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# The Use of *N*-Type Ligands in the Enantioselective Liquid–Liquid Extraction of Underivatized Amino Acids

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The first palladium based extraction system using chiral *N*-based ligands in the enantioselective liquid–liquid extraction (ELLE) of underivatized amino acids, is presented. The system shows the highest selectivity for the ELLE of methionine with metal complexes as hosts reported to date. Furthermore, the host can be prepared in situ from commercially available compounds. The dependency of the system on parameters such as pH, organic solvent, and temperature has been established. The intrinsic selectivity was deduced by determination of the association constants of the palladium complex with the tryptophan enantiomers.

## Introduction

The access to enantiopure compounds is of prime importance to the pharmaceutical industry[1] and can be provided by resolution of racemates, isolation from natural sources, fermentation, asymmetric catalysis and biocatalysis, with resolution still being used most frequently.[2] Among the currently used resolution methods are classical resolution and chromatography,[3] kinetic resolution[4] using enzymes or chiral catalysts, or dynamic kinetic resolution.[5] Sometimes the unwanted isomer can be racemized so that it can be recycled.[6] In terms of the amount of different enantiopure compounds produced, the most widely applied method in the fine chemical and pharmaceutical industries is still classical resolution.[1,7] However, this production method sometimes suffers from reproducibility problems, might be laborious and is relatively expensive.[8] New effective separation methods are highly desirable. Among the methods being explored are attrition-enhanced deracemization,[9] membrane-assisted[10] and chiral simulated moving bed (SMB)[17] separations, diastereomer separation by distillation,[11] supercritical extraction,[12–14] fractional enantioselective extraction.[15,16]

If an enantiopure host is able to react enantiospecifically and reversibly with a racemic substrate, enantioselective liquid–liquid extraction (ELLE) is possible (Figure 1). An enantiomeric separation of the substrate can occur between the two phases in a single step, provided that the formed complex is confined to one phase in a biphasic system. If the separation is imperfect, a fractional extraction Scheme is needed.[18,19] A minimal selectivity of 1.5 is generally viewed being necessary to avoid the requirement for an excessive number of fractional extraction steps.[20] With a versatile host, the separation of racemates of an entire class of compounds is potentially achievable.

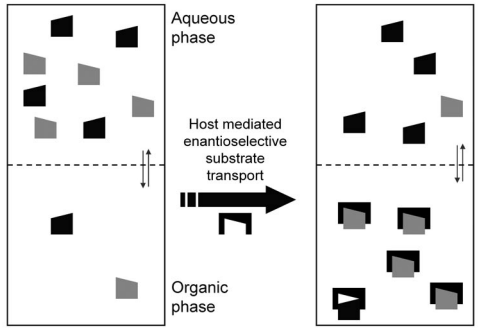


Figure 1. Schematic representation of ELLE. Symbols: grey blocks: (*S*)-substrate, black blocks: (*R*)-substrate, black brackets: chiral host.

Chiral hosts can also be applied catalytically in U-tubes or membranes.[21,22] We have recently employed chiral palladium phosphane complexes to transport amino acids through a liquid membrane enantioselectively.[23] Alternatively, copper complexes with chiral diaminoethane derivatives[24] or hydroxyproline derivatives[25] have been used.

Maier and Lindner have reported the use of a centrifugal partition chromatograph containing an MTBE solution of bis-1,4-(dihydroquinidinyl)phthalazine as the stationary chiral host solution and were able to fully separate the herbicide dichlorprop which was fed as a solution in aqueous buffer as the mobile phase.[26] As these methods are not

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scalable we have developed the use of centrifugal separators as a highly efficient method for continuous extraction.[27–29] Applying a number of these in series allows for the full separation of a racemate.[30]

With the achievement of a novel fully scalable continuous enantioseparation process, a pressing need for improved chiral host compounds remains.[20] In our labs, the separation of chiral primary amines has been achieved by the use of chiral phosphoric acids as hosts.[31] However, the enantioselective extraction of underivatized amino acids persists to be one of the great challenges within the field of ELLE. Besides the seminal work of the groups of Cram and de Mendoza,[32–34] proline-copper complexes[20,35] and β-diketonato-lanthanide complexes[36] have been studied with variable success. Recently we have shown that chiral palladium phosphane complexes show the highest selectivity in the enantioselective extraction of tryptophan using metal complexes thusfar reported.[23] The selective extraction of α-amino acids over their β-amino acid isomers even allowed for the isolation of enantiopure β-amino acids in a single extraction step.[37]

These findings led us to explore the nature of the chiral ligand used for the palladium complex. The use of $C_2$-symmetric chiral bis(oxazoline) ligands, which have shown their success in the field of asymmetric catalysis[38] would not only offer new options for enantioselective extraction, but would also be the first use of these class of ligands in the field of ELLE.

In this paper, we show the first use of palladium complexes containing *N*-based ligands for the enantioselective extraction of underivatized amino acids. The Pd-pyBOX complex shows the best performance with the separation of methionine and gives the highest operational selectivity using metal complexes reported to date.

## Results and Discussion

Two chiral bisoxazoline (BOX) ligands were used to study the properties of chiral palladium complexes as hosts in ELLE. The structure of [2,2′-isopropylidenebis((4*S*)-4-*tert*-butyl-2-oxazoline)$Pd^{II}Cl_2$] (Pd-*t*BuBOX)[39] is depicted in part a of Figure 2. The second readily made palladium complex that was tested for the ELLE of amino acids is [2,6-bis((4*R*)-4-phenyl-2-oxazolinyl)pyridine$Pd^{II}Cl]^+$ $SbF_6^-$ (Pd-pyBOX)[40] (Figure 2, b).

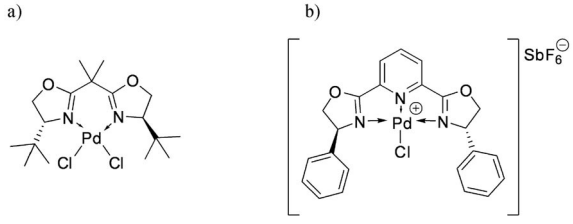


Figure 2. Structure of (a) 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]$Pd^{II}Cl_2$ (Pd-*t*BuBOX) and (b) [2,6-bis((4*R*)-4-phenyl-2-oxazolinyl)pyridine$Pd^{II}Cl]^+$ $SbF_6^-$ (Pd-pyBOX).

### ELLE with Pd-*t*BuBOX as a Host

The Pd-*t*BuBOX complex was tested in combination with Trp at different temperatures, pH and ratio's between host and guest as shown in Table 1. Enantioselective liquid–liquid extractions were performed with equivolumous amounts of palladium complex dissolved in the organic phase and the amino acid racemate confined in the aqueous layer. When [host] = 1.0 mM, low distributions were obtained. To increase the distribution, the host concentration was increased. The highest operational selectivity ($\alpha_{op}$) of 2.0 was achieved at low distribution (entry 4). At a moderate distribution of 0.7 (entry 5) the $\alpha_{op}$ decreased to 1.2.

Table 1. ELLE of Trp with Pd-*t*BuBOX as a host.[a]

| Entry | pH | [host] [mM] | *T* | *D*(org/aq.)[b] | $\alpha_{op}$[c] |
|---|---|---|---|---|---|
| 1 | 6.0 | 1.0 | r.t. | 0.2 | 1.3 |
| 2 | 7.0 | 1.0 | r.t. | 0.5 | 1.4 |
| 3 | dd.[d] | 1.0 | r.t. | 0.3 | 1.0 |
| 4 | 6.0 | 2.0 | r.t. | 0.2 | 2.0 |
| 5 | 7.0 | 2.0 | r.t. | 0.7 | 1.2 |
| 6 | dd. | 2.0 | r.t. | 0.4 | 1.2 |
| 7 | 6.0 | 1.0 | 6 °C | 0.4 | 1.3 |
| 8 | 7.0 | 1.0 | 6 °C | 1.2 | 1.2 |

[a] Conditions: *T* = 6 °C, host: $PdCl_2$-*t*BuBOX, substrate: Trp, [substrate] = 2.0 mM, organic phase: dcm. [b] The distribution *D*(org/aq.) of the substrate (AA) over the two phases is defined as the ratio of the concentration of the substrate over the two phases ($D = [AA]_{org}/[AA]_{aq.}$). [c] The operational selectivity ($\alpha_{op}$) is defined as the ratio of distribution of enantiomers ($\alpha_{op} = D_{D-AA}/D_{L-AA}$). [d] Double-distilled water.

### Substrate Scope with Pd-*t*BuBOX

Extractions of other amino acids gave the results listed in Table 2. All amino acids except histidine in entry 10 showed significant distribution. The amino acids Met at pH = 7.0 and Phe in double distilled water show that an $\alpha_{op}$ of, respectively, 1.3 and 1.7 can be achieved (entries 1 and 4). The pH of the aqueous phase in the case of double distilled water is between 5.0 and 6.0. The distribution is clearly dependent on the pH and shows the same behaviour as observed with the palladium phosphane complexes: a higher pH results in a higher distribution.[23] What is distinct from

Table 2. Substrate scope of ELLE with Pd-*t*BuBOX as host.[a]

| Entry | Substrate | pH | *D*(org/aq.) | $\alpha_{op}$ |
|---|---|---|---|---|
| 1 | Met | 7.0 | 1.7 | 1.3 |
| 2 | Met | dd. | 0.4 | 1.1 |
| 3 | Phe | 7.0 | 0.8 | 1.1 |
| 4 | Phe | dd. | 0.2 | 1.7 |
| 5 | Pge | 7.0 | 1.8 | 1.1 |
| 6 | Pge | dd. | 0.2 | – |
| 7 | Tyr | 7.0 | 21.6 | – |
| 8 | Tyr | dd. | 0.2 | – |
| 9 | His | 7.0 | 1.5 | 1.0 |
| 10 | His | dd. | 0.0 | 1.1 |

[a] Conditions: *T* = 6 °C, host: $PdCl_2$-*t*BuBOX, [host] = 1.0 mM [substrate] = 2.0 mM, organic phase: dcm.

  

the palladium phosphane system is the dependence of the $\alpha_{op}$ on the pH of the aqueous phase. For example, Phe gives a higher $\alpha_{op}$ at lower pH (entries 3 and 4).

### Solvent Dependence with Pd-*t*BuBOX

Also the dependence of the distribution and $\alpha_{op}$ on the solvent was investigated for a list of halogenated solvents, as presented in Table 3. It can be seen that the ELLE of Met with Pd-*t*BuBOX performs best in chloroform where it has a good distribution and a reasonably large operational selectivity of 1.4 (entry 3). Like the palladium phosphane system,[23] aromatic solvents does not result in significant selectivity (entry 4).

Table 3. Solvent dependence of the ELLE of Met with Pd-*t*BuBOX as a host.[a]

| Entry | Solvent | *D*(org/aq.) | $\alpha_{op}$ |
|---|---|---|---|
| 1 | dichloromethane | 1.7 | 1.3 |
| 2 | 1,2-dichloroethane | 0.6 | 1.2 |
| 3 | chloroform | 1.1 | 1.4 |
| 4 | chlorobenzene | 0.9 | 1.1 |

[a] Conditions: $T$ = 6 °C, host: PdCl2-tBuBOX, substrate: Met, [host] = 1.0 mm [substrate] = 2.0 mm, pH = 7.0, organic phase: dcm.

### ELLE with Pd-pyBOX

The system was first tested for enantioselective binding to tryptophan and these results are listed in Table 4.

Table 4. The ELLE of Trp with Pd-pyBOX as a host.[a]

| Entry | pH | [host] | $T$ | *D*(org/aq.) | $\alpha_{op}$ |
|---|---|---|---|---|---|
| 1 | 6.0 | 1.0 | r.t. | 0.7 | 1.1 |
| 2 | 7.0 | 1.0 | r.t. | 0.9 | 1.4 |
| 3 | 8.0 | 1.0 | r.t. | 2.1 | 1.2 |
| 4 | dd. | 1.0 | r.t. | 0.5 | 1.0 |
| 5 | 6.0 | 1.0 | 6 °C | 0.4 | 1.0 |
| 6 | 7.0 | 1.0 | 6 °C | 1.1 | 1.1 |
| 7 | 8.0 | 1.0 | 6 °C | 1.4 | 1.1 |
| 8 | 7.0 | 2.0 | r.t. | 1.1 | 1.1 |

[a] Conditions: $T$ = 6 °C, host: $PdCl_2$-pyBOX, substrate: Trp, [substrate] = 2.0 mM, organic phase: dcm.

The distributions are generally between 0.2 and 1.1. At pH = 8.0 distributions are increased up to 2.1 at room temp. (entry 3). The $\alpha_{op}$ is significant in six of the eight cases. Especially entry 2 shows a promising $\alpha_{op}$ of 1.4. Additionally, entries 2 and 8 show that when the host concentration is doubled the distribution only increases slightly, while the $\alpha_{op}$ decreased substantially from 1.4 to 1.1. When the conditions in entry 1 are compared to those of Pd-*t*BuBOX (Table 1, entry 4) the performance in distribution is much better for Pd-pyBOX, but the $\alpha_{op}$ is non-significant, compared to a good $\alpha_{op}$ of 2.0 in the case of Pd-*t*BuBOX.

### Substrate Scope with Pd-pyBOX

Several other amino acids in addition to Trp were examined for enantioselective complexation with Pd-pyBOX, see Table 5. As can be seen in Table 5, the substrates show a significant distribution. The distributions using double distilled water as the aqueous phase are between 0.6–1.6. At pH = 7.0, the distribution is typically higher, except in the case of Met (entry 1). The distribution of Tyr rises to 5.9 (entry 7). It is apparent that the Pd-pyBOX host is susceptible to complexation with substrate stoichiometries greater

Table 5. The substrate scope of the ELLE with Pd-pyBOX.[a]

| Entry | Substrate | pH | *D*(org/aq.) | $\alpha_{op}$ |
|---|---|---|---|---|
| 1 | Met | 7.0 | 1.2 | 1.5 |
| 2 | Met | dd. | 1.6 | 1.4 |
| 3 | Phe | 7.0 | 0.9 | 1.0 |
| 4 | Phe | dd. | 0.6 | 1.0 |
| 5 | Pge | 7.0 | 1.2 | 1.0 |
| 6 | Pge | dd. | 0.4 | 1.1 |
| 7 | Tyr | 7.0 | 5.9 | 1.2 |
| 8 | Tyr | dd. | 0.6 | 1.0 |
| 9 | His | 7.0 | 1.4 | 1.0 |
| 10 | His | dd. | 1.3 | 1.0 |

[a] Conditions: $T$ = 6 °C, host: $PdCl_2$-pyBOX, [host] = 1.0 mM, [substrate] = 2.0 mM, organic phase: dcm. Temperature and pH dependence with Pd-pyBOX

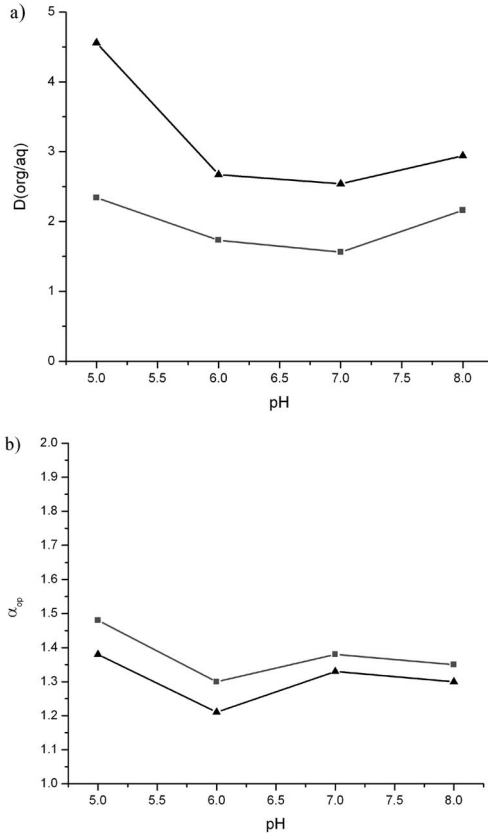


Figure 3. The distribution (a) and $\alpha_{op}$ (b) dependence on pH at 6 °C (grey lines) and room temp. (black lines) of the ELLE of Met with Pd-pyBOX as a host. Conditions: host: Pd-pyBOX, substrate: Met, [host] = 1.0 mM, [substrate] = 2.0 mM, organic phase: dcm.

  

than 1, which is a property also observed with $PdCl_2$[(*S*)-BINAP] as a host, albeit at higher pH. Interestingly, the Pd-pyBOX host shows a distribution of 1.3 for histidine (entry 10), where under corresponding conditions the Pd-*t*BuBOX shows no significant distribution (Table 2, entry 10).

The operational selectivities observed are significant in the case of Met (entries 1 and 2). The other substrates do not show significant selectivity. The thioether functionality of Met, which is known to coordinate to palladium[41] may play an important role in the selective binding to the Pd-pyBOX complex.

Further testing with Met at two different temperatures and various pH's gave the results shown in Figure 3. At 6 °C, the distribution is essentially constant over the pH interval 5.0–8.0. At room temp. the distribution is higher overall compared to that at $T$ = 6 °C. It shows a significant increase at pH = 5.0, where $D$(org/aq.) = 4.6. When the distribution profile of Met extracted by Pd-pyBOX is compared to the results of the extraction of Trp by $PdCl_2$[(*S*)-BINAP] a different distribution behavior is evident. The pH dependent extraction with $PdCl_2$[(*S*)-BINAP] shows a gradual increase in distribution from 0.1 to 1.2. Apparently, the mechanism of complexation is dissimilar compared to that of $PdCl_2$[(*S*)-BINAP], possibly because the aforementioned role of the sulfur atom of Met and the fact that the pyBOX ligand is tridentate.

### Solvent Dependence with Pd-pyBOX

In Table 6 the solvent dependence on the ELLE of Met with Pd-pyBOX as a host is presented. In 1,2-dichloroethane as a solvent, the $\alpha_{op}$ is 1.7 at pH = 7.0 and the $\alpha_{op}$ is 2.1 at pH = 8.0 at a substrate concentration of 2.0 mM (entries 2 and 8). With chlorobenzene as a solvent, an $\alpha_{op}$ of 2.3 is observed at high distributions. This $\alpha_{op}$ is the highest selectivity observed for Met using metal complexes as hosts reported to date. Strikingly, this optimum performance is achieved in an aromatic organic phase. The observed selectivity for Pd-*t*BuBOX (Table 3, entry 4) and $PdCl_2$[(*S*)-BINAP][23] is non-significant in aromatic solvents.

Table 6. The solvent dependence on the ELLE of Met with Pd-pyBOX.[a]

| Entry | pH | [substrate] | Solvent | $D$(org/aq.) | $\alpha_{op}$ |
|---|---|---|---|---|---|
| 1 | 7.0 | 2.0 | chloroform | 4.3 | 1.5 |
| 2 | 7.0 | 2.0 | 1,2-dichloromethane | 10.0 | 1.7 |
| 3 | 7.0 | 2.0 | chlorobenzene | 5.9 | 1.3 |
| 4 | 7.0 | 4.0 | chloroform | 0.7 | 1.2 |
| 5 | 7.0 | 4.0 | 1,2-dichloromethane | 2.0 | 1.2 |
| 6 | 7.0 | 4.0 | chlorobenzene | 1.0 | 1.2 |
| 7 | 8.0 | 2.0 | chloroform | 4.2 | 1.7 |
| 8 | 8.0 | 2.0 | 1,2-dichloromethane | 12.7 | 2.1 |
| 9 | 8.0 | 2.0 | chlorobenzene | 9.7 | 2.3 |
| 10 | 8.0 | 4.0 | chloroform | 0.9 | 1.2 |
| 11 | 8.0 | 4.0 | 1,2-dichloromethane | 1.0 | 1.2 |
| 12 | 8.0 | 4.0 | chlorobenzene | 1.1 | 1.3 |

[a] Conditions: $T$ = 6 °C, host: $PdCl_2$-pyBOX, substrate: Met, [host] = 1.0 mM.

### UV/Vis Spectroscopy with Pd-pyBOX

Titration of L-Trp with Pd-pyBOX was followed by UV/Vis spectroscopy to determine binding and association constants. The spectra are shown in parts a and b of Figure 4. The spectra show a decrease in absorption around 290 nm and an increase around 310 nm upon an increase in concentration of L-Trp. An isosbestic point is maintained at 300 nm.

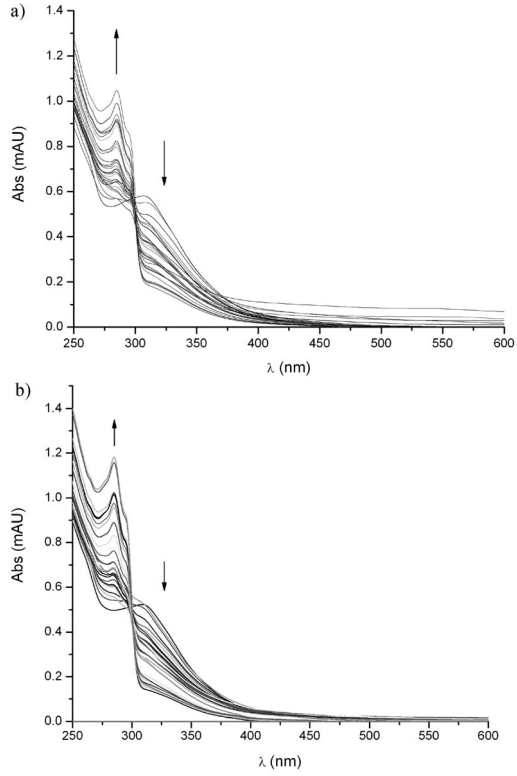


Figure 4. UV/Vis spectra of the organic layer with Pd-pyBOX after extraction with 0.0–10.0 mM D-Trp (a) and L-Trp (b).

The spectra of Pd-pyBOX with the Trp enantiomers show the same trend of increasing absorbance around 280 nm, a decreasing absorbance around 320 and an isosbestic point at approximately 300 nm.

UV/Vis measurements of an aqueous Trp solution showed that Trp has a large absorption between 255 and 300 nm and no absorption is observed above 305 nm (Figure 5, b). The distinct increase at 290 nm (Figure 4, a and b) can be ascribed to the absorption of Trp at this wavelength. Since Trp shows no absorption above 305 nm it can be concluded that the decrease in absorption at 310 nm is a result of the complexation of the Trp to the Pd-pyBOX complex.

The differential UV/Vis spectra for Pd-pyBOX with L-Trp are shown in Figure 5 (a). They show a clear minimum at 308 nm and a maximum around 297 nm, the latter being due to the absorption of Trp itself.

The differential spectra shown in Figure 5 (a) were used to determine the association constants of the Trp enantiomers to Pd-pyBOX, according to the method previously described.[23] The association constants ($K_a$) and intrinsic

  

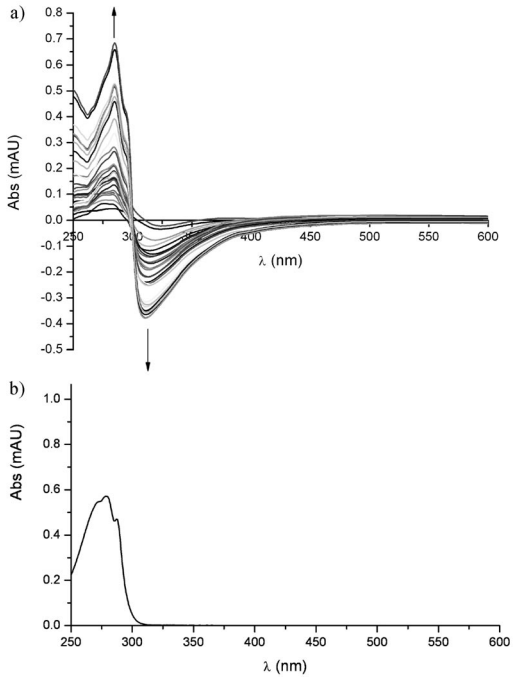


Figure 5. UV/Vis differential spectra of the titration of L-Trp to Pd-pyBOX (a) and the UV/Vis spectrum of DL-Trp in a 1.0 mM aqueous solution (b).

selectivities ($\alpha_{int}$) are presented in Table 7. The $\alpha_{op}$ is 1.4 at corresponding ELLE conditions (Table 4, entry 2). The $\alpha_{int}$ corresponds well to the $\alpha_{op}$, which supports an interface extraction mechanism.[23] The corresponding distribution of 0.9 under these conditions suggests a host to guest complexation in a 1:1 ratio.

Table 7. Association constants and intrinsic selectivity of the extraction of Trp with Pd-pyBOX.

| | $K_a$ | $\alpha_{int}$ |
|---|---|---|
| D-Trp | 900 ± 107 | 1.51 |
| L-Trp | 1350 ± 103 | |

## Conclusions

The ELLE experiments with bisoxazoline-palladium complexes as hosts show that palladium complexes with ligands other then phosphane-type ligands are capable of extracting underivatized amino acids with significant distribution and selectivity. The extraction conditions were optimized by variation of the pH of the aqueous phase, temperature and type of organic solvent. With Pd-pyBOX as a host, the highest observed $\alpha_{op}$ of 2.3 in the ELLE of Met using metal complexes as a host is reported. The Pd-pyBOX host showed a distribution behavior different from that of the palladium BINAP host with Met as a substrate, which suggests a different complexation mechanism. As in the case of the palladium BINAP host, the intrinsic selectivity of the ELLE of Trp was determined and corresponds well with the observed operational selectivity. The enantioselective extraction of a variety of amino acids using palladium complexes with *N*-type ligands displays potential for the advanced chiral separation of (un)natural amino acids.

## Experimental Section

The palladium *t*BuBOX complex was generated in situ by adding the *cis*-$[PdCl_2(CH_3CN)_2]_2$ precursor and 2,2′-isopropylidene-bis[(4*S*)-4-*tert*-butyl-2-oxazoline] in equimolar amounts to the appropriate organic solvent. The reaction mixture was stirred overnight and diluted to the desired concentration. The palladium pyBOX complex was synthesized and purified following literature procedures and spectroscopic and analytical data correspond with those reported.[40]

The racemic amino acid was dissolved in double distilled water (adding 1 equiv. of sodium hydrogen carbonate in the case of Trp-Na) or in the appropriate sodium phosphate buffer ($c$ = 0.100 M) at a concentration of $c$ = 2.0 mM. The two stock solutions were put together in a vial in equivolumous amounts (0.40 mL) and stirred overnight at 6 °C. All extractions were performed at least in duplo. A sample of the aqueous phase was analysed using a RP-HPLC equipped with a Crownpak(+) column.

Extractions were carried out as indicated above with the aqueous phase at pH = 7.0. The equivolumous amounts of the liquid phases of the extraction were increased to $V$ = 0.6 mL. DCM was used in UV/Vis and CD spectroscopy experiments. The host concentration was kept at 1.0 mM. The amino acid was enantiomerically pure and its concentration was varied between 0.20 mM and 10.0 mM. After extraction, the organic phase was isolated and subsequently UV/Vis and CD spectra were recorded.

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