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Synthesis of an amidosulfonate-tagged biphenyl phosphine and its application in the Suzuki–Miyaura reaction affording biphenyl-substituted amino acids in water

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Dedicated to Professor Georg Süss-Fink on the occasion of his 65th birthday.

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ABSTRACT

An amidosulfonate-tagged phosphinobiphenyl, *viz* triethylammonium 2-(dicyclohexylphosphino)-4′-{[(sulfonatomethyl)amino]carbonyl}biphenyl (**3**), was prepared in two steps from 2-(dicyclohexylphosphino)biphenyl-4′-carboxylic acid and fully characterized including the crystal structure determination. As a highly polar phosphine ligand, compound **3** was employed in the Pd-catalyzed Suzuki–Miyaura cross-coupling of *N*-Boc protected 4-bromo and 4-chlorophenylalanine with aromatic boronic acids to afford the corresponding biphenyls in aqueous *N,N*-dimethylformamide or pure water. The coupling was demonstrated to proceed very well and without the loss of the Boc protecting group when the bromo-substituted substrate is reacted in the presence of 1 mol.% of Pd/**3** catalyst in water at 40 °C. Reactions with boronic acids bearing electron-withdrawing substituents and, mainly, those with the less reactive chlorophenylalanine substrate required slightly higher reaction temperature and more catalyst to achieve similar results.

Introduction

Environmental and economic concerns have recently raised the demand for the implementation of highly efficient and environmentally benign approaches toward the synthesis of organic compounds. Since catalysts can be advantageously employed to increase the rate and selectivity of chemical reactions (thereby decreasing the energy consumption and waste production) [1], significant attention is currently being paid to the search for new efficient and practically applicable catalytic processes. Among various approaches introduced to date, a particular attention has been devoted to the development of catalytic reactions proceeding in water or aqueous mixtures (solutions or biphasic mixtures).

Water as a reaction medium is not only attractive due to its low price, relatively easy recycling and non-toxic nature, but also owing to its unique physicochemical properties that may alter the course of organic transformations [2]. In order to perform metal-catalyzed reactions in water, one naturally has to ensure sufficient solubility of the particular transition metal catalysts in the aqueous solvent used, typically by means of water-soluble ligands. The design of such donors for catalytic applications, most often phosphines, is also well established, relying predominantly on modifications of the successful ligands through the introduced hydrophilic substituents among which the highly polar sulfonato moieties play a prominent role [3].

Monophosphines combining the sterically demanding biphenyl-2-yl backbone with an electron rich phosphine substituent (typically dialkylphosphine) emerged as a class of versatile ligands affording active catalytic systems for Suzuki–Miyaura biaryl coupling [4,5]. Particular derivatives sulfonated at the biphenyl moiety allowed to perform this reaction in water [6] while carboxylic acid **1** (Scheme 1) and amidation reactions were employed to conjugate the 2-(dicyclohexyl)biphenyl ligating moiety with glucosamine [7] or to immobilize it covalently onto amine-substituted polymers [8] or aminopropylated silica gel [9] with retention of its favorable catalytic properties. In order to prepare further molecular donors, we decided to convert acid **1** into an

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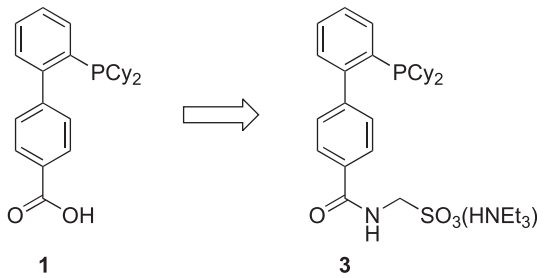


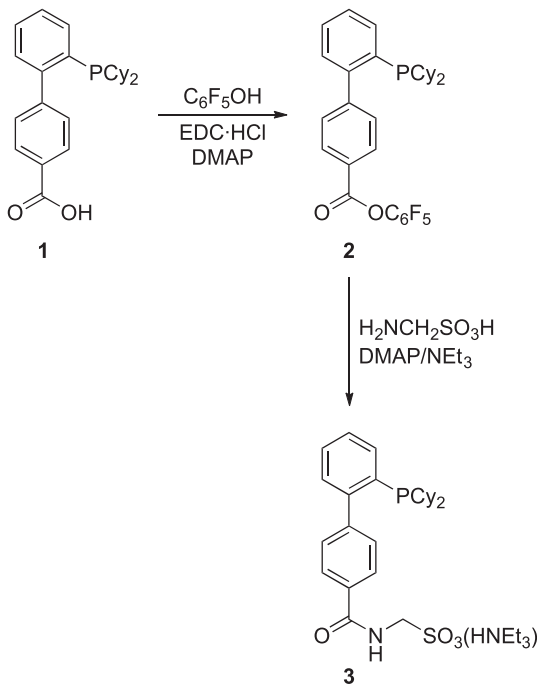
Scheme 1.

anionic amidosulfonate **3** (Scheme 1), making use of the approach which we have recently employed in the preparation of water-soluble phosphinoferrocene donors [10]. In this contribution, we describe the synthesis of a novel (dicyclohexylphosphino)biphenyl amidophosphine ligand **3** [11] possessing a water-solubilizing anionic amidosulfonate tag and its application as a ligand for Pd-catalyzed biaryl coupling of various aromatic boronic acids with halogen-substituted N-protected phenylalanine in water.

Results and discussion

Syntheses and structural characterization

The target compound was prepared (Scheme 2) from 2-(dicyclohexylphosphino)biphenyl-4′-carboxylic acid (**1**) using the active ester method [12]. In the first step, the acid was converted to the respective pentafluorophenyl ester via treatment with pentafluorophenol in the presence of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl) and 4-(dimethylamino)pyridine in dichloromethane. As a second step, the active ester was reacted with aminomethanesulfonic acid in a mixture of *N*,*N*-dimethylformamide, dichloromethane and triethylamine containing a catalytic amount of 4-(dimethylamino)pyridine. Following crystallization from hot ethyl acetate, the amidophosphine was isolated in the form of stoichiometric solvate **3**·1/2CH_3CO_2Et in a very good overall yield (80% over the two steps).



Scheme 2. Synthesis of amidophosphine **3**.

The compound was characterized by multinuclear NMR spectroscopy, IR spectroscopy, electrospray-ionization mass spectrometry and by elemental analysis. The ^{1}H NMR spectra of **3** show two sets of complicated multiplets attributable to the cyclohexyl substituents and the biphenyl moiety. Also seen are the discrete signals due to the amide proton and its bonded methylene group (δ_H 8.65 (t) and 4.16 (d) with $^3J_{HH}$ of 6.3 Hz, respectively), and the resonances of the ethyl groups in the Et_3N^+ cation. The ^{13}C NMR spectra support the formulation, displaying ten distinct resonances due to the biphenyl unit, the signals of the CH_2 linker (δ_C 55.84) and the Et_3N^+ cation as well as those of the phosphorus-bound cyclohexyl groups in a typical pattern [13]. The presence of the amide unit is clearly manifested by a ^{13}C NMR resonance at δ_C 165.31 and by amide bands in the IR spectrum (amide I: 1655 cm^{-1}, amide II: 1544 cm^{-1}). The IR spectrum further display strong characteristic bands of the terminal sulfonate group (i.e., $\nu_s(SO_3)$ at 1042 cm^{-1}, and $\nu_{as}(SO_3)$ at 1159 cm^{-1}).

Single crystals of *unsolvated* **3** suitable for X-ray diffraction analysis were obtained from hot acetonitrile. The compound crystallizes with the symmetry of the monoclinic space group *C*2/*c*. Its molecular structure is depicted in Fig. 1 and the selected geometric parameters are presented in Table 1.

The benzene rings constituting the biphenyl moiety in the amidosulfonate anion of **3** are mutually rotated by ca. 58° (see Table 1), presumably because of the presence of the bulky dicyclohexylphosphino moiety in the position adjacent to the pivotal C1—C11 bond. A similar twisting can be found in the crystal structure of 2-(dicyclohexylphosphino)-4′-(dimethylamino)-biphenyl (twist angle: 55°) [14]. Nonetheless, the phosphine substituent in **3** appears to be attached without any significant torsion at its parent aromatic ring as indicated by the torsion angle C1—C11—C12—P of −1.9(2)°. The substituents at the phosphorus atom are directed away from the parent benzene ring C(11—26) so that the P—C17 and P—C23 bond intersect the ring plane at 72.32(8)° and 32.98(8)°, respectively. The cyclohexane rings adopt chair conformations, which is manifested by the ring puckering parameters [15]: Q = 0.576(2) Å, θ = 177.8(2)° and Q = 0.569(2) Å, θ = 5.5(2)° for the rings C(17—22) and C(23—29), respectively. (Note: the ideal chair is characterized by θ = 0/180°.) Both P—C bonds assume equatorial positions, further minimizing a possible steric strain.

The amide plane constituted by the atoms C7, N1 and O1 is also twisted with respect to its bonding benzene ring though only by ca. 16°. The C8 atom lies in this plane (the distance of C8 from the amide plane is 0.001(2) Å) but its sulfonate substituent is oriented away (cf. the angle between the C8—S bond and the amide plane of 66.2(2)° and the torsion angle C7—N1—C8—S being 96.5(2)°), which in turn diverts both functional substituents (PR_2 and SO_3) into roughly opposite positions with respect to the central biphenyl moiety.

The triethylammonium cation assumes the usual geometry [16] and is connected to the amidosulfonate anion via the N2—H2···O3 hydrogen bond (Fig. 2). The sulfonate moiety is further involved in hydrogen bonding to the amide proton in an adjacent amidosulfonate moiety related by the crystallographic inversion. As the result, the solid-state structure is built up from hydrogen-bonded aggregates constituted by two amidosulfonate anions and two Et_3NH^+ cations (see Fig. 2), that are further interlinked only by the soft C—H···O_3S interactions. It is also noteworthy, that the different hydrogen-bonding interactions differentiate the S—O bonds within the terminal sulfonate moiety. The distance between the sulfur atom and oxygen O3 forming a charge-supported hydrogen bond to

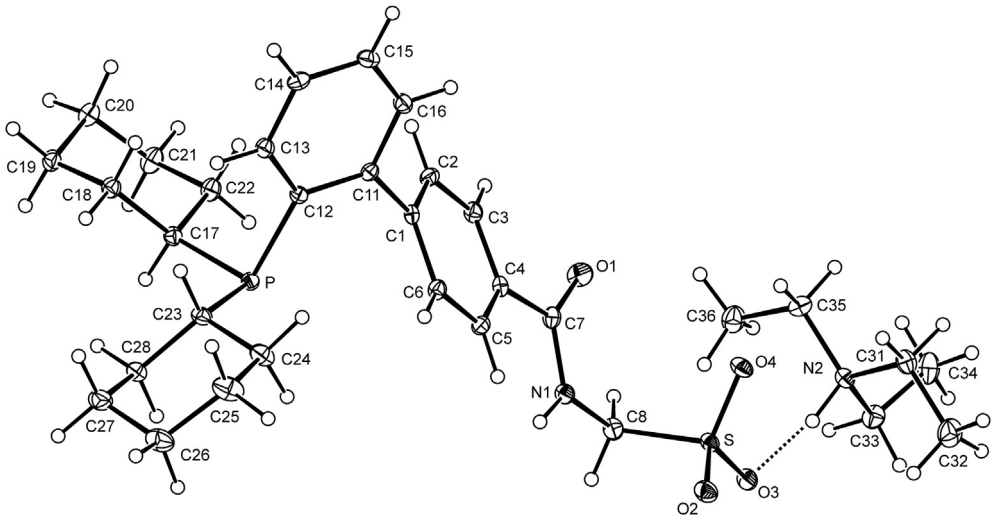


Fig. 1. PLATON plot of the molecular structure of **3**. The displacement ellipsoids enclose the 30% probability level. The N2–H2N···O3 hydrogen bond is indicated by a dotted line.

the triethylammonium cation is slightly yet statistically significantly elongated (S–O3 ≈ 1.47 Å) compared to the remaining two S–O distances (S–O2/4 ≈ 1.45 Å) pertaining to the oxygen atoms employed in O···H–N bonding (O2) or not involved in secondary binding in the crystal state (O4). Consistently, the N2···O3 distance is by ca. 0.1 Å shorter (stronger) than the N1···O2 contact (2.1760(2) vs. 2.866(2) Å).

Catalytic evaluation

Palladium-catalyzed Suzuki–Miyaura cross-coupling evolved as a versatile synthetic tool and has accordingly found numerous applications in organic synthesis [17]. It tolerates a wide range of functional groups and is relatively easy to carry out under practically applicable, moderate reactions conditions and often with commercially available starting materials. Importantly, it can be advantageously performed in aqueous media due to the hydrolytic stability of many organoboron reagents [18], which led us to evaluate the newly prepared amidophosphine ligand **3** in this particular type of cross-coupling reaction. For testing, we chose the biaryl coupling of aryl boronic acids with *N*-Boc protected [19], racemic phenylalanines halogenated in position 4 of the benzene ring (**4a** and **4b**) as the model substrates leading to biphenyl-substituted α-amino acids (Scheme 3).

Table 1
Selected interatomic distances and angles for **3** (in Å and deg).[a]

C1–C2	1.391(2)	φ_1	58.36(8)
C4–C7	1.499(2)	φ_2	15.5(2)
C7–O1	1.227(2)	O1–C7–N1	122.5(2)
C7–N1	1.351(2)	C7–N1–C8	120.9(1)
N1–C8	1.439(2)	N1–C8–S	113.0(1)
C8–S	1.793(2)	O2–S–O3	112.93(8)
S–O2	1.451(1)	O2–S–O4	113.07(7)
S–O3	1.469(1)	O3–S–O4	112.28(7)
S–O4	1.450(1)	C12–P–C17	100.49(8)
P–C12	1.849(2)	C12–P–C23	100.52(7)
P–C17	1.873(2)	C17–P–C23	105.54(8)
P–C23	1.858(2)	C1–C11–C12–P	−1.9(2)
N2–C31	1.497(2)	C31–N2–C33	113.9(2)
N2–C33	1.507(2)	C31–N2–C35	109.7(1)
N2–C35	1.501(3)	C33–N2–C35	113.6(1)

[a] Definitions: φ_1 is the dihedral angle subtended by the least-squares benzene planes C(1–6) and C(11–16) while φ_2 denotes the dihedral angle between the amide plane (C7, O1 and N1) and its bonding benzene ring C(1–6).

Because of an easy monitoring by ^{1}H NMR spectroscopy, the initial screening experiments were performed with 4-methoxyphenylboronic acid (**5e**) [20] and aryl chloride **4a** which enables for a better differentiation of the influence of the individual reaction parameters owing to is relatively lower reactivity. The reactions were performed at 100 °C and over short reaction times in order to avoid unwanted removal of the Boc protecting group, which proceeds in parallel with the coupling process affecting either **5e** or the formed **6e** and thus diminishes the yield of the desired coupling product **6e**.

The first experiments were carried out in pure water and with various bases in the presence of catalyst generated from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and ligand **3** at Pd:P molar ratio of 1:1. The NMR yields determined after 4 h at 100 °C (Table 2) revealed a pronounced effect of the base additive on the reaction outcome, reflecting very likely both the efficiency of the base in the cross-coupling reaction itself and the rate at which the base promotes removal of the protecting group. Alkali metal acetates (Na–Cs; entries 1–4) showed rather similar efficacy (24–34% yields of **6e**), while the yield achieved in the reaction with $KHCO_3$ was exactly the half of that obtained with the corresponding "normal" salt (cf. entries 2 and 5). The results obtained with the alkali metal phosphates

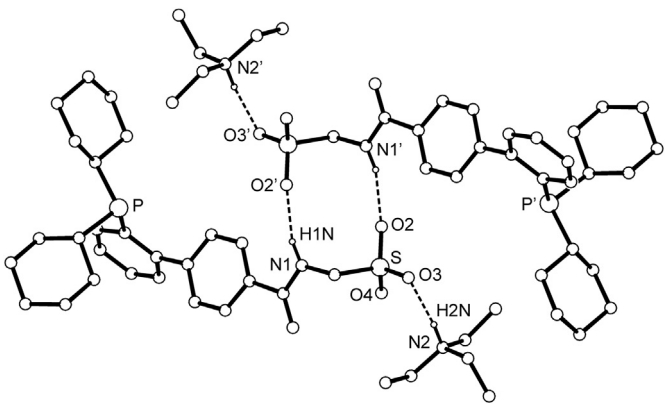
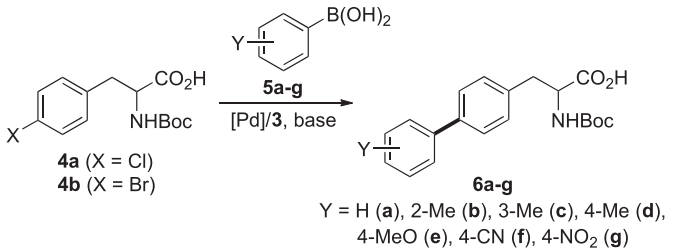


Fig. 2. View of the hydrogen bonded dimers in the structure of **3**. For clarity, only the NH hydrogens are shown. Hydrogen bond parameters are as follows: N1–H1N···O2^i, N1···O2^i = 2.866(2) Å, angle at H1N = 158°; N2–H2N···O3, N2···O3 = 2.760(2) Å, angle at H2N = 156°; i. (1/2 − x, 5/2 − y, 2 − z).



Scheme 3. Suzuki–Miyaura cross-coupling of N-protected amino acids **4** with boronic acids **5**.

(entries 6–8) differed significantly more. Whereas no coupling product was detected in the reaction mixture containing Li_3PO_4, the corresponding potassium salts afforded the best yield among the bases tested (46%). Finally, the yields obtained with KOH or KO*t*-Bu, which is hydrolyzed *in situ* to the former base, were ca. 26%, whereas potassium acetate, commonly used in this type of reactions, surprisingly failed to provide any coupling product.

The influence of the reaction solvent was evaluated next (Table 3) using potassium phosphate as the base and the same catalytic system at 100 °C for 4 h. Changing the reaction medium from water (46% yield) to pure dioxane and dioxane-water (1:1) decreased the yield of **6e** by approximately 10% (compare entries 1–3 in Table 3). Although the reaction in pure *N,N*-dimethylformamide (DMF) afforded a rather disappointing result (20% yield), addition of water to this solvent markedly increased the catalytic efficacy even at a shorter reaction time (2 h; cf. entries 4–6). On the other hand, reactions performed in propionitrile and 1-propanol ensued in comparably lower yields, similar to those achieved in water. Addition of water to these solvents had an opposite effect: The yield obtained in aqueous propionitrile was markedly better than in the pure organic solvent whereas the addition of water to 1-propanol reduced the yield of **6e** from 45% in pure solvent to 34% for the aqueous mixture (entries 7–10). These results together with the fact that the yields achieved in dioxane and aqueous dioxane are practically the same, implicate an "individual" effect of the added water for a particular solvent and, hence, the need for testing all possible combinations.

A subsequent examination of various palladium precursors has shown that the palladium source also plays a vital role in determining the efficacy of the Pd/**3** catalyst (Table 4). For instance, palladium(II) acetate, a very typical palladium source for various cross-coupling reactions, provided a 51% yield of **6e** at 2 mol.% loading and Pd:P ratio of 1:1. Increasing the amount ligand to two equivalents with respect to Pd decreased the yield of the coupling product to 30%. The yield of **6e** achieved with palladium(II) chloride was by ca. 10% better than with the acetate salt and thus similar to that obtained with $[(L^{NC})PdCl]_2$ possessing an auxiliary *ortho*-palladated *N,N*-dimethylbenzylamine ligand. The "ligated" palladium(II) dichloride surrogate, $[PdCl_2(cod)]$, performed similarly to $Pd(OAc)_2$. The best result (89% of **6e**) was obtained with the catalyst generated from **3** and (π-allyl)palladium chloride dimer, $[PdCl(\eta^3\text{-}C_3H_5)]_2$. In contrast, catalyst generated from $[Pd_2(dba)_3]$ as an imminent source of Pd(0) performed by far the worst, furnishing only an 8% yield of **6e** under the standard reaction conditions.

Having established that the catalytic system generated from **3** and $[PdCl(\eta\text{-}C_3H_5)]_2$ efficiently mediates the coupling of the model substrates in aqueous DMF in the presence of potassium phosphate, we next turned to testing of different substrates under these conditions. The results summarized in Table 5 indicate that the cross-coupling reaction with the more reactive substrate **4b** proceeds very well even at 40 °C and with 1 mol.% of *in situ* generated Pd-catalyst, resulting in complete conversions to the target product **6e** within 4 h. A shorter reaction time (2 h) lowered the yield only slightly (cf. entries 1 and 2). When **4b** was replaced with the corresponding aryl chloride **4a**, the reaction not only required a higher catalyst loading (2 mol.% of Pd) but also a higher reaction temperature (100 °C/4 h in *N,N*-dimethylformamide) to achieve similar results (entry 3). This trend was reproduced also in the case of couplings with unsubstituted phenylboronic acid **5a** (entries 4 and 5).

The reaction was affected also by substituents at the aromatic ring of the boronic acid component. Substitution leading to increased steric demands around the reaction site (2-Me) as well as electron-withdrawing substituents (4-CN and 4-NO_2) reduced the yield of the respective coupling products even at a higher

Table 2
Evaluation of various bases in the model cross-coupling reaction.[a]

Entry	Base	^{1}H NMR yield [%]
1	Na_2CO_3	28
2	K_2CO_3	34
3	Rb_2CO_3	24
4	Cs_2CO_3	28
5	$KHCO_3$	17
6	Li_3PO_4	0
7	Na_3PO_4	21
8	K_3PO_4	46
9	KOH	27
10	KO*t*-Bu	25
11	KOAc	0

[a] Conditions: **4a** (0.5 mmol), **5e** (0.65 mmol), base (2.0 mmol), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5.0 μmol) and ligand **3** (10.0 μmol) in water (3 mL), 4 h at 100 °C. For details, see Experimental section.

Table 3
Influence of the reaction solvent on the model cross-coupling reaction.[a]

Entry	Solvent	^{1}H NMR yield [%]
1	Water	46
2	Dioxane	32
3	Dioxane-water (1:1 v/v)	34
4	Dimethylformamide	20
5	Dimethylformamide/water (1:1 v/v)	89
6	Dimethylformamide/water (1:1 v/v)[b]	77
7	Propionitrile	37
8	Propionitrile/water (1:1 v/v)	63
9	Propanol	45
10	Propanol/water (1:1 v/v)	34

[a] Conditions: **4a** (0.5 mmol), **5e** (0.65 mmol), K_3PO_4 (2.0 mmol), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5.0 μmol) and ligand **3** (10.0 μmol) in water (3 mL), 4 h at 100 °C. For details, see Experimental section.
[b] The reaction time was reduced to 2 h.

Table 4
Influence of the palladium source on the model cross-coupling reaction.[a]

Entry	Palladium salt[b]	^{1}H NMR yield [%]
1	$Pd(OAc)_2$	51
2	$Pd(OAc)_2$[c]	30
3	$PdCl_2$	62
4	$[PdCl_2(cod)]$	54
5	$[L^{NC}PdCl]_2$	66
6	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	89
7	$[Pd_2(dba)_3]$	8

[a] Conditions: **4a** (0.5 mmol), **5e** (0.65 mmol), K_3PO_4 (2.0 mmol), palladium precursors (2 mol.% Pd) and ligand **3** (2 mol.%; Pd:P = 1:1) in water-dimethylformamide (3 mL, 1:1 v/v), 4 h at 100 °C. For details, see Experimental section.
[b] Legend: dba = dibenzylideneacetone, cod = η^5:η^5-cycloocta-1,5-diene, L^{NC} = 2-[(dimethylamino-κ*N*)methyl]phenyl-κ*C*^{1}.
[c] 4 mol.% of **3** were used (Pd:P = 1:2).

Table 5
The results of screening of various substrates.[a]

Entry	Aryl halide (X)	Boronic acid (R)	T (°C)	Time (h)	Product	^{1}H NMR yield (isolated yield) [%]
1	**4b** (Br)	**5e** (4-MeO)	40	4	**6e**	100 (94)
2	**4b** (Br)	**5e** (4-MeO)	40	2	**6e**	92
3	**4a** (Cl)	**5e** (4-MeO)[b]	100	4	**6e**	89
4	**4b** (Br)	**5a** (H)	40	4	**6a**	100 (96)
5	**4a** (Cl)	**5a** (H)[b]	100	4	**6a**	86
6	**4b** (Br)	**5b** (2-Me)[c]	60	4	**6b**	72
7	**4b** (Br)	**5c** (3-Me)	40	4	**6c**	100 (83)
8	**4b** (Br)	**5d** (4-Me)	40	4	**6d**	100 (85)
9	**4b** (Br)	**5f** (4-CN)[c]	60	4	**6f**	89
10	**4b** (Br)	**5g** (4-NO_2)[c]	60	4	**6g**	91

[a] Conditions: **4a** or **4b** (0.5 mmol), boronic acid (0.55 mmol), K_3PO_4 (2.0 mmol), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (2.5 μmol; 1 mol.% Pd) and **3** (5.0 μmol) in 3 mL of water unless specified otherwise.
[b] Reaction performed with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5.0 μmol; 2 mol.% Pd) and **3** (10.0 μmol) in 3 mL of water-dimethylformamide (1:1 v/v).
[c] Reaction performed with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5.0 μmol; 2 mol.% Pd) and **3** (10.0 μmol) in 3 mL of water.

temperature (60 °C) and with 2 mol.% of the catalyst. In contrast, methyl substituents in position 3 or 4 of the aromatic ring did not affect the coupling, the respective coupling products being obtained with full NMR and good isolated yields.

Conclusion

The newly designed and synthesized amidosulfonate **3** combining the bulky (dicyclohexylphoshino)biphenyl coordinating moiety with an anionic amidosulfate solubilizing tag gives rise to an active palladium catalyst for Suzuki–Miyaura cross-coupling of *N*-Boc protected 4-halophenylalanines with aromatic boronic acids. A thorough survey of the reaction parameters revealed the need for a careful optimization of the reaction conditions such as the solvent, base additive and palladium source to ensure good yields of the coupling products in the aforementioned reaction. Under the optimized conditions, the biaryl coupling could be performed with high to complete conversions and very good isolated yields in water or a 1:1 water-*N*,*N*-dimethylformamide mixture over practical reaction times and with negligible loss of the target product due to unwanted removal of the amine protecting group.

Experimental

Materials and methods

2-(Dicyclohexylphosphino)biphenyl-4′-carboxylic acid (**1**) was prepared according to the literature procedure [8]. Dichloromethane was dried over potassium carbonate and distilled under argon. Distilled water was saturated with argon prior to the catalytic experiments. Anhydrous *N*,*N*-dimethylformamide (Sigma–Aldrich) and other solvents (Lachner, Czech Republic) were used as received. ^{1}H NMR spectra were recorded at 25 °C on a Varian UNITY Inova 400 spectrometer (^{1}H 399.95 MHz, $^{13}C\{^1H\}$ 100.58 MHz, ^{19}F 376.29 MHz, and $^{31}P\{^1H\}$ 161.90 MHz). Chemical shifts (δ/ppm) are given relative to internal tetramethylsilane (^{1}H; ^{13}C), external neat $CFCl_3$ (^{19}F), or to external 85% aqueous H_3PO_4 (^{31}P). Electrospray ionization mass spectra (ESI-MS) were recorded with Bruker Esquire 3000 or Finnigan LCQ Deca spectrometers using solutions in HPLC-grade methanol. Infrared spectra were collected on a Thermo Nicolet AVATAR 370 FT-IR instrument in the range 400–4000 cm^{-1}. The samples were diluted with spectroscopy-grade KBr and the spectra were recorded in diffuse reflectance (DRIFT) mode.

*Synthesis of pentafluorophenyl 2-(dicyclohexylphosphino)biphenyl-4′-carboxylate (**2**)*

A two-necked flask was charged with acid **1** (1.48 g, 3.75 mmol), pentafluorophenol (1.17 g, 5.63 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl; 1.08 g, 5.63 mmol) and 4-(dimethylamino)pyridine (0.12 g, 0.94 mmol), flushed with argon and sealed with a rubber septum. Anhydrous dichloromethane (50 mL) was introduced via a syringe and the resulting mixture was stirred at room temperature overnight. The reaction was terminated by addition of distilled water (25 mL), the layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 25 mL). The combined organic layers were washed with brine (25 mL) and dried over magnesium sulfate. Then, the solvents were removed under vacuum, and the solid residue was purified by column chromatography (silica gel, ethyl acetate/hexanes, 1:15 v/v) to afford analytically pure pentafluorophenyl 2-(dicyclohexylphosphino)biphenyl-4′-carboxylate as a white solid. Yield of **2**: 1.93 g (92%).

^{1}H NMR ($CDCl_3$): δ 0.98–1.31 (m, 10H), 1.54–1.78 (m, 10H), and 1.82–1.91 (m, 2H, PCy_2); 7.28–7.30 (m, 1H), 7.38–7.49 (m, 4H), 7.62–7.68 (m, 1H), and 8.19–8.22 (m, 2H, $C_{12}H_8$). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 26.35 (2C), 27.10 (2C), 27.20 (d, J_{PC} = 6 Hz, 2C), 29.20 (d, J_{PC} = 8 Hz, 2C), 30.41 (d, J_{PC} = 16 Hz, 2C), and 34.55 (d, J_{PC} = 10 Hz, 2C) (PCy_2); 125.22, 127.47, 128.80, 129.87 (d, J_{PC} = 6 Hz), 130.00, 131.21 (d, J_{PC} = 4 Hz), 133.32 ($C_{12}H_8$); 138.0 (dm, $^1J_{FC}$ = 253 Hz), 139.5 (dm, $^1J_{FC}$ = 253 Hz), 141.5 (dm, $^1J_{FC}$ = 252 Hz, C_6F_5); 149.10 (d, J_{PC} = 29 Hz), 149.65 (d, J_{PC} = 5 Hz), 162.61 (C=O). ^{19}F NMR ($CDCl_3$): δ −162.7 (m, 2 F, F_{meta} of C_6F_5), −158.5 (t, $^3J_{FF}$ = 22 Hz, 1 F, F_{para} of C_6F_5), −152.6 (m, 2 F, F_{ortho} of C_6F_5). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −12.6 (s). IR (Nujol): 2935 s, 2920 m, 2893 w, 2857 m, 1760 vs, 1604 w, 1521 vs, 1476 vw, 1446 w, 1254 m, 1239 s, 1183 m, 1147 v, 1051 vs, 1021 m, 1003 s, 991 s, 851 m, 755 s, 701 w cm^{-1}. MS (ESI+): *m*/*z* 583.1 ($[M + Na]^+$), 561.2 ($[M + H]^+$). Anal. Calcd. for $C_{31}H_{30}PO_2F_5$: C 66.42, H 5.39%. Found: C 66.66, H 5.41%.

*Preparation of triethylammonium 2-(dicyclohexylphosphino)-4′-{[(sulfonatomethyl)amino]carbonyl}biphenyl (**3**)*

A reaction flask equipped with a stirring bar was charged with active ester **2** (0.56 g, 1.0 mmol), aminomethanesulfonic acid (0.17 g, 1.5 mmol) and 4-(dimethylamino)pyridine (6 mg, 0.05 mmol), flushed with argon and sealed with a septum. The solid educts were suspended in the mixture of anhydrous *N*,*N*-dimethylformamide (10 mL), dichloromethane (2 mL) and triethylamine (2 mL), and the reaction mixture was stirred overnight. The resulting transparent solution was evaporated to dryness and the crude product was isolated by flash chromatography (silica gel, dichloromethane/methanol/triethylamine, 20:1:1 v/v). Subsequent crystallization from hot ethyl acetate afforded solvated salt **3**·½AcOEt as a white crystalline solid. Yield 0.55 g (87%).

^{1}H NMR (DMSO-d_6): δ 0.86–1.29 (m, 10H, PCy_2), 1.17 (t, $^3J_{HH}$ = 7.3 Hz, 9H, CH_3 of Et_3NH^+), 1.42–1.2 (m, 2H), 1.53–1.68 (m, 8H), and 1.80–1.89 (m, 2H, PCy_2); 3.09 (q, $^3J_{HH}$ = 7.3 Hz, 6H, CH_2 of Et_3NH^+), 4.16 (d, $^3J_{HH}$ = 6.3 Hz, 2H, SCH_2N), 7.24–7.32 (m, 3H), 7.39–7.46 (m, 2H), 7.62–7.67 (m, 1H), 7.87–7.93 (m, 2H,$C_{12}H_8$); 8.65 (t, $^3J_{HH}$ = 6.3 Hz, 1H, NH). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 8.60 (9C, CH_3 of Et_3NH^+), 25.91 (2C), 26.37 (2C), 26.46 (d, J_{PC} = 5 Hz, 2C), 28.96 (d, J_{PC} = 9 Hz, 2C), 30.14 (d, J_{PC} = 18 Hz, 2C), and 34.02 (d, J_{PC} = 15 Hz, 2C) (PCy_2); 45.70 (6C, CH_2 of Et_3NH^+), 55.84 (SCH_2N), 126.49, 127.08, 128.55, 129.68 (d, J_{PC} = 5 Hz), 130.20 (d, J_{PC} = 5 Hz), 132.39, 132.89 (d, J_{PC} = 3 Hz), 133.58 (d, J_{PC} = 23 Hz), 145.16 (d, J_{PC} = 6 Hz), and 149.13 (d, J_{PC} = 29 Hz) ($C_{12}H_8$); 165.31 (C=O). $^{31}P\{^1H\}$ NMR (DMSO-d_6): δ −13.1 (s). IR (KBr): 3318 m, 3046 w, 3001 w, 2968 w, 2926 vs, 2848 s, 2758 v, 2684 m, 2558 w, 2519 w, 2489 w, 1655 s,

1610 w, 1583 w, 1544 s, 1503 m, 1476 m, 1470 m, 1449 m, 1389 m, 1329 s, 1287 m, 1254 m, 1201 vs, 1159 vs, 1042 vs, 1009 m, 854 m, 749 s, 740 mw, 662 m, 611 m, 528 s, 501 m cm^{-1}. MS (ESI−): *m*/*z* 485.9 ([M − $HNEt_3$]$^-$). Anal. Calcd. for $C_{32}H_{49}PO_4N_2S\cdot$½AcOEt: C 64.53, H 8.44, N 4.43%. Found: C 64.16, H 8.33, N 4.48%.

*Synthesis of racemic N-Boc-4-chlorophenylalanine (**4a**)*

Racemic 4-chlorophenylalanine (10.0 g, 50 mmol) and sodium hydroxide (6.0 g, 150 mmol) were dissolved in distilled water (150 mL) in a round-bottom flask equipped with a stirring bar and a dropping funnel. The reaction mixture was cooled in ice and a solution of di-*tert*-butyl dicarbonate (13.1 g, 60 mmol) in tetrahydrofurane (150 mL) was slowly introduced from the dropping funnel. The resulting mixture was allowed to warm to room temperature and then stirred overnight. The resulting solution was transferred into a separatory funnel and washed twice with diethyl ether (100 mL). The aqueous phase was acidified with 3 M aqueous citric acid to pH 4–5 and the obtained suspension was extracted with dichloromethane (3 × 150 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give **4a** as a white solid. Yield: 13.8 g (92%).

^{1}H NMR (DMSO-d_6): δ 1.32 (s, 9H, CMe_3), 2.74–3.05 (m, 2H, CH_2), 3.97–4.12 (m, 1H, CH), 7.11 (d, $^3J_{HH}$ = 8.5 Hz, 1H, NH), 7.27 (d, $^3J_{HH}$ = 8.4 Hz, 2H, C_6H_4); 7.33 (d, $^3J_{HH}$ = 8.4 Hz, 2H, C_6H_4), 12.64 (br s, 1H, CO_2H). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 28.03 (9C, CMe_3), 35.66 (CH_2), 54.84 (CH), 77.98 (CMe_3), 127.94 (2C), 130.90 (2C), and 136.99 (C_6H_4); 155.33 (C═O), 173.27 (CO_2H). One of the C_6H_4 carbons was not found. MS (ESI−): *m*/*z* 299.1 ([M − H]$^-$). Anal. Calcd. for $C_{14}H_{18}ClNO_4$: C 56.09, H 6.05, N 4.67%. Found: C 55.99, H 6.07, N 4.60%.

*Synthesis of racemic N-Boc-4-bromophenylalanine (**4b**)*

Compound **4b** was prepared similarly to **4a** starting from racemic 4-bromophenylalanine (5.0 g, 20.4 mmol) and sodium hydroxide (2.5 g, 61.2 mmol) in distilled water (75 mL), and di-*tert*-butyl dicarbonate (5.4 g, 24.7 mmol) in tetrahydrofurane (75 mL), and was isolated as a white solid. Yield 6.1 g (87%).

^{1}H NMR (DMSO-d_6): δ 1.32 (s, 9H, CH_3), 2.70–3.04 (m, 2H, CH_2), 3.97–4.12 (m, 1H, CH), 7.11 (d, $^3J_{HH}$ = 8.4 Hz, 1H, NH), 7.21 (d, $^3J_{HH}$ = 8.3 Hz, 2H, Ph), 7.47 (d, $^3J_{HH}$ = 8.3 Hz, 2H, Ph); 12.64 (br s, 1H, CO_2H). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 28.02 (9C, CH_3), 35.70 (CH_2), 54.77 (CH), 77.98 (CMe_3), 119.4, 130.86 (2C), 131.3 (2C), 137.4 (C_6H_4), 155.3 (C═O), 173.2 (CO_2H). MS (ESI−): *m*/*z* 343.0 ([M − H]$^-$). Anal. Calcd. for $C_{14}H_{18}BrNO_4$: C 48.85, H 5.27, N 4.07%. Found: C 48.81, H 5.19, N 3.85%.

*Suzuki–Miyaura cross-coupling of protected amino acids **4a** and **4b** with boronic acids **5***

The respective palladium precursor (5 μmol of Pd) and ligand **3** (2.9 mg, 5 μmol; unless noted otherwise) were placed into a Schlenk tube and dissolved in dichloromethane (0.5 mL). The mixture was stirred for 15 min and then evaporated under vacuum. The appropriate protected halogenated amino acid **4** (0.50 mmol), boronic acid (0.55 mmol) and base (2.0 mmol) were added to the Schlenk tube, and the reaction vessel was degassed by three vacuum–argon cycles, filled with argon and sealed with a rubber septum. Degassed solvent (3 mL) was introduced and the reaction vessel was placed into a pre-heated oil bath. After stirring for 4 h, the reaction was terminated by cooling in ice and simultaneous addition of 3 M aqueous HCl (3 mL), ethyl acetate (3 mL) and mesitylene (0.50 mmol; an internal standard). The organic layer was analyzed by NMR spectroscopy. For isolation of the coupling product, the aqueous layer was extracted with ethyl acetate (2 × 5 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The products were purified by column chromatography over silica gel column using dichloromethane-methanol (20:1 v/v) as the eluent and, following evaporation under reduced pressure, were isolated as white solids. Amino acids **6** often tend to retain traces of dichloromethane used during the chromatography, which cannot be removed even upon prolonged evacuation. The amount of the residual solvent was always verified by NMR analysis.

*Analytical data for the cross-coupling products **6***

*Rac-2-{[(tert-butyloxy)carbonyl]amino}-3-(biphenyl-4-yl)propionic acid (**6a**)*

White solid. ^{1}H NMR (DMSO-d_6): δ 1.33 (s, 9H, CH_3), 2.78–3.09 (m, 2H, CH_2), 4.01–4.17 (m, 1H, CH), 7.14 (d, $^3J_{HH}$ = 8.4 Hz, 1H, NH), 7.33–7.37 (m, 3H, $C_{12}H_8$), 7.43–7.47 (m, 2H, $C_{12}H_8$); 7.57–7.59 (m, 2H, $C_{12}H_8$), 7.63–7.65 (m, 2H, $C_{12}H_8$), 12.62 (br s, 1H, CO_2H). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 28.1, 36.0, 55.1, 78.1, 126.4, 126.5, 127.2, 127.3, 128.9, 129.7, 134.5, 137.3, 138.2, 140.0, 155.5, 173.6. MS (ESI−): *m*/*z* 340.0 ([M − H]$^-$). The data are in accordance with the literature [21].

*Rac-2-{[(tert-butyloxy)carbonyl]amino}-3-(2′-methylbiphenyl-4-yl)propionic acid (**6b**)*

Colorless viscous oil. ^{1}H NMR (DMSO-d_6): δ 1.33 (s, 9H, CH_3), 2.22 (s, 3H, CH_3), 2.78–3.12 (m, 2H, CH_2), 4.03–4.21 (m, 1H, CH), 7.12–7.19 (m, 2H, $C_{12}H_8$ and NH), 7.20–7.36 (m, 7H, $C_{12}H_8$), 12.65 (br s, 1H, CO_2H). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 20.15 (CH_3), 28.13 (9C, CH_3), 36.19 (CH_2), 55.00 (CH), 78.00 (CMe_3), 125.88, 127.14, 128.67, 128.95, 129.45, 130.29, 134.66, 136.66, 139.22, 141.11 ($C_{12}H_8$); 155.45 (C═O), 173.60 (CO_2H). MS (ESI−): *m*/*z* 354.0 ([M − H]$^-$). Anal. Calcd. for $C_{21}H_{25}NO_4\cdot0.1CH_2Cl_2$: C 69.64, H 6.98, N 3.85%. Found: C 69.62, H 7.05, N 3.64%.

*Rac-2-{[(tert-butyloxy)carbonyl]amino}-3-(3′-methylbiphenyl-4-yl)propionic acid (**6c**)*

White solid. ^{1}H NMR (DMSO-d_6): δ 1.33 (s, 9H, CH_3), 2.37 (s, 3H, CH_3), 2.78–3.08 (m, 2H, CH_2), 4.01–4.16 (m, 1H, CH), 7.09–7.18 (m, 2H, $C_{12}H_8$ and NH), 7.29–7.37 (m, 3H, $C_{12}H_8$), 7.39–7.47 (m, 2H, $C_{12}H_8$), 7.53–7.59 (m, 2H, $C_{12}H_8$), 12.64 (br s, 1H, CO_2H). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 21.07 (CH_3), 28.09 (9C, CH_3), 36.00 (CH_2), 55.09 (CH), 78.01 (CMe_3), 123.57, 126.35, 127.13, 127.81, 128.72, 129.58, 137.18, 137.93, 138.27, 139.91 ($C_{12}H_8$); 155.42 (C═O), 173.51 (CO_2H). MS (ESI−): *m*/*z* 354.0 ([M − H]$^-$). Anal. Calcd. for $C_{21}H_{25}NO_4\cdot0.05CH_2Cl_2$: C 70.29, H 7.03 N 3.90%. Found: C 70.53, H 7.07, N 3.77%.

*Rac-2-{[(tert-butyloxy)carbonyl]amino}-3-(4′-methylbiphenyl-4-yl)propionic acid (**6d**)*

White solid. ^{1}H NMR (DMSO-d_6): δ 1.32 (s, 9H, CH_3), 2.33 (s, 3H, CH_3), 2.76–3.08 (m, 2H, CH_2), 4.01–4.16 (m, 1H, CH), 7.12 (d, $^3J_{HH}$ = 8.3 Hz, 1H, NH), 7.24–7.26 (m, 2H, $C_{12}H_8$), 7.30–7.32 (m, 2H, $C_{12}H_8$), 7.51–7.56 (m, 4H, $C_{12}H_8$), 12.63 (br s, 1H). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 20.64 (CH_3), 28.14 (9C, CH_3), 36.05 (CH_2), 55.16 (CH), 78.05 (CMe_3), 126.14, 126.31, 129.48, 129.64, 136.48, 136.99, 137.10, 138.11 ($C_{12}H_8$); 155.47 (C═O), 173.57 (CO_2H). MS (ESI−): *m*/*z* 354.0 ([M − H]$^-$). Anal. Calcd. for $C_{21}H_{25}NO_4$: C 70.96, H 7.09, N 3.94%. Found: C 71.23, H 7.31, N 3.51%.

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*Rac-2-{[(tert-butyloxy)carbonyl]amino}-3-(4′-methoxybiphenyl-4-yl)propionic acid (**6e**)*

White solid. ^{1}H NMR (DMSO-d_6): δ 1.33 (s, 9H, CH_3), 2.75–3.08 (m, 2H, CH_2), 3.79 (s, 3H, CH_3O), 3.99–4.16 (m, 1H, CH), 6.99–7.02 (m, 2H, C_6H_4), 7.07 (d, $^3J_{HH}$ = 8.4 Hz, 1H, NH), 7.29–7.31 (m, 2H, C_6H_4); 7.51–7.53 (m, 2H, C_6H_4), 7.56–7.59 (m, 2H, C_6H_4), 12.67 (br s, 1H, CO_2H). ^{13}C{^{1}H} NMR (DMSO-d_6): δ 28.15 (9C, CH_3); 36.06 (CH_2), 55.14 (CH_3O), 55.23 (CH); 78.02 (*C*Me$_3$), 114.31, 125.89, 127.55, 129.63, 132.37, 136.57, 137.86 ($C_{12}H_8$); 155.4 (C═O), 158.74 (*C*–OMe), 173.61 (CO_2H). MS (ESI–): *m*/*z* 370.0 ([M − H]$^-$). The data are in agreement with the literature [22].

*Rac-2-{[(tert-butyloxy)carbonyl]amino}-3-(4′-cyanobiphenyl-4-yl) propionic acid (**6f**)*

White solid. ^{1}H NMR (DMSO-d_6): δ 1.32 (s, 9H, CH_3), 2.80–3.14 (m, 2H, CH_2), 4.02–4.18 (m, 1H, CH), 7.16 (d, $^3J_{HH}$ = 8.4 Hz, 1H, NH), 7.39 (d, $^3J_{HH}$ = 8.3 Hz, 2H, $C_{12}H_8$), 7.68 (d, $^3J_{HH}$ = 8.3 Hz, 2H, $C_{12}H_8$), 7.85–7.92 (m, 4H, $C_{12}H_8$), 12.57 (br s, 1H, CO_2H). ^{13}C{^{1}H} NMR (DMSO-d_6): δ 28.04 (9C, CH_3), 35.98 (CH_2), 54.93 (CH), 77.99 (*C*Me$_3$), 109.71, 118.81 (C≡N), 126.73, 127.24, 129.87, 132.73, 136.16, 138.84, 144.37 ($C_{12}H_8$); 155.39 (C═O), 173.41 (CO_2H). MS (ESI–): *m*/*z* 365.0 ([M − H]$^-$). Anal. Calcd. for $C_{21}H_{22}N_2O_4 \cdot 0.05CH_2Cl_2$: C 68.21, H 6.01, N 7.56%. Found: C 67.90, H 6.12, N 6.93%.

*Rac-2-{[(tert-butyloxy)carbonyl]amino}-3-(4′-nitrobiphenyl-4-yl) propionic acid (**6g**)*

Ochre yellow solid. ^{1}H NMR (DMSO-d_6): δ 1.32 (s, 9H, CH_3), 2.80–3.14 (m, 2H, CH_2), 4.02–4.18 (m, 1H, CH), 7.17 (d, $^3J_{HH}$ = 8.5 Hz, 1H, NH), 7.40–7.43 (d, $^3J_{HH}$ = 8.2 Hz, 2H, $C_{12}H_8$), 7.72–7.74 (d, $^3J_{HH}$ = 8.2 Hz, 2H, $C_{12}H_8$), 7.94–7.76 (m, 2H, $C_{12}H_8$), 8.28–8.31 (m, 2H, $C_{12}H_8$), 12.63 (br s, 1H, CO_2H). ^{13}C{^{1}H} NMR (DMSO-d_6): δ 28.08 (9C, CH_3), 35.99 (CH_2), 54.91 (CH), 78.0 (*C*Me$_3$), 123.99, 126.93, 127.49, 129.93, 135.72, 139.21, 146.36, 146.42 ($C_{12}H_8$); 155.39 (C═O), 173.38 (CO_2H). MS (ESI–): *m*/*z* 385.0 ([M − H]$^-$). Anal. Calcd. for $C_{20}H_{22}N_2O_6 \cdot 0.1CH_2Cl_2$: C 61.13, H 5.67, N 7.10. %. Found: C 61.33, H 5.64, N 6.97%.

X-ray crystallography

Single crystals of **3** suitable for X-ray diffraction analysis were obtained from hot acetonitrile (colorless plate, 0.06 × 0.29 × 0.48 mm^3). The diffraction data (θ_{max} = 27.5°; data completeness: 100%) were collected with a Nonius Kappa CCD diffractometer equipped with an APEX-II CCD detector (Bruker) and a Cryostream Cooler (Oxford Cryosystems) at 150(2) K using graphite monochromated MoKα radiation (λ = 0.71073 Å). The data were corrected for absorption using routines included in the diffractometer software.

The structure was solved by direct methods (SHELXS97) and refined by full-matrix least squares based on F^2 (SHELXL97) [23]. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms residing at the nitrogen atoms (NH protons) were identified on the difference electron density map and refined as riding atoms with U_{iso}(H) = 1.2 U_{eq}(N). Hydrogens bonding to the carbon atoms were included in their calculated positions and refined analogously. Relevant crystallographic data and structure refinement parameters for **3** are as follows.

$C_{32}H_{49}N_2O_4PS$ (588.76 g mol^{-1}), monoclinic, space group *C*2/*c* (no. 15), *a* = 42.405(2) Å, *b* = 7.2386(3) Å, *c* = 21.8731(9) Å, β = 109.110(2)°, *V* = 6344.0(5) Å, *Z* = 8, D_{calc} = 1.233 g cm^{-3}; μ(MoKα) = 0.190 mm^{-1}, 46,095 diffractions were collected, of which 7281 were independent (R_{int} = 5.55%) and 5429 observed according to the $I_o \geq 2\sigma(I_o)$ criterion. The refinement converged (Δ/σ < 0.001 for 364 parameters) with *R* = 4.08% for the observed diffractions and *R* = 6.57% and *wR* = 9.88% for all data. Extremes on the residual electron density map were 0.33 and −0.42e Å^{-3}.

Geometric data and all structural drawings were obtained with a recent version of the PLATON program [24]. The numerical values are rounded with respect to their estimated standard deviations (ESDs) given with one decimal. Parameters pertaining to atoms in constrained positions are given without ESDs.

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Appendix A. Supplementary data

CCDC 1040352 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via the Internet at http://www.ccdc.cam.ac.uk.

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