Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 5443

www.rsc.org/obc

PAPER

Palladium-catalyzed cross-coupling of various phosphorus pronucleophiles with chloropyrazines: synthesis of novel Am(III)-selective extractants†

Nicolai I. Nikishkin,[a] Jurriaan Huskens,[a] Jana Assenmacher,[b] Andreas Wilden,[b] Giuseppe Modolo[b] and Willem Verboom*[a]

Received 24th April 2012, Accepted 1st June 2012
DOI: 10.1039/c2ob25787d

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

Introduction

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

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

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

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

Results and discussion

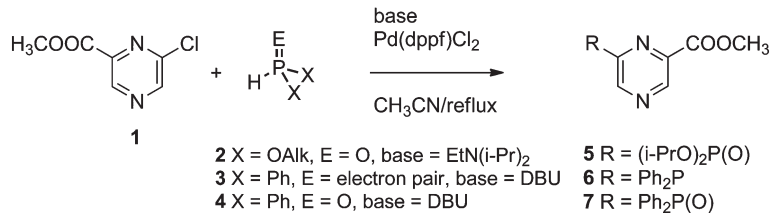
Palladium-catalyzed cross-coupling reactions with chloropyrazines

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

Reaction of **1** with 1.05 equiv. of diisopropyl phosphite (**2**) in the presence of 1.05 equiv. of Huenig base and 1 mol% of $Pd(dppf)Cl_2$ for 15 h afforded methyl 6-(diisopropylphosphono)-

[a]*Laboratory of Molecular Nanofabrication, MESA+ Institute for Nanotechnology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands. E-mail: w.verboom@utwente.nl*
[b]*Forschungszentrum Jülich GmbH, Institut für Energie- und Klimaforschung – Nukleare Entsorgung und Reaktorsicherheit (IEK-6), 52425 Jülich, Germany*

†Electronic supplementary information (ESI) available: Copies of the ^1H NMR and ^{13}C NMR spectra of the novel compounds. See DOI: 10.1039/c2ob25787d



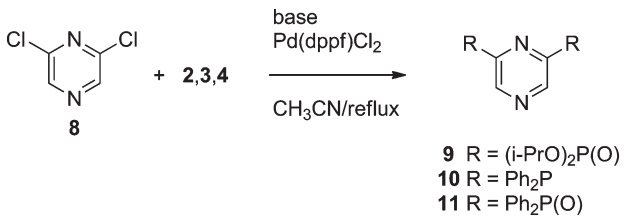
Scheme 1 Palladium-catalyzed coupling reactions on 6-chloropyrazine-2-carboxylate (**1**).

pyrazine-2-carboxylate (**5**) in 92% isolated yield. In the ^{1}H NMR spectra the signals for the pyrazine protons were shifted from 8.79 and 9.20 ppm in **1** to 9.20 and 9.34 ppm in **5**, respectively. The peak at 9.34 ppm for the proton adjacent to the phosphonate group was split into a doublet (J = 3.6 Hz) due to phosphorus–hydrogen coupling. The formation of **5** was also confirmed by the molecular ion peak in the electrospray mass spectrum.

However, under these conditions with diphenylphosphine (**3**) and diphenylphosphine oxide (**4**) no reaction occurred. Apparently, Huenig base is too weak to perform the reaction. In a study carried out in DMSO the pK_a values of diphenylphosphine (**3**) and diphenylphosphine oxide (**4**) were found to be approximately four and two orders of magnitude larger, respectively, than that of dialkylphosphites.[18] Therefore, using DBU as a base, reaction of **1** with **3** and **4** afforded methyl 6-(diphenylphosphino)- (**6**) and methyl 6-(diphenylphosphoryl)pyrazine-2-carboxylate (**7**) in 85% and 90% yield, respectively. In the case of the more acidic diphenylphosphine oxide (**4**) the reaction was already completed within 3 h, while starting from diphenylphosphine (**3**) the reaction required 20 h. In the ^{1}H NMR spectra the characteristic peaks of the pyrazine protons of **1** were shifted from 8.79 and 9.20 ppm to 8.39 and 9.12 ppm for **6** and to 9.34 and 9.59 ppm (d, J = 3.0 Hz) for **7**. All compounds showed characteristic $[M + H]^+$ peaks in their electrospray mass spectra.

To further explore the scope of the palladium-catalyzed cross-coupling of phosphorus pronucleophiles with chloropyrazines, the same series of experiments was performed with 2,6-dichloropyrazine (**8**) (Scheme 2). Thus reaction of **8** with 2.1 equiv. of diisopropylphosphite (**2**) in the presence of 2.1 equiv. of Huenig base and 1 mol% of Pd(dppf)Cl$_2$ in refluxing acetonitrile for 20 h afforded 2,6-bis(diisopropylphosphono)pyrazine (**9**) in 90% yield.

Performing the reaction of **8** under exactly the same conditions with 2 equiv. of diphenylphosphine (**3**) and diphenylphosphine oxide (**4**) in the presence of 2 equiv. of DBU gave the corresponding 2,6-bis(diphenylphosphino)- (**10**) and 2,6-bis(diphenylphosphoryl)pyrazines (**11**) in 81% and 95% yield, respectively.



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

Also here the difference in reactivity between diphenylphosphine (**3**) and diphenylphosphine oxide (**4**) is reflected in reaction times of 3 h and 24 h, respectively. This significant difference in reaction times can be easily explained considering the lower acidity of **3** on the one hand and the pyrazine ring deactivation towards the second oxidative addition (*vide infra*) to the palladium catalyst by the introduction of an electron-donating diphenylphosphino group on the other hand.

The ^{1}H NMR spectra of **9**, **10**, and **11** showed a double resonance for the pyrazine protons at 9.12, 8.24, and 9.39 ppm, respectively, as a pair of superimposed doublets. The slight difference in the chemical shifts of the protons is probably due to a different spatial orientation of the substituents and hindered rotation of the bulky (i-PrO)$_2$P(O), Ph$_2$P, and Ph$_2$P(O) groups. In addition to the ^{1}H NMR spectra, all compounds exhibited characteristic $[M + H]^+$ peaks in their electrospray mass spectra.

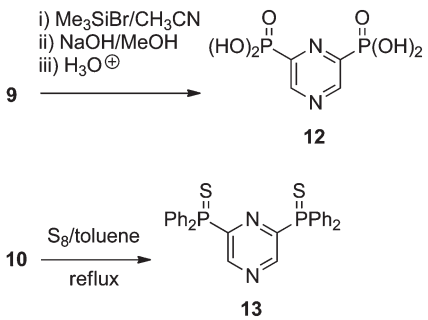
With regard to the mechanism of the reaction, we assume that the reaction follows the established mechanism of the palladium-catalyzed coupling of aryl halides and phosphorus nucleophiles.[19] To our knowledge, no detailed mechanistic study of palladium-catalyzed reactions of phosphorus pronucleophiles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

Synthesis of pyrazine-based lanthanide/actinide ligands

As part of a project aimed at the design and synthesis of novel extracting agents for actinide/lanthanide separation with improved selectivity for nuclear waste treatment,[22–24] we have

developed a series of pyrazine-based lipophilic and water-soluble ligands **12**, **13**, **15**, **20**, and **21**, containing amide, phosphinoxide, phosphonate and in one case phosphine sulfide moieties. The lipophilic ligands are typically used to extract f-block elements from highly acidic radioactive waste solutions, while the water-soluble complexants are applied to strip metal ions back.[25] Pyridine-based ligands, picolinamides for instance, are known to lose their extraction ability significantly at a pH < 3, due to protonation of the pyridine nitrogen.[25] Pyrazine will be less acid sensitive, since the pyrazine nitrogen ($pK_{b,pyrazine}$ = 13.8) is much less basic than that of pyridine ($pK_{b,pyridine}$ = 8.8).[26] It was anticipated that the introduction of phosphinoxides or phosphonates will further decrease the basicity of the pyrazine nitrogens, hence increasing the affinity towards actinides over lanthanides, the first ones being slightly softer cations than the lanthanides. In general, picolinamides show a reasonable extraction selectivity of Am(III) over lanthanides, although the amide substituents and the diluent play an important role.[27] The well known carbamoylphosphinoxides are highly efficient extractants among the bidentate organophosphorus compounds for the recovery of trivalent actinides and lanthanides from highly acidic nuclear waste solutions.[22,23]

The synthesis of the pyrazine-based ligands **12**, **13**, **15**, **20**, and **21** is mainly based on the above described methodology. Pyrazine-2,6-diyldiphosphonic acid (**12**) was synthesized in 98% yield (Scheme 3) by performing phosphonate ester cleavage of **9** with trimethylbromosilane in acetonitrile and subsequent hydrolysis with NaOH in methanol.

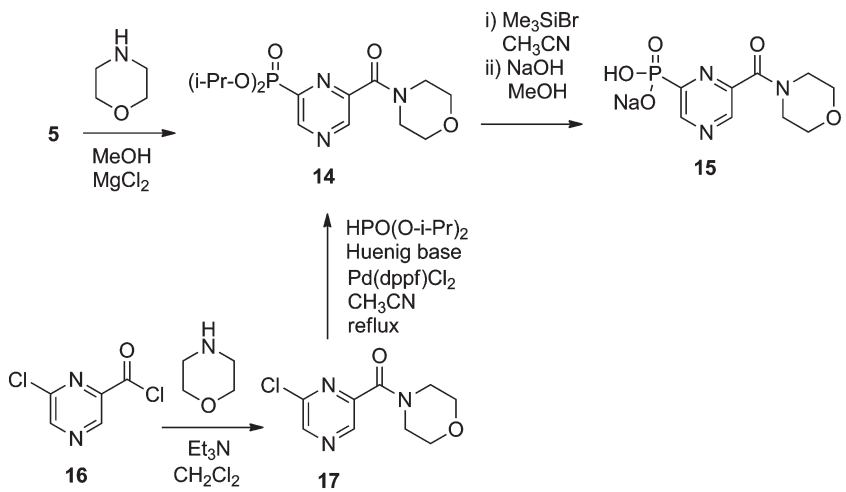


Scheme 3 Synthesis of ligands **12** and **13**.

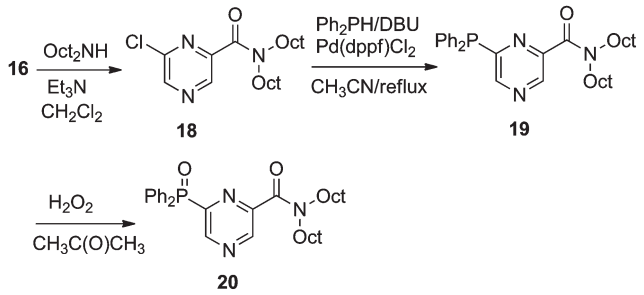
The ^{1}H NMR spectrum of **12** shows a triplet (J = 1.8 Hz) for the pyrazine protons at 8.91 ppm, and complete disappearance of the characteristic phosphonate isopropyl group signals. The electrospray mass spectrum of **12** gave the correct $[M + H]^+$, $2[M + H]^+$, and $3[M + H]^+$ peaks.

Simple oxidation of diphosphine **10** with 2 equiv. of elementary sulphur in refluxing toluene gave pyrazine-2,6-diylbis-(diphenylphosphine sulfide) (**13**) in quantitative yield (Scheme 3). In addition to the correct peak of the molecular ion in the electrospray mass spectrum, the ^{1}H NMR spectrum of **13** reveals two overlapped doublets for the pyrazine protons at 9.79 ppm, which is 0.40 ppm higher, than in the case of diphosphorylpyrazine **11**, with a negative spin-coupling constant (J = −4.2 Hz), as can be concluded from the decreased intensity of the inner lines of the multiplet.[28]

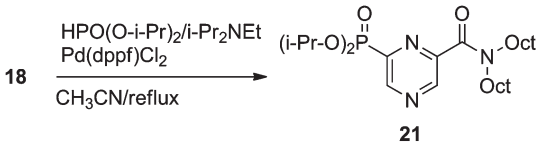
Initially, sodium hydrogen(6-(morpholine-4-carbonyl)pyrazin-2-yl)phosphonate (**15**) was prepared in 59% yield in two steps starting with amidation of ester **5** with morpholine in the presence of $MgCl_2$ [29] in methanol and followed by phosphonate cleavage of the resulting product **14** with trimethylbromosilane (Scheme 4). However, due to the modest reactivity of ester **5**, amidation of it required a 3-fold excess of the amine, which in turn promoted morpholine alkylation by diisopropyl phosphonate, complicating the purification and significantly decreasing the yield of **14**. Therefore, the synthetic sequence was altered. Starting from 6-chloropyrazine-2-carbonyl chloride (**16**), the corresponding amide **17** was obtained in quantitative yield upon reaction with morpholine. Performing P–C coupling of **17** with **2**, following the established procedure, afforded **14** in 90% yield. The ^{1}H NMR spectrum reveals two singlets for the pyrazine protons at 8.66 and 8.88 ppm, also displaying characteristic signals for the diisopropylphosphonate group at 4.67–4.80 and 1.36 ppm (d). Treatment of **14** with trimethylbromosilane in acetonitrile and subsequent hydrolysis with NaOH in methanol gave amidophosphonate **15** in 96% yield. In its ^{1}H NMR spectrum, the characteristic peaks of the pyrazine protons did not undergo a significant shift compared to **14**, however, the



Scheme 4 Synthesis of amidophosphonate **15**.



Scheme 5 Synthesis of ligand **20**.



Scheme 6 Synthesis of ligand **21**.

successful cleavage of the phosphonate ester group was proven by the complete absence of the isopropyl signals as present in **14**. The electrospray mass spectrum of **15** demonstrated the molecular ion peak.

Surprisingly, pyrazine ester **7** proved to be completely unreactive towards dioctylamine, hence it was decided to apply the same approach, as described for **15**, and to perform amidation prior to P–C coupling. Treatment of pyrazine acid chloride **16** with dioctylamine gave pyrazine dioctylamide **18** in quantitative yield. Reaction of **18** with 1 equiv. of diphenylphosphine (**3**) in the presence of 1 equiv. of DBU and 1 mol% of Pd(dppf)Cl_2 in refluxing acetonitrile overnight, followed by oxidation of the diphenylphosphino group with hydrogen peroxide in acetone, afforded 6-(diphenylphosphoryl)-*N*,*N*-dioctylpyrazine-2-carboxamide (**20**) in 75% yield (Scheme 5). In the ^{1}H NMR spectrum the signals for the pyrazine protons of **18** at 8.62 and 8.80 ppm were shifted to 8.24 and 8.72 ppm, respectively, for **19** and to 8.99 (d, J = 3.3 Hz) and 9.41 ppm, after oxidation of the phosphine, for **20**. The electrospray mass spectrum confirmed the formation of **20**, exhibiting the molecular ion peak.

Diisopropyl (6-(dioctylcarbamoyl)pyrazin-2-yl)phosphonate (**21**) was obtained by reaction of **18** with 1.05 equiv. of diisopropyl phosphite (**2**) in the presence of 1.05 equiv. of Huenig base and 1 mol% of Pd(dppf)Cl_2 in refluxing acetonitrile overnight in 87% yield (Scheme 6). In the ^{1}H NMR spectrum the signals for the pyrazine protons of **18** at 8.62 and 8.80 ppm were shifted to 8.98 ppm (d, J = 3.6 Hz) and 9.08 ppm, respectively, for **21**. The formation of **21** was also confirmed by the molecular ion peak in the electrospray mass spectrum.

Extraction results

Lipophilic ligands

Preliminary solvent extraction experiments were carried out to determine the ability of the new lipophilic ligands **11**, **13**, **20**, and **21** to extract f-block elements from highly acidic radioactive solutions into an organic phase. Therefore, organic solutions

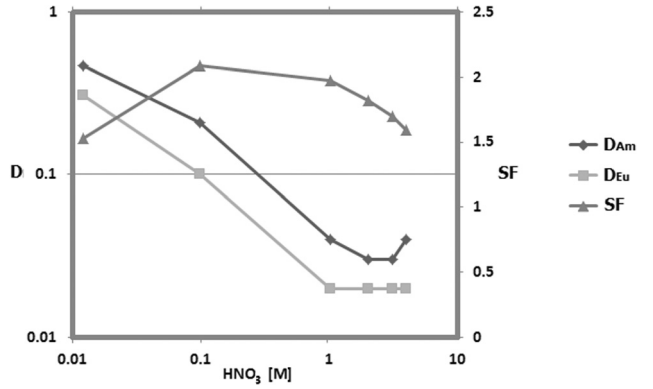


Fig. 1 D ratios of ^{241}Am(III) and ^{152}Eu(III) and SF values as a function of the initial HNO_3 concentration by ligand **11**. Organic phase: 0.05 mol L^{-1} **11** in TPH. Aqueous phase: variable concentrations of HNO_3, tracers: ^{241}Am, ^{152}Eu, mixing time: 60 min, T = 22 °C ± 1 °C.

of the ligands were contacted with nitric acid solutions (0.01 mol L^{-1}–4 mol L^{-1}) containing ^{241}Am and ^{152}Eu radiotracers. These conditions are commonly used for testing the extraction properties of extractants relevant for nuclear waste treatment.

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

$$D_M = \frac{[M]_{org}}{[M]_{aq}} \quad (1)$$

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

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

$$SF\frac{Eu}{Am} = \frac{D_{Eu}}{D_{Am}} \quad (3)$$

The extraction results of ligand **11** are presented in Fig. 1. It shows that ligand **11** is a poor extractant under the tested conditions. The distribution ratios for Am(III) and Eu(III) are below 1 in the region between 0.01 and 4 mol L^{-1} nitric acid. Since the *D*-values decrease with increasing acidity, it is assumed that **11** is protonated at the central N atom, and the poor extraction of Am(III) (D_{Am} = 0.5 at 0.01 mol L^{-1} HNO_3) may be explained by ion-pair extraction. However, this is only a hypothesis and needs to be studied by additional extraction studies *e.g.* testing synergistic mixtures with lipophilic anions.

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

To increase the solubility and possibly the affinity for trivalent actinides with the new pyrazine-based ligands, two modifications were realized: (a) one phosphoryl group was replaced by an

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

Water-soluble ligands

Actinide separation processes developed over the last 20 years are predominantly based on multi-cycle processes, *i.e.* the combined extraction of actinides (An(III)) and lanthanides (Ln(III)) from the PUREX raffinate (Plutonium Uranium Recovery by Extraction) followed by their subsequent group separation. In single-cycle processes, on the other hand, An(III) + Ln(III) are also simultaneously separated. Following an An(III)/Ln(III) co-extraction step, the trivalent actinides are selectively back-extracted (stripped) from the loaded organic phase, *e.g.* using a hydrophilic polyaminocarboxylic acid such as diethylenetriaminepentaacetic acid (DTPA). However, they have a limited solubility, which also greatly depends on the pH of the aqueous solution. Among the most important developments of this process, in Europe the so-called "innovative SANEX" (Selective ActiNide EXtraction) concept is being studied.[30,31] It is basically a DIAMEX (DIAMide EXtraction) process (An(III) and Ln(III) co-extraction) with selective back extraction of An(III) from the loaded organic phase. Instead of a water-soluble complexing agent such as DTPA, which requires in most cases buffering agents to adjust the pH, the search is for stronger acid resistant water-soluble ligands.

In the present study the new hydrophilic ligands **12** and **15** were tested for selective stripping of Am(III) from loaded organic solutions into an aqueous phase. An organic solution containing TODGA (*N*,*N*,*N*′,*N*′-tetra-*n*-octyl diglycolamide) (0.2 mol L^{-1}) and 5 vol% 1–octanol in TPH was used as a solvent.[32] The TODGA molecule is known to efficiently extract trivalent lanthanides and actinides from moderate to high nitric acid concentrations.[33,34] A weighted amount of the hydrophilic ligand was dissolved in an aqueous NH_4NO_3 (0.5 mol L^{-1}) solution followed by pH adjustment (HNO_3 or NaOH) and addition of traces of ^{241}Am(III) and ^{152}Eu(III). The nitrate ion was used as a salting-out agent to compensate the metal charge, since TODGA extracts metals only as neutral species (solvating extraction mechanism).[35]

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

Fig. 2 displays the distribution ratios as a function of the initial pH of different concentrations of ligand **12**. For comparison, the results of the reference system (TODGA) are expressed by the dotted lines in Fig. 2. TODGA shows a slightly higher affinity for Eu(III) over Am(III). High distribution ratios for Am (III) and Eu(III) were obtained and they were not affected by the initial pH of the aqueous phase due to the salting-out effect of NO_3^-. The *D* values for Am are between 34 and 76, whereas higher *D* values (250–323) were obtained for Eu, resulting in $SF_{Eu/Am}$ values between 4.5 and 7.2.

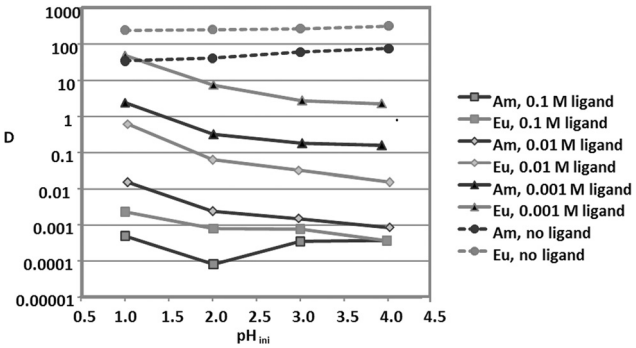


Fig. 2 *D* ratios of ^{241}Am(III) and ^{152}Eu(III) as a function of the initial pH and the influence of the concentration of ligand **12**. Organic phase: 0.2 mol L^{-1} TODGA + 5 vol% 1-octanol in TPH. Aqueous phase: 0.5 mol L^{-1} NH_4NO_3, variable pH_{ini}, variable concentrations of ligand **12**, tracers: ^{241}Am, ^{152}Eu, mixing time: 60 min, $T = 22\ °C \pm 1\ °C$.

Table 1 Percentages of retained ions in the aqueous phase and Eu/Am separation factors using ligands **12** and **15**

Ligand conc. [mol L^{-1}]	Initial pH	Ligand **12**			Ligand **15**		
		% $Am_{aq,eq}$	% $Eu_{aq,eq}$	$SF_{Eu/Am}$	% $Am_{aq,eq}$	% $Eu_{aq,eq}$	$SF_{Eu/Am}$
0	1	2.8	0.4	7.2	2.8	0.4	7.2
	2	2.4	0.4	6.3	2.4	0.4	6.3
	3	1.6	0.4	4.5	1.6	0.4	4.5
	4	1.3	0.3	4.3	1.3	0.3	4.3
0.001	1	29.3	2.0	20	2.3	0.3	7.4
	2	75.8	11.8	23	3.4	0.5	7.2
	3	84.7	26.4	15	5.7	1.1	5.6
	4	86.3	30.3	15	5.3	1.3	4.3
0.01	1	98.5	62.0	40	2.1	0.3	6.7
	2	99.8	94.1	26	10.3	1.0	11
	3	99.9	96.9	21	22.9	3.2	9.0
	4	99.9	98.5	18	24.9	4.5	7.1
0.1	1	99.9	99.8	4.6	8.5	0.9	11
	2	99.9	99.9	~1	61.4	10.3	14
	3	99.9	99.9	~1	87.0	35.2	12
	4	99.9	99.9	~1	84.2	30.5	12

Calculated using eqn (2) and (3) using the distribution ratios from Fig. 2 and 3, respectively.

Ligand **12** exhibits a very strong extractability for ^{241}Am and ^{152}Eu. At a ligand concentration of 0.1 mol L^{-1} nearly 100% of Am(III) and Eu(III) are complexed in the aqueous phase (Table 1). As expected, the distribution ratios increase with decreasing ligand concentration. However, the one of ^{152}Eu increases at a much higher rate than that of ^{241}Am. Therefore, it becomes possible to separate Am over Eu at lower ligand concentrations. The separation factor $SF_{Eu/Am}$ of Eu over Am at an initial pH of 1 increases from 4.6 to 40, upon decreasing the ligand concentration from 0.1 mol L^{-1} to 0.01 mol L^{-1} (Table 1). While decreasing the ligand concentration to 0.001 mol L^{-1} the distribution ratios increase further.

It is possible to adjust conditions, which are of great interest for the innovative-SANEX concept.[29] At a ligand concentration of 0.001 mol L^{-1} and an initial pH between 2 and 4, Eu(III) is held back preferentially in the organic phase, whereas Am(III) is

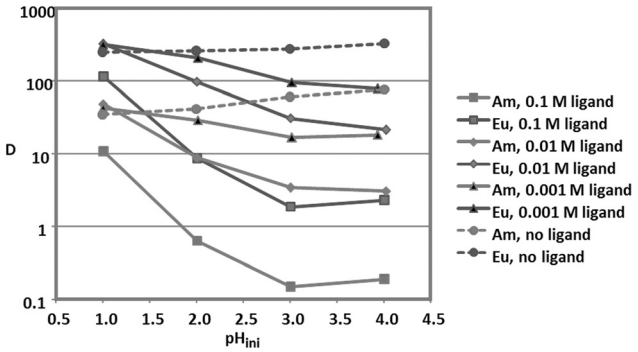


Fig. 3 D ratios of ^{241}Am(III) and ^{152}Eu(III) as a function of pH_{ini} and the influence of the concentration of ligand **15**. Organic phase: 0.2 mol L^{-1} TODGA + 5 vol% 1-octanol in TPH. Aqueous phase: 0.5 mol L^{-1} NH_4NO_3, variable pH_{ini}, variable concentrations of ligand **15**, tracers: ^{241}Am, ^{152}Eu, mixing time: 60 min, T = 22 °C ± 1 °C.

complexed selectively in the aqueous phase. The D_{Am} values are between 0.3 and 0.2 (Fig. 2), which expresses that 76% to 86% of the metal is retained in the aqueous phase. However, the D_{Eu} values are between 2 and 7, which means that >70% of the metal is kept in the organic phase. In a multi-step counter-current extraction process these conditions can be used for a complete group separation. As the ligand concentration is very low, the system may be very sensitive to loading effects.

The back extraction results with ligand **15** are depicted in Fig. 3 and also summarized in Table 1. At a low ligand concentration of 0.01 mol L^{-1} or 0.001 mol L^{-1}, the extraction of Am and Eu is less pronounced, compared to ligand **12**; only a moderate amount (<50%) of the radionuclides is extracted into the aqueous phase (Table 1). However, at a ligand concentration of 0.1 mol L^{-1}, the conditions are again interesting for the innovative-SANEX concept. The D_{Am} values are <1 in the initial pH-range between 2 and 4, but those of Eu are >1, which makes a selective separation of both radionuclides possible. Although the observed separation factors are lower than those of ligand **12** ($SF_{Eu/Am}$ ~ 10–14), due to the higher ligand concentrations, the process will be less sensitive to metal loading effects. This makes this ligand a good candidate for the innovative SANEX process.[36]

Conclusions

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

Experimental

General

The solvents, catalyst, and all reagents were obtained from commercial sources and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity INOVA (300 MHz) spectrometer. ^{1}H NMR chemical shift values (300 MHz) are reported as δ using the residual solvent signal as an internal standard ($CDCl_3$, δ = 7.257). ^{13}C NMR chemical shift values (75 MHz) are reported as δ using the residual solvent signal as an internal standard ($CDCl_3$, δ = 77.0 ppm). Electrospray ionization (positive mode) mass spectra were recorded on a WATERS LCT (Micromass KC-340) mass spectrometer. Infrared spectra were taken on a Thermo Scientific spectrometer. All reactions were performed under a nitrogen atmosphere.

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

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

Diisopropyl (6-(methoxycarbonyl)pyrazin-2-yl)phosphonate (5). Yield 2.78 g, 92%. ^{1}H NMR ($CDCl_3$): δ = 9.34 (d, 1 H, $^3J_{HP}$ = 3.6 Hz, PyzH), 9.20 (s, 1 H, PyzH), 4.92–4.82 (m, 2 H, C*H*$(CH_3)_2$), 4.02 (s, 3 H, $CH_3OC(O)$), 1.42 and 1.36 (d, 6 H, J = 6.0 Hz, CH(C*H*$_3)_2$). ^{13}C NMR: δ = 164.2, 150.3 (d, J_{CP} = 4.2 Hz), 149.9 (d, J_{CP} = 4.2 Hz), 147.6 (m), 147.5 (m), 73.3 (t, $^2J_{CP}$ = 6.8 Hz), 53.4, 24.2–24.8 (set of doublets). IR (ν_{max}/cm^{-1}): 2981, 1728, 1441, 1387, 1377, 1311, 1251, 1125, 1102, 985, 894, 780. MS (ES^+) (m/z): 303.0 $[M + H]^+$. HRMS-TOF (m/z): $[M + H]^+$ calcd 303.1110, found 303.1108.

Diisopropyl (6-(morpholino-4-carbonyl)pyrazin-2-yl)phosphonate (14). Yield 3.22 g, 90%. ^{1}H NMR ($CDCl_3$): δ = 8.88 (s, 1 H, PyzH), 8.66 (s, 1 H, PyzH), 4.80–4.67 (m, 2 H, C*H*$(CH_3)_2$), 3.84–3.79 (m, 4 H, OCH_2CH_2N), 3.75–3.64 (m, 4 H, OCH_2CH_2N), 1.36 (d, 12 H, J = 6.0 Hz, CH(C*H*$_3)_2$). ^{13}C NMR: δ = 165.8, 149.2, 148.5, 147.8 (d, $^1J_{CP}$ = 16.2 Hz), 147.1 (d, $^2J_{CP}$ = 4.3 Hz), 73.3 (d, $^2J_{CP}$ = 3.0 Hz), 73.2 (d, $^2J_{CP}$ = 3.0 Hz), 67.9, 67.0, 48.1, 43.5, 25.6–25.0 (set of doublets, $^3J_{CP}$ = 1.5 Hz). IR (ν_{max}/cm^{-1}): 2925, 2855, 1636, 1466, 1376, 1253, 1168, 1009, 887, 768. HRMS-TOF (m/z): $[M + H]^+$ calcd 358.1532, found 358.1536.

Diisopropyl (6-(dioctylcarbamoyl)pyrazin-2-yl)phosphonate (21). Yield 4.45 g, 87%. ^{1}H NMR ($CDCl_3$): δ = 9.08 (s, 1 H, PyzH), 8.98 (d, 1 H, $^3J_{HP}$ = 3.6 Hz, PyzH), 4.86–4.76 (m, 2 H, C*H*(CH_3)$_2$), 3.50 and 3.40 (t, 2 H, J = 7.5 Hz, CH_2N), 1.15–1.75 (m, 36 H, AlkH), 0.86 (t, 6 H, J = 7.6 Hz, CH_3). ^{13}C NMR: δ = 163.2, 149.0, 148.6, 147.7 (d, $^1J_{CP}$ = 16.5 Hz), 147.2 (d, $^2J_{CP}$ = 4.5 Hz), 73.2 (d, $^2J_{CP}$ = 3.0 Hz), 73.1 (d, $^2J_{CP}$ = 3.0 Hz), 32.1, 31.8, 29.8, 29.6, 29.5, 28.4, 28.0, 27.3, 26.5, 22.8, 21.9, 20.8, 14.3. IR (ν_{max}/cm^{-1}): 2979, 1638, 1519, 1386, 1255, 1143, 995, 883, 766. HRMS-TOF (*m*/*z*): [M + H]$^+$ calcd 512.3617, found 512.3621.

Methyl 6-(diphenylphosphoryl)pyrazine-2-carboxylate (7). To a solution of **1** (1.74 g, 10 mmol), Pd(dppf)Cl_2 (0.073 g, 1 mol%) and HP(O)Ph_2 (2.02 g, 10 mmol) in CH_3CN (50 mL) was added DBU (1.5 mL, 10 mmol). The resulting mixture was refluxed for 3 h and then all the volatiles were removed *in vacuo*. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and the solution was passed through a short plug of silica. The resulting solution was dried *in vacuo* yielding **7** as an amber oil (3.04 g, 90%). ^{1}H NMR ($CDCl_3$): δ = 9.59 (s, 1 H, PyzH), 9.34 (d, 1 H, $^3J_{HP}$ = 3.0 Hz, PyzH), 7.97–7.90 (m, 4 H, ArH), 7.53–7.40 (m, 6 H, ArH), 4.02 (s, 3 H, $CH_3OC(O)$). ^{13}C NMR: δ = 166.8, 151.2 (d, $^1J_{CP}$ = 17.3 Hz), 148.6, 148.3, 146.9, 133.1, 132.5, 132.4, 131.3, 131.0, 129.6, 129.0, 128.8, 128.7, 128.6, 128.5, 128.3, 56.5. IR (ν_{max}/cm^{-1}): 2954, 1750, 1522, 1439, 1399, 1306, 1198, 1167, 1152, 1121, 972, 861, 725. MS (ES$^+$) (*m*/*z*): 362.2 [M + Na]$^+$. HRMS-TOF (*m*/*z*): [M + H]$^+$ calcd 339.0899, found 339.0898.

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

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

6: yield 85%, ^{1}H NMR ($CDCl_3$): δ = 9.12 (s, 1 H, PyzH), 8.39 (d, 1 H, $^3J_{HP}$ = 1.5 Hz, PyzH), 7.41–7.35 (m, 10 H, ArH), 3.99 (s, 3 H, $CH_3OC(O)$). MS (ES$^+$) (*m*/*z*): 323.1 [M + H]$^+$.

2,6-Bis(diisopropylphosphono)pyrazine (9). To a solution of **8** (1.49 g, 10 mmol) and Pd(dppf)Cl_2 (0.146 g, 2 mol%) in CH_3CN (50 mL) were subsequently added HPO(O-i-Pr)$_2$ (3.5 mL, 21.0 mmol) and i-Pr_2NEt (3.7 mL, 21.0 mmol). The resulting mixture was refluxed for 3 h and then all the volatiles were removed *in vacuo*. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and the solution was passed through a short plug of silica. The resulting solution was dried *in vacuo* to give **9** (3.67 g, 90%). ^{1}H NMR ($CDCl_3$): δ = 9.12 (d, 2 H, $^3J_{HP}$ = 4.5 Hz, PyzH), 4.86–4.76 (m, 4 H, C*H*(CH_3)$_2$), 1.37 and 1.31 (d, 12 H, J = 6.0 Hz, CH(CH_3)$_2$). ^{13}C NMR: δ = 151.1 (d, $^1J_{CP}$ = 17.3 Hz), 149.3 (t, $^2J_{CP}$ = 4.1 Hz), 148.9 (t, $^2J_{CP}$ = 4.1 Hz), 148.1 (d, $^1J_{CP}$ = 17.3 Hz), 73.2 (d, $^2J_{CP}$ = 3.0 Hz), 73.1 (d, $^2J_{CP}$ = 3.0 Hz), 73.0 (d, $^2J_{CP}$ = 3.0 Hz), 72.9 (d, $^2J_{CP}$ = 3.0 Hz), 24.0–24.5 (set of doublets, $^3J_{CP}$ = 1.5 Hz). IR (ν_{max}/cm^{-1}): 2982, 1377, 1238, 1179, 1143, 1105, 964. MS (ES$^+$) (*m*/*z*): 409.2 [M − H]$^+$. HRMS-TOF (*m*/*z*): [M + H]$^+$ calcd 409.1657, found 409.1654.

2,6-Bis(diphenylphosphino)pyrazine (10). To a solution of **8** (1.49 g, 10 mmol) and Pd(dppf)Cl_2 (0.146 g, 2 mol%) in CH_3CN (50 mL) were subsequently added $HPPh_2$ (3.4 mL, 20 mmol) and DBU (3.0 mL, 20 mmol). The resulting mixture was refluxed for 24 h and then all the volatiles were removed *in vacuo*. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and the solution was passed through a short plug of silica. The resulting solution was dried *in vacuo*. The crude product was crystallized from toluene–hexane affording pure **10** (3.63 g, 81%). Mp 116–118 °C. ^{1}H NMR ($CDCl_3$): δ = 8.24 (d, 2 H, $^3J_{HP}$ = 3.0 Hz, PyzH), 7.28–7.24 (m, 20 H, ArH). ^{13}C NMR: δ = 153.4 (d, $^1J_{CP}$ = 13.5 Hz), 151.8 (d, $^1J_{CP}$ = 13.5 Hz), 149.5 (d, $^2J_{CP}$ = 1.3 Hz), 149.2 (d, $^2J_{CP}$ = 1.3 Hz), 132.9, 132.8, 132.6, 132.3, 132.1, 131.5, 130.1, 129.1, 129.0, 128.9, 128.7, 128.5. MS (ES$^+$) (*m*/*z*): 448.9 [M + H]$^+$. HRMS-TOF (*m*/*z*): [M + H]$^+$ calcd 449.1336, found 449.1335.

2,6-Bis(diphenylphosphoryl)pyrazine (11). To a solution of **8** (1.49 g, 10 mmol) and Pd(dppf)Cl_2 (0.146 g, 2 mol%) and HP(O)Ph_2 (4.04 g, 20 mmol) in CH_3CN (50 mL) was added DBU (3.0 mL, 20 mmol). The resulting mixture was refluxed for 3 h and then all the volatiles were removed *in vacuo*. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and the solution was passed through a short plug of silica. The resulting solution was dried *in vacuo*. The crude product was crystallized from toluene–hexane to give **11** (4.56 g, 95%). Mp 206–208 °C. ^{1}H NMR ($CDCl_3$): δ = 9.39 (dd, 2 H, $^3J_{HP}$ = 3.6 Hz, $^5J_{HP}$ = −3.3 Hz, PyzH), 7.57–7.50 (m, 12 H, ArH), 7.29–7.25 (m, 8 H, ArH). ^{13}C NMR: δ = 149.3 (d, $^1J_{CP}$ = 22.5 Hz), 148.6, 132.8–132.0 (m), 131.5, 130.1, 129.1–128.2 (m), 123.0. MS (ES$^+$) (*m*/*z*): 480.8 [M + H]$^+$. HRMS-TOF (*m*/*z*): [M + H]$^+$ calcd 481.1235, found 481.1231.

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

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

Pyrazine-2,6-diyldiphosphonic acid (12). Yield 2.35 g, 98%. Mp 205–206 °C. ^{1}H NMR ((CD_3)$_2$SO): δ = 8.91 (t, 2 H, $^3J_{HP}$ = 1.8 Hz, PyzH). ^{13}C NMR: δ = 154.3 (d, $^1J_{CP}$ = 15.8 Hz), 151.4 (d, $^1J_{CP}$ = 15.8 Hz), 147.6 (t, $^2J_{CP}$ = 4.5 Hz), 147.3 (t, $^2J_{CP}$ =

4.5 Hz). MS (ES^+) (*m*/*z*): 241.0 $[M + H]^+$. HRMS-TOF (*m*/*z*): $[M + H]^+$ calcd 240.9779, found 240.9772.

(6-(Morpholino-4-carbonyl)pyrazin-2-yl)phosphonic acid (15). Yield 2.63 g, 96%. ^1H NMR ($(CD_3)_2SO$): δ = 8.95 and 8.85 (s, 1 H, PyzH), 3.65 (bs, 4 H, OCH_2CH_2N), 3.55 and 3.44 (t, 2 H, J = 3.0 Hz, OCH_2CH_2N). ^{13}C NMR: δ = 163.7, 148.1, 147.4, 145.7 (d, $^1J_{CP}$ = 3.8 Hz), 143.6 (d, $^1J_{CP}$ = 5.3 Hz), 67.0, 66.9, 47.9, 43.1. IR (ν_{max}/cm^{-1}): 2971, 1632, 1362, 1442, 1268, 1068, 1025, 1008, 803, 767. HRMS-TOF (*m*/*z*): $[M + H]^+$ calcd 274.0593, found 274.0585.

2,6-Bis(diphenylthiophosphoryl)pyrazine (13). A suspension of **10** (4.48 g, 10 mmol) and elementary sulfur (0.64 g, 20 mmol) in toluene (100 mL) was refluxed overnight forming a brown solution. Then all the volatiles were removed *in vacuo*. The residue was recrystallized from hot EtOH giving **13** as orange crystals (4.51 g, 88%). Mp 154–157 °C. ^1H NMR: δ = 9.79 (dd, 2 H, $^3J_{HP}$ = 3.6 Hz, $^5J_{HP}$ = −4.2 Hz, PyzH), 7.56–7.45 (m, 12 H, ArH), 7.33–7.26 (m, 8 H, ArH). ^{13}C NMR: δ = 151.9 (d, $^1J_{CP}$ = 11.3 Hz), 150.5 (d, $^1J_{CP}$ = 11.3 Hz), 149.5 (d, $^2J_{CP}$ = 3.8 Hz), 149.2 (d, $^2J_{CP}$ = 3.8 Hz), 132.5, 132.4, 132.2, 131.6, 130.4, 128.8, 128.7, 128.6. MS (ES^+) (*m*/*z*): 512.9 $[M + H]^+$. HRMS-TOF (*m*/*z*): $[M + H]^+$ calcd 513.0778, found 513.0775.

(6-Chloropyrazin-2-yl)(morpholino)methanone (17). To a solution of acid chloride **16** (5.3 mmol) in dry CH_2Cl_2 (25 mL) was added dropwise a solution of morpholine (0.48 mL, 5.5 mmol) and Et_3N (1.5 mL, 10 mmol) in dry CH_2Cl_2 (25 mL). The resulting mixture was stirred for 2 h and then all the volatiles were removed *in vacuo*. The residue was partitioned between H_2O (30 mL) and EtOAc (70 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed *in vacuo*, giving **17** in quantitative yield as a pale yellow oil. ^1H NMR: δ = 8.88 and 8.66 (s, 1 H, PyzH), 3.83–3.78 (m, 4 H, OCH_2CH_2N), 3.75–3.64 (m, 4 H, OCH_2CH_2N). ^{13}C NMR: δ = 163.7, 148.2, 147.5, 145.8, 143.7, 67.1, 47.9, 43.2. IR (ν_{max}/cm^{-1}): 2971, 1636, 1393, 1066, 668, 654. HRMS-TOF (*m*/*z*): $[M + H]^+$ calcd 200.0591, found 200.0599.

6-Chloro-*N*,*N*-dioctylpyrazine-2-carboxamide (18). To a solution of acid chloride **16** (10 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise a solution of di-*n*-octylamine (3.0 mL, 10 mmol) and Et_3N (3.0 mL, 20 mmol) in dry CH_2Cl_2 (50 mL). The resulting mixture was stirred overnight and then all the volatiles were removed *in vacuo*. The residue was partitioned between H_2O (30 mL) and EtOAc (70 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed *in vacuo*, to afford **18** in quantitative yield as a yellow oil. ^1H NMR: δ = 8.80 and 8.62 (s, 1 H, PyzH), 3.48 and 3.32 (t, 2 H, J = 7.5 Hz, CH_2N), 1.65–1.55 (m, 4 H, AlkH), 1.39–1.15 (m, 20 H, AlkH), 0.88–0.78 (m, 6 H, CH_3). ^{13}C NMR: δ = 162.8, 148.1, 147.3, 144.9, 143.5, 32.0, 31.9, 29.6, 29.5, 29.4, 29.3, 29.0, 27.3, 26.5, 23.0, 22.6, 21.3, 14.1. IR (ν_{max}/cm^{-1}): 2927, 2854, 1632, 1558, 1541, 1507, 669. HRMS-TOF (*m*/*z*): $[M + H]^+$ calcd 382.2625, found 382.2632.

6-(Diphenylphosphoryl)-*N*,*N*-dioctylpyrazine-2-carboxamide (20). A solution of the crude phosphine **19** (2.23 g, 5 mmol) and H_2O_2 (30% aqueous, 0.8 mL) in acetone (25 mL) was stirred for 12 h and then 1 M HCl (10 mL) was added. After stirring the reaction mixture for 30 min all the volatiles were removed *in vacuo* and the residue was partitioned between H_2O (30 mL) and $CHCl_3$ (30 mL). The organic phase was dried over Na_2SO_4 and passed through a short plug of silica, giving **20** after evaporation of the solvent as a yellow oil (2.05 g, 75%). ^1H NMR: δ = 9.41 (s, 1 H, PyzH), 8.99 (d, 1 H, $^3J_{HP}$ = 3.3 Hz, PyzH), 7.85–7.75 (m, 8 H, ArH), 7.60–7.35 (m, 12 H, ArH), 3.46 and 3.11 (t, 2 H, J = 7.5 Hz, CH_2N), 1.70–0.70 (m, 30 H, AlkH). ^{13}C NMR: δ = 165.8, 150.1 (d, $^1J_{CP}$ = 17.3 Hz), 148.3, 147.3, 145.8, 133.0, 132.4, 132.2, 131.3, 130.9, 129.5, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 32.0, 31.9, 29.6, 29.5, 29.4, 29.3, 29.0, 27.2, 26.6, 22.9, 22.8, 20.8, 14.3. IR (ν_{max}/cm^{-1}): 2922, 2852, 1631, 1436, 1209, 1114, 1013, 723, 694. HRMS-TOF (*m*/*z*): $[M + H]^+$ calcd 548.3406, found 548.3405.

Solvent extraction studies

The batch experiments were performed in 2 mL glass vials. Organic and aqueous phases (500 μL) were prepared as described below, spiked with 10 μL of radiotracer (^{241}Am, ^{152}Eu, approx. 25 kBq mL^{-1}) and shaken by a vortex mixer for 60 min. The radiotracers were supplied by Isotopendienst M. Blaseg GmbH, Waldburg (Germany). Separation of the phases by centrifugation was followed by sampling 200 μL of each phase for analysis using a high-purity germanium spectrometer system obtained from EG&G Ortec, München, Germany, and equipped with the gamma vision software. The γ-lines at 59.5 and 121.8 keV were examined for ^{241}Am and ^{152}Eu, respectively. The distribution ratio D_M was measured as the ratio between the radioactivity of an isotope in the organic and the aqueous phases. Distribution ratios between 0.01 and 100 exhibit a maximum error of ±5%. The error may be up to ±20% for smaller and larger values.

Lipophilic ligands

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

The obtained organic solvent was contacted with nitric acid of variable concentrations (0.01–4 mol L^{-1}) containing traces of Am(III) and Eu(III). Nitric acid solutions were prepared by diluting concentrated nitric acid (Merck KGa, Darmstadt, Germany) with ultrapure water (resistivity, 18 MΩ cm). The acidity was checked by titration with NaOH.

Water-soluble ligands

All the aqueous solutions were prepared by dissolution of weighted amounts of the ligand in ultrapure water (resistivity, 18 MΩ cm) containing 0.5 mol L^{-1} NH_4NO_3 (salting-out agent). The initial pH of the aqueous phase was adjusted using ammonia or diluted nitric acid. The organic solvent consisted of 0.2 mol L^{-1} TODGA (extractant) and 5 vol% 1-octanol dissolved in TPH. The organic phase was not loaded with Am and Eu followed by stripping as TODGA extracts significant amounts of HNO_3 which would prevent obtaining reasonable

results at pH > 1 without using a buffer. Instead, each of the aqueous phases (500 μL) was spiked with the radiotracers and contacted with the organic solvent (500 μL). The acidities of the initial aqueous solutions were determined using a 691 Metrohm pH meter (3 mol L^{-1} KCl).

Acknowledgements

The authors gratefully acknowledge the financial support from the EU ACSEPT (Actinide reCycling by SEParation and Transmutation) project (FP7 collaborative project 211267).

References

1 H.-N. Wang, J.-S. Qin, D.-Y. Du, G.-J. Xu, X.-L. Wang, K.-Z. Shao, G. Yuan, L.-J. Li and Z.-M. Su, *Inorg. Chem. Commun.*, 2010, **13**, 1227–1230.
2 C.-F. Lee, S.-C. Hsu, K.-C. Chan, M. Nurnabi, C.-C. Lee, J.-Y. Wu, L.-L. Lai and K.-L. Lu, *CrystEngComm*, 2011, **13**, 2960–2972.
3 V. B. Romakh, G. Süss-Fink and G. B. Shul'pin, *Pet. Chem.*, 2008, **48**, 440–443.
4 V. B. Romakh, Yu. N. Kozlov, G. Süss-Fink and G. B. Shul'pin, *Russ. J. Phys. Chem. A*, 2007, **81**, 1221–1229.
5 D. Buccella, J. A. Horowitz and S. J. Lippard, *J. Am. Chem. Soc.*, 2011, **133**, 4101–4114.
6 M. Mosrin, T. Bresser and P. Knochel, *Org. Lett.*, 2009, **11**, 3407–3409.
7 P. J. J. Colbon, A. C. Foster and M. E. Giles, *J. Heterocycl. Chem.*, 2008, **45**, 1451–1456.
8 D. R. Carver, A. P. Komin, J. S. Hubbard and J. F. Wolfe, *J. Org. Chem.*, 1981, **46**, 294–299.
9 C. R. Hopkins and N. Collar, *Tetrahedron Lett.*, 2004, **45**, 8631–8633.
10 I. Malik, M. Hussain, A. Ali, S.-M. Tengho Toguem, F. Z. Basha, C. Fischer and P. Langer, *Tetrahedron*, 2010, **66**, 1637–1642.
11 W. Phakhodee, M. Toyoda, C.-M. Chou, N. Khunnawutmanotham and M. Isobe, *Tetrahedron*, 2011, **67**, 1150–1157.
12 J. J. Li and G. W. Gribble, *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*, Elsevier, Amsterdam, 2nd edn, 2006.
13 K. Bravo-Altamirano, Z. Huang and J.-L. Montchamp, *Tetrahedron*, 2005, **61**, 6315–6329.
14 Y. Belabassi, S. Alzghari and J.-L. Montchamp, *J. Organomet. Chem.*, 2008, **693**, 3171–3178.
15 F. Palacios, A. M. O. de Retana, J. I. Gil and R. L. de Munain, *Org. Lett.*, 2002, **4**, 2405–2408.
16 M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 7217–7218.
17 J. F. Hartwig, *Synlett*, 1997, 329–340.
18 J.-N. Li, L. Liu, Y. Fu and Q.-X. Guo, *Tetrahedron*, 2006, **62**, 4453–4462.
19 O. Herd, A. Hessler, M. Hingst, M. Tepper and O. Stelzer, *J. Organomet. Chem.*, 1996, **522**, 69–76.
20 K. Damian, M. L. Clarke and C. J. Cobley, *Appl. Organomet. Chem.*, 2009, **23**, 272–276.
21 M. C. Kohler, T. V. Grimes, X. Wang, T. R. Cundari and R. A. Stockland, *Organometallics*, 2009, **28**, 1193–1201.
22 H. H. Dam, D. N. Reinhoudt and W. Verboom, *Chem. Soc. Rev.*, 2007, **36**, 367–377.
23 Z. Kolarik, *Chem. Rev.*, 2008, **108**, 4208–4252.
24 F. W. Lewis, M. J. Hudson and L. M. Harwood, *Synlett*, 2011, 2609–2632.
25 M. Iqbal, J. Huskens, M. Sypula, G. Modolo and W. Verboom, *New J. Chem.*, 2011, **35**, 2591–2600.
26 M. Galletta, L. Baldini, F. Sansone, F. Ugozzoli, R. Ungaro, A. Casnati and M. Mariania, *Dalton Trans.*, 2010, **39**, 2546–2553.
27 See e.g. (*a*) E. Makrlík, P. Vaňura, P. Selucký, V. A. Babain and I. V. Smirnov, *J. Radioanal. Nucl. Chem.*, 2010, **284**, 629–633; (*b*) M. Yu. Alyapyshev, V. A. Babain, L. I. Tkachenko, I. I. Eliseev, A. V. Didenko and M. L. Petrov, *Solvent Extr. Ion Exch.*, 2011, **29**, 619–636; (*c*) A. Casnati, N. Della Ca, M. Fontanella, F. Sansone, F. Ugozzoli, R. Ungaro, K. Liger and J.-F. Dozol, *Eur. J. Org. Chem.*, 2005, 2338–2348; (*d*) E. Macerata, F. Sansone, L. Baldini, F. Ugozzoli, F. Brisach, J. Haddaoui, V. Hubscher-Bruder, F. Arnaud-Neu, M. Mariani, R. Ungaro and A. Casnati, *Eur. J. Org. Chem.*, 2010, 2675–2686; (*e*) R. Wietzke, M. Mazzanti, J.-M. Latour, J. Pécaut, P.-Y. Cordier and Ch. Madic, *Inorg. Chem.*, 1998, **37**, 6690–6697; (*f*) L. Karmazin, M. Mazzanti, Ch. Gateau, C. Hill and J. Pécaut, *Chem. Commun.*, 2002, 2892–2893 and references cited therein
28 H. J. Jakobsen, *J. Mol. Spectrosc.*, 1970, **34**, 245–256.
29 Z. Guo, E. D. Dowdy, W.-S. Li, R. Polniaszek and E. Delaney, *Tetrahedron Lett.*, 2001, **42**, 1843–1845.
30 S. Bourg, C. Hill, C. Caravaca, C. Rhodes, C. Ekberg, R. Taylor, A. Geist, G. Modolo, L. Cassayre, R. Malmbeck, M. Harrison, G. de Angelis, A. Espartero, S. Bouvet and N. Ouvrier, *Nucl. Eng. Des.*, 2011, **241**, 3427–3435.
31 C. M. Ruff, U. Müllich, A. Geist and P. J. Panak, *ATW Int. J. Nucl. Power*, 2011, **56**, 489–491.
32 A. Geist and G. Modolo, Proceedings of GLOBAL (The Nuclear Fuel Cycle: Sustainable Options & Industrial Perspectives), Paris, 2009, pp. 1022–1026, paper 9193.
33 S. A. Ansari, P. Pathak, P. K. Mohapatra and V. K. Manchanda, *Chem. Rev.*, 2012, **112**, 1751–1772.
34 For recent examples from our laboratories see: (*a*) P. K. Mohapatra, M. Iqbal, D. R. Raut, W. Verboom, J. Huskens and S. V. Godbole, *Dalton Trans.*, 2012, **41**, 360–363; (*b*) A. Sengupta, P. K. Mohapatra, M. Iqbal, W. Verboom and J. Huskens, *Dalton Trans.*, 2012, **41**, 6970–6979.
35 S. Nave, G. Modolo, C. Madic and F. Testard, *Solvent Extr. Ion Exch.*, 2004, **22**, 527–551.
36 Delangle c. s. studied the back extraction of *N*,*N*-bis(2-pyrazylmethyl)-ethylenediamine-*N*′,*N*′-diacetic acid, a tetrapodal ligand containing two pyrazine rings and two carboxylic acid groups. However, the results cannot be compared, since our ligands have a completely different backbone and the extraction mechanism is totally different: (*a*) M. Heitzmann, F. Bravard, C. Gateau, N. Boubals, C. Berthon, J. Pécaut, M.-C. Charbonnel and P. Delangle, *Inorg. Chem.*, 2009, **48**, 246–256; (*b*) M. Heitzmann, C. Gateau, L. Chareyre, M. Miguirditchian, M.-C. Charbonnel and P. Delangle, *New J. Chem.*, 2010, **34**, 108–116.