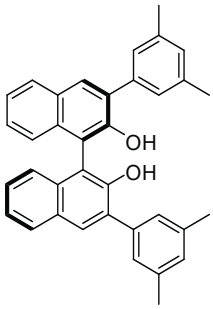


CAS Registry Number: 161979-28-8

From 1,3,5-trimethoxybenzene (1 mmol, 168 mg), 1-chlorobenzene (5 mmol, 563 mg) and 790 μL of *t*-BuLi in heptane.

White solid obtained after filtration over a silica plug (SiO_2, *n*-pentane/Et_2O 100:0-5), 345 mg, 87% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 – 7.31 (m, 15H), 3.90 (s, 3H), 3.84 (s, 3H), 3.81 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.28, 161.16, 160.19, 137.09, 136.93, 133.88, 133.65, 130.32, 130.18, 129.22, 129.03, 95.85, 58.70, 58.58, 58.00.

3,3'-bis(3,5-dimethylphenyl)-[1,1'-binaphthalene]-2,2'-diol (8c).[67]

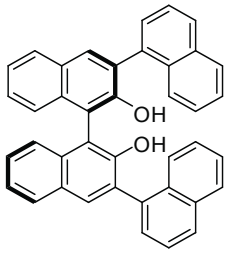


CAS Registry Number: 215433-51-5

From 2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (1 mmol, 374 mg), 1-chloro-3,5-dimethylbenzene (3 mmol, 522 mg) and 790 μL of *t*-BuLi in heptane.

Colourless solid obtained after recrystallization from cyclohexane, 435 mg, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 2H), 7.91 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.28 (m, 8H), 7.27 – 7.21 (m, 2H), 7.06 (s, 2H), 5.39 (s, 2H), 2.40 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.61, 140.81, 139.90, 135.65, 133.59, 133.49, 132.16, 132.02, 130.99, 129.97, 129.74, 127.04, 126.79, 115.41, 24.06.

[1,3':1',1":3",1"']-Quaternaphthalene]-2",3'-diol (8d).[69]

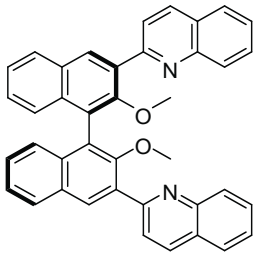


CAS Registry Number: 851615-07-1

From 2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (1 mmol, 374 mg), 1-chloronaphthalene (3 mmol, 338 mg) and 790 μL of *t*-BuLi in heptane.

White solid obtained after recrystallization from cyclohexane, 468 mg, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 2H), 8.02 (d, *J* = 8.4 Hz, 3H), 8.00 – 7.94 (m, 3H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.47 – 7.31 (m, 5H), 7.23 – 7.15 (m, 3H), 5.02 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.60, 136.52, 135.65, 134.11, 134.03, 133.45, 133.38, 133.33, 131.89, 131.29, 131.15, 131.08, 130.38, 129.99, 129.74, 128.81, 128.76, 128.72, 127.95, 127.45, 126.87, 116.13.

2,2′-(2,2′-dimethoxy-[1,1′-binaphthalene]-3,3′-diyl)diquinoline (8e).[70]



CAS Registry Number: 1429427-22-4

From 2,2′-dimethoxy-1,1′-binaphthalene (0.1 mmol, 31.4 mg), 2-chloroquinoline (0.2 mmol, 33 mg) and 79 μL of *t*-BuLi in heptane.

Yellow solid obtained after recrystallization from cyclohexane, 44.3 mg, 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 2H), 8.30 (d, *J* = 8.4 Hz, 2H), 8.21 (d, *J* = 8.6 Hz, 2H), 8.09 (d, *J* = 8.4 Hz, 2H), 8.03 (t, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 7.9 Hz, 3H), 7.78 (d, *J* = 7.2 Hz, 2H), 7.63 – 7.55 (m, 2H), 7.44 (dt, *J* = 14.9, 6.7 Hz, 3H), 7.30 (dd, *J* = 13.1, 6.5 Hz, 4H), 3.28 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.02, 156.77, 151.11, 138.45, 137.21, 134.79, 133.63, 132.34, 132.20, 131.57, 130.20, 129.91, 129.69, 129.17, 128.55, 128.40, 127.85, 125.78, 123.73, 64.13.

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Chapter 7

Nederlandse samenvatting

Samenvatting

In de jaren 60 van de afgelopen eeuw was het met grote regelmaat it wereldwijd in het nieuws; het Softenon schandaal. Softenon is de Nederlandse merknaam van het medicijn Thalidomide, wat door het Duitse bedrijf Chemie Grünenthal op de markt gebracht werd als slaapmiddel, pijnstiller en ochtenmisselijkheid-remmer. Het slaapmiddel leek eerst bijzonder effectief en relatief veilig, en werd op multi-ton schaal geproduceerd en voorgeschreven. Een aantal jaren later werden de dramatische bijwerkingen zichtbaar, met name misvormingen bij kinderen wiens moeders Softenon had gebruikt. Uitgebreid onderzoek bracht de oorzaak van het probleem naar boven; Thalidomide was een mengsel van twee verschillende producten die gelijk waren in veel fysische eigenschappen, maar elkaars spiegelbeelden zijn. Dit zijn zogenaamde enantiomeren. Het bleek dat een van de enantiomeren inderdaad het bijzonder effectieve medicijn was, maar dat het ander verantwoordelijk was voor de giftige bijwerkingen.

Uit dit voorbeeld blijkt het belang van het scheiden van enantiomeren uit racemische mengsels voor de farmaceutische en fijnchemische industrie. Tot op heden is de meest toegepaste techniek hiervoor gebaseerd op kristallisatie. Helaas zijn niet alle producten op deze manier te scheiden. Alternatieven berusten op relatief dure chirale kolom technieken, met de bijbehorenden hoge kapitaalinvesteringen.

Enantioselectieve vloeistof-vloeistof extractie is een veelbelovende techniek voor de scheiding van enantiomeren uit een racemisch mengsel. In een typisch ELLE experiment wordt een in water opgelost racemaat in contact gebracht met een enantiomeer zuiver gastheer molecuul(chirale host)die zich in de organische laag bevindt. Onmisbaar voor het succes van het experiment zijn de niet-mengbaarheid van de twee vloeistoffen en het verschil in complexatie-energie tussen de twee enantiomeren en de chirale host. In literatuur worden twee typen mechanismen voor extractie beschreven; een waarbij de extractie alleen op het oppervlak tussen de twee onmengbare vloeistoffen plaatsvindt, en een waarbij de complexatie plaatsvindt in de vloeistoflaag waar de host zich bevindt. Een literatuur overzicht over ELLE wordt gegeven in hoofdstuk 1, waar ook de twee mechanismen in meer detail worden beschreven. Bovendien worden de onderliggende chemische principes en de gebruikte parameters belicht. Het literatuur overzicht bevat een historisch overzicht van de meest belangrijke ontdekkingen in het veld, ingedeeld naar het mechanisme waarmee zij werken.

De applicatie van chirale fosforzuren in asymmetrische katalyse werd voor het eerst beschreven in 1994 en is sindsdien gegroeid tot een interessant veld, dat zich kan meten met de veel langer bestaande katalyse met chirale metaalcomplexenDe relatief milde

condities waaronder zij opereren, ten aanzien van pKa en oplosbaarheid, maakt ze uitstekende kandidaten voor complexatie en supramoleculaire chemie. Uitbreiding van hun toepassing van het asymmetrische katalyse veld naar het ELLE veld werd voor het eerste beschreven door onze groep, en is uitgebreid verder onderzocht in hoofdstuk 2. Hierin worden ook het effect op de enantiosectiviteit van verschillende functionele groepen op een aantal posities van het BINOL skelet onderzocht tijdens de enantioselectieve extractie van amino alcoholen en amino zuren. Hierbij is een aantal variaties aangebracht aan de aryl substituenten op de 3- en 3'- posities naast variaties van alkyl groupen op de 6- en 6-'posities, waarna applicatie testen werden gedaan. Hun invloed op enantioselectieve overmaat, extractie efficientie en terug extractie capaciteiten werden getest onder verschillendecondities waaronder variaties in pH, temperatuur, concentratie en oplosmiddel.

Verder onderzoek naar de enantioselectieve extractive van amino alcoholen en amino zuren is beschreven in hoofdstuk 3. De veranderingen beschreven in dit hoofdstuk omvatten voornamelijk veranderingen in de chirale fosforzuur host, waar het standaard BINOL skelet vervangen wordt door een SPINOL skelet. Deze verandering van chirale host group veranderde niet alleen de chirale regio rondom de fosforzuur bindingsplaats, maar heeft ook invloed op de pKa van het fosforzuur. In dit hoofdstuk wordt beschreven hoe een vier op SPINOL gebaseerde forsforzuren worden gesynthetiseerd en getest in enantioselectieve extractie applicatie testen. Het belangrijkste resultaat is de hoogste selectiviteit tot nu toe ooit gevonden voor deze chirale scheidingen middels ELLE. Bovendien werd een bijzondere invloed van het oplosmiddel waargenomen, wat resulteerde in een nieuwe scheidingsmethode. In deze methode worden drie oplosmiddel lagen gebruikt waarbij beide enantiomeren door dezelfde katalysator vanuit de waterfase met hoge selectiviteit naar een andere fase getransporteerd worden.

Het onderzoek aan het effect van de structuur van het skelet van de chirale fosforzuur hosts wordt voortgezet in hoofdstuk 4. Hier worden de introductie van de commercieel verkrijgbare VAPOL en VANOL structuren voor het eerst geëvalueerd. Door hun meer starre structuur werd gevonden dat dit zeer efficiente hosts zijn voor de enantioselectieve extractie van amino alcoholen. Bovendien lieten zij minder temperatuursafhankelijkheid zien ten aanzien van de extractie efficiënty. Vervolgens werden de gehydrogeneerde versies van het BINOL skelet, de zogenaamde H8-BINOL afgeleide fosforzuren gesynthestiseerd en getest. Met deze hosts werd wel extractie, maar geen enantioselectiviteit geobserveerd. Als laatste werd de efficiëntie van TADDOL afgeleide fosforzuren voor de extractie van amino alcoholen bekeken.

Hierbij werd wel reactieve extractie, maar geen enantioselectiviteit geobserveerd.
In hoofdstuk 5 wordt het onderzoek naar eennieuwe synthesemethode beschreven. De synthese van verscheidene chirale fosforzuren and hun basis-structuur (zoals toegepast in hoofdstuk 2-4) beslaat meestal meerdere stappen. Een breed gebruikte methode voor de introductie van substituenten in deze synthese route is een palladium gekatalyseerde koolstof-koolstof koppeling. Een variatie op een eerder door onze groep gerapporteerde soortgelijke koppeling die gebruik maakt van aryl- or alkyl-lithium verbindingen is beschreven in dit hoofdstuk. Onder zeer geconcentreerde condities werd veel sneller volledige omzetting verkregen, namelijk in maar 10 minuten. Bovendien kon voor veel voorbeelden de katalysator hoeveelheid en reactie temperatuur worden verlaagd. Verschillende interessante voorbeelden zijn beschreven, waarbij een aantal mogelijk toepasbaar zijn in industriële processen. Opschaling van het process naar meerdere grammen diende als bewijs voor de robuustheid van de methodologie.
Een uitbreiding op de in hoofdstuk 5 gerapporteerde methodologie wordt beschreven in hoofdstuk 6. Hier ligt de focus op de synthese van biaryls, zowel via homo- als via hetero koppeling processen. Omdat biaryls belangrijke bouwstenen zijn in katalyse, natuurlijke producten, farmaceutische wetenschappen en polymeren, was de formatie van biaryls het onderwerp van veel onderzoekgedurende de laatste decennia. Onder hoog geconcentreerde condities worden twee gehalogeneerde aryl startmaterialen bij elkaar gebracht voor de formatie van een nieuwe koolstof-koolstof binding door de additie van een lithium verbinding in 10 minuten. Hoge opbrengsten en hoge selectiviteiten worden beschreven, die deze methodologie bij uitstek geschikt maakt voor de synthese van BINOL afgeleide structuren voor de formatie van bijvoorbeeld de chirale fosforzure hosts zoals gebruik in hoofdstuk 2.

Chapter 8

List of publications

List of publications

1. E.B. Pinxterhuis, M. Giannerini, V. Hornillos, B.L. Feringa, Fast, Greener and Scalable Direct Coupling of Organolithium Compounds with No Additional Solvent, Nat. Commun. 2016, 7, 11698

2. E.B. Pinxterhuis, J.-B. Gualtierotti, H.J. Heeres, J.G. De Vries, B.L.Feringa, Highly Efficient Enantioselective Liquid-Liquid Extraction of 1,2-Amino- Alcohols using SPINOL Based Phosphoric Acid Hosts, Chem. Sci. 2017, 8, 6409-6418

3. Susanti, T.G. Meinds, E.B. Pinxterhuis, B. Schuur, J.G. De Vries, B.L. Feringa, Proof of Concept for Continuous Enantioselective Liquid-Liquid Extraction in Capillary Microreactors using 1-Octanol as a Sustainable Solvent, Green Chem. 2017, 19, 4334-4343

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5. E.B. Pinxterhuis, J.-B. Gualtierotti, S.J. Wezenberg, J.G. De Vries, B.L. Feringa, Highly Efficient and Robust Enantioselective Liquid-Liquid Extraction of 1,2-Amino Alcohols Utilizing VAPOL- and VANOL- Based Phosphoric Acid Hosts, ChemSusChem 2018, 11, 1, 178-184

Chapter 9

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