CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201203006

A Modular Synthesis of Teraryl-Based α-Helix Mimetics, Part 2: Synthesis of 5-Pyridine Boronic Acid Pinacol Ester Building Blocks with Amino Acid Side Chains in 3-Position

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Dedicated to Professor Bernhard Kräutler

Abstract: One of the most common protein–protein interactions (PPI) is the interaction of the α-helix of one protein with the surface of the second one. Terphenylic scaffolds are bioinspired motifs in the inhibition of PPIs and have been identified as suitable α-helix mimetics. One of the challenging aspects of this strategy is the poor solubility of terphenyls under physiological conditions. In the literature pyrrolopyrimidine-, pyrimidine- or pyridazine-based mimetics have been reported to show improved solubility. We present a new convergent strategy for the synthesis of linear pyridine-type teraryls based on a phenylic core unit. A general approach for the synthesis of 3,5-disubstituted pyridine-based boronic acid pinacol esters with amino acid side chains in the 3-position (representing Phe, Leu, Ile, Lys, Asp, Asn) is presented and exploits the functional group tolerance of the Knochel–Grignard reagents. The building blocks have been used in a convergent in situ two-step synthesis of teraryl α-helix mimetics.

Keywords: cross-coupling · Knochel–Grignard · peptidomimetics · protein–protein interactions · pyridine-based 1,4-teraryls

Introduction

Protein–protein interactions (PPIs) are recognized as one of the main factors in controlling protein function in living cells. The number of different PPIs in human cells is estimated to be approximately 65000,[1,2] and α-helices play a prominent role in the interaction sites.[3] Typically, PPI domains comprise about 35–150 amino acids.[4] For the study and pharmaceutical intervention of PPIs tool compounds are needed that allow the control of a particular interaction of a specific target protein.[5] Hamilton and co-workers have presented a quite general approach of mimicking α-helices by suitable positioning of amino acid side chains around a terarylic scaffold (Figure 1a).[6] They could impressively demonstrate that for several examples selective PPI inhibitors (terphenyl-based α-helical mimetics) with an affinity in the nanomolar range can be developed using this design approach.[7]

As many of these terphenyls show poor solubility in aqueous solvents, more polar heteroaryl-based helical mimetics have been developed, such as pyrimidine-,[8] pyridazine-,[9] pyrrolopyrimidine-,[10] piperidino-,[11] or triazolo-based[12] scaffolds. In addition, pyridine-based teraryls are known, but their synthesis has turned out to be inflexible[13] and the linear approach makes this work very time consuming.[14]

Here, we describe efficient synthetic access to amino acid surrogate pyridine boronic acid building blocks **2**, which together with our accompanying paper on convergent assembly strategy, presents a universal and flexible approach for the synthesis of pyridine-based heteroteraryl-based α-helix mimetics **1** (Figure 1b).[15]

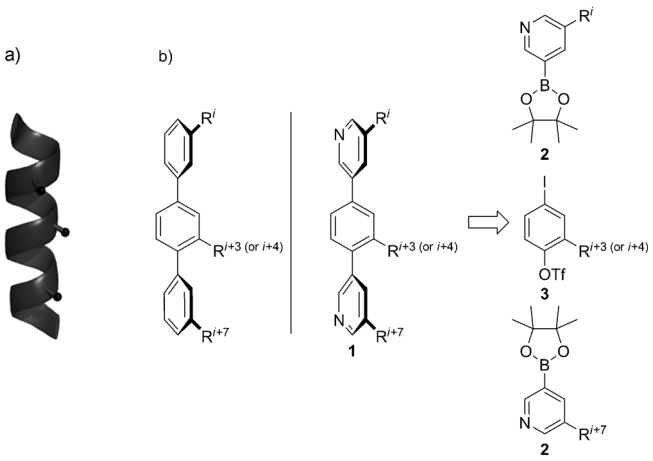

Figure 1. a) Schematic depiction of Hamilton's terphenylic scaffold for mimicking an α-helix. b) Retrosynthesis of our teraryls **1** as a convergent synthesis starting from a *para*-iodo-triflate core unit **3**.

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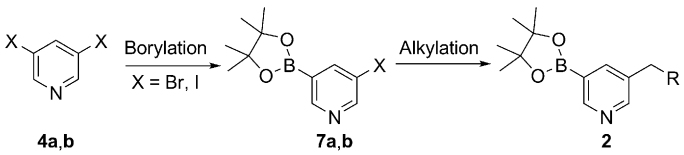
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201203006.

Results and Discussion

We have already presented a convergent strategy for the synthesis of linear terphenyls, using a benzene core unit featuring two leaving groups of differentiated reactivity in the Pd-catalyzed cross-coupling reaction.[15] Although this design is in principle suitable for several α-helix mimetics featuring highly polar side chains, the intrinsically poor solubility of the benzene-based terphenyl core structure imposes limitations for the use of this core structure as a scaffold for hydrophobic side chains under physiological conditions. To circumvent this problem, the design of more soluble teraryls, containing pyridine moieties, is established.

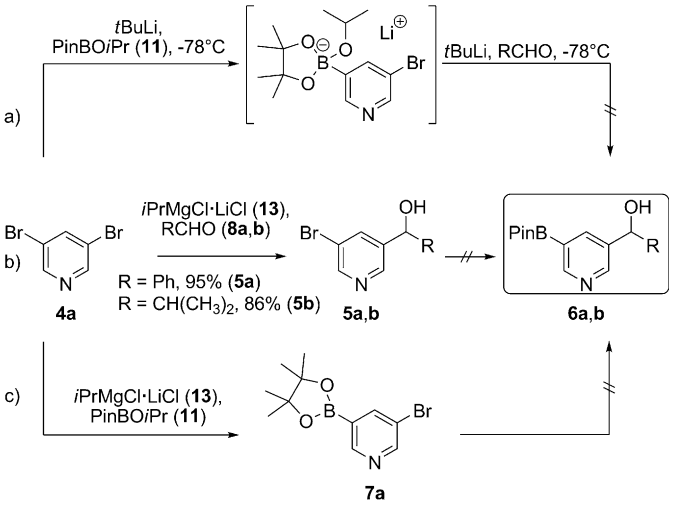
For our design, we envisioned that pyridines as the top and the bottom rings would increase the polarity and solubility of our teraryl scaffold. We would prefer to have the polar nitrogen atom at the site opposite to the amino acid side chain, as this represents the water exposed surface of the teraryl, and potentially has an advantageous effect on the entropic cost of binding.[16] As a consequence of this design, we required a universal approach to 3,5-disubstituted pyridine boronic esters **2** featuring the amino acid side chain as substituent in the 3-position (Scheme 1). We speculated that the pinacol ester function could be first introduced by electrophilic quenching of a suitable organolithium derivative of pyridines **4a**,**b** utilizing electrophiles, such as PinBO*i*Pr (**11**), which could then be followed by the introduction of the amino acid side chain to finally afford the desired boronic acid ester building blocks **2**.



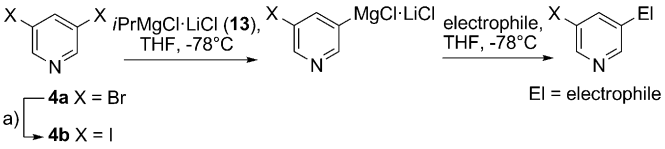
Scheme 1. Original concept of synthesizing 5-pyridine boronic acid pinacol esters with amino acid side chains in 3-position.

In our initial attempt we followed a protocol by Zhichkin and co-workers and first used a modified *t*BuLi-mediated method for the borylation of 3,5-disubstitued bromopyridine **4a**, followed by an in situ second electrophilic quenching with an aldehyde (Scheme 2, route a). However, we were not able to isolate the desired 3-(hydroxymethyl)-5-BPin-pyridine derivatives **6** with this in situ method.[17]

After several unsuccessful attempts to explore the dilithiation of suitable pyridine derivatives, we were pleased to see that in our hands the "turbo-Grignard" approach introduced by Knochel[18] and other research groups[19] appears to be the key to the successful substitution of dihalopyridine derivatives **4a**,**b**.[20] This method has the advantage that the halides can successively be substituted with the combination of magnetization/electrophilic quench on electron poor heterocycles (Scheme 3). Evidence from the literature suggested that the attractive orthogonality of this "turbo-Grignard" chemistry[21] should not only tolerate nitriles, −OMe or $-CF_3$ groups, but also esters or amides.[20a,22]



Scheme 2. Overview of the attempts of synthesizing 3-(hydroxymethyl)-5-BPin-pyridine derivatives **6a**,**b** starting from 3,5-dibromopyridine (**4a**).

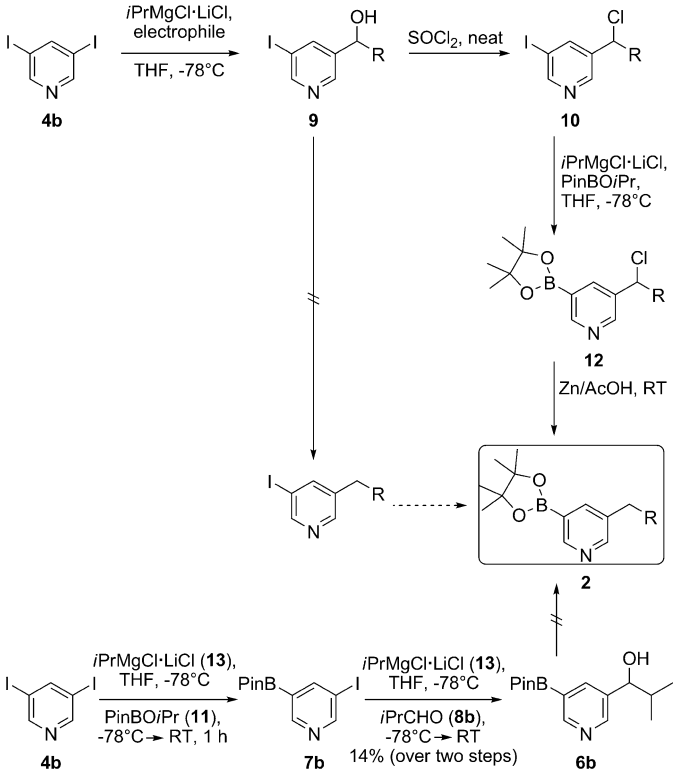


Scheme 3. "Turbo-Grignard" approach for the derivatization of electron poor N-heterocyclic compounds, such as pyridines.[20a] a) CuI (10 mol%), NaI (4.0 equiv), *N*,*N*'-dimethylethylenediamine 1,4-dioxane (10 mol%), 120 °C, 86% (gram scale).

When using dibromopyridine **4a**, the first metal–halide exchange worked quantitatively and dependent on the electrophile the corresponding benzyl alcohol **5a**,**b** or the BPin derivative **7a** could be isolated in good to excellent yields (Scheme 2, routes b and c). However, the bromo derivatives **5a**,**b** or **7a** turned out to be problematic substrates for the second metal–halide exchange under the same reaction conditions due to increased byproduct formation and dramatically prolonged reaction times.

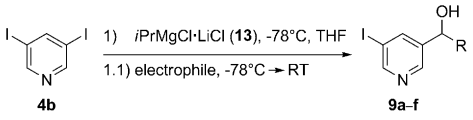
We speculated that with the more reactive 3,5-diiodopyridine (**4b**) we could address the problem of the second metal–halide reaction (Scheme 3). After several failed efforts to synthesize **4b** by the sequential *t*BuLi mediated dilithiation and diiodination of 3,5-dibromopyridine (**4a**), we turned our attention to Buchwald's variant for Finkelstein-like iodination of haloarenes.[23] Buchwald and co-workers had demonstrated the monoiodination of aryls and heteroaryls. Gratifyingly, this reaction worked also for the diiodination of our substrate. The halide exchange was catalyzed by CuI in the presence of *N*,*N*'-dimethylethylenediamine and furnished the desired product **4b** in 86% on a multigram scale (Scheme 3).

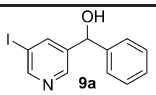
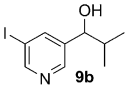
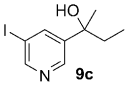
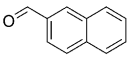
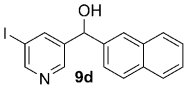
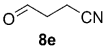
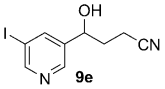
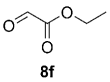
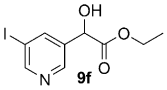
Much to our delight, the twofold metal–halide exchange reaction occurred with the more reactive 3,5-diiodopyridine



Scheme 4. Strategy for the synthesis of 3,5-substituted pyridine-based boronic acid pinacol esters **2**.

Table 1. First iodine–magnesium exchange followed by electrophilic quenching with the carbonyl derivatives **8a–f** to synthesize 3-(hydroxymethyl)-5-iodopyridine derivatives **9a–f**.



Entry	Carbonyl electrophile	Grignard product	Yield [%][a]
1	 8a	 9a	99
2	 8b	 9b	95
3	 8c	 9c	99[b]
4	 8d	 9d	68
5	 8e	 9e	83
6	 8f	 9f	84

[a] Isolated yields. [b] Crude product; used in the next step without further purification.

(**4b**) now as desired. First, we tried a modified reaction sequence of a twofold Grignard reaction as described by Knochel and co-workers, in which we introduced the diverse elements of the side chains after having first formed the basic pyridine boronic acid ester core (Scheme 4).[20a,24] The diiodopyridine **4b** was borylated, to furnish the 5-BPin derivative **7b**. After a second metal–halide exchange, the corresponding 3-(hydroxymethyl)-5-BPin-pyridine derivative **6b** could be isolated (14%, starting from diiodopyridine **4b**), but because of the unexpected instability of compound **6b** we failed to deoxygenate the benzylic alcohol **6b** to the corresponding desired final product **2b**. Although this sequence, if successful, would have represented the most flexible access to our desired 3-substituted 5-pyridine boronic acid building blocks **2**, we speculated that changing the order of the sequence in the electrophile addition might lead us to the desired products.

Scheme 4 summarizes both the attempted as well as the ultimately successful synthetic route for the assembly of 3,5-disubstituted pyridine-based boronic acid pinacol esters **2**. The most critical step of the synthesis was the introduction of the amino acid side chain during the first Grignard formation.

As a test case for our strategy, we attempted to synthesize the "Phe" building block **2a**. For the introduction of the side chain, we experimented with benzyl bromide as electrophile. Despite considerable optimization efforts, we did not obtain decent coupling yields using this type of electrophile, but struggled with alkylation of the pyridine nitrogen instead. Fortunately, we found that highly reactive aldehyde electrophiles (e.g., benzaldehyde, **8a**; Table 1, entry 1), but also comparably less reactive ketones (e.g., butan-2-one, **8c**; Table 1, entry 3) are excellent reactants for the electrophilic quenching of the pyridine Grignard reagent, delivering products **9a–f** in good to excellent yields. Indeed the Knochel conditions also tolerated functional groups such as nitrile and ester in the electrophile (Table 1, entries 5 and 6).

For most natural amino side chains (except Thr and Ser), it is necessary to remove the superfluent hydroxyl group to achieve the native alkyl form. A possible strategy is the acid-catalyzed elimination of H_2O leading to the unsaturated form, which easily occurs for tertiary alcohols like **9c** (Table 1, entry 3).[25] An alternative, and more general route, is the reduction of the benzylic 3-(hydroxymethyl)-5-iodopyridine derivatives **9** into the corresponding deoxygenated form. However, none of the common reduction methods we tried (H_2, PtO_2, MeOH; H_2, Pd/C, MeOH; H_2, $Pd(OH)_2$/C, MeOH; Zn, AcOH) led to the desired reduction product, as any successful deoxygenation was afflicted with a concomitant deiodination process as the main side reaction. In order to overcome this problem we decided to convert the hydroxyl group first into chlorine, which should be amenable to dehalogenation by a less aggressive reducing agent. In the event, the pyridine carbinols **9** were smoothly transformed into the corresponding 3-(chloromethyl)-5-iodopyridine derivatives **10** with thionyl chloride ($SOCl_2$) under neat condi-

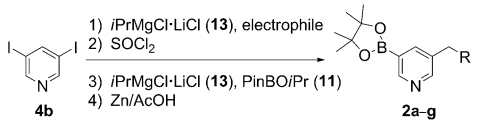
tions (Scheme 4). Gratifyingly, the second iodine–magnesium exchange on substrates **10** proceeds without any side reaction from the potential internal electrophile represented by the α-aryl chloride. Therefore, the electrophilic quench with PinBO*i*Pr (**11**) produced the borylated 3-(chloromethyl)-5-BPin-pyridine derivatives **12**. As these compounds proved to be sensitive to heat and were also not stable on silica gel, we used the intermediates **12** without any further purification in the next step, in which they were easily dehalogenated with Zn/AcOH. Importantly, this rather mild reduction method did not cause any deborylation of the desired products **2** (Scheme 4).

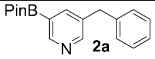
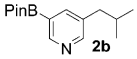
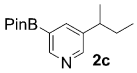
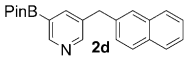
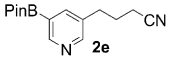
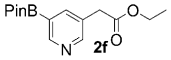
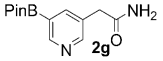
In order to establish the scope and limitations of this synthetic approach leading to 3,5-disubstituted pyridine boronic esters **2**, we selected target structures, which should be representative not only for the reactivity of electrophiles (first iodine–magnesium exchange), but also for the various classes of amino acid side chains. We could confirm that nonpolar/hydrophobic (**2a–c**, Table 2, entries 1–3), basic (**2e**, Table 2, entry 5), acidic (**2f**, Table 2, entry 6), polar/neutral (**2g**, Table 2, entry 7) and even non-natural (**2d**, Table 2, entry 4) side chains are accessible by this approach with 24–73% overall yields with the four-step reaction sequence. For synthetic reasons we decided to synthesize the building blocks for the "Lys" and "Asp" surrogates in a masked form, as these are more stable in storage and more advantageous in the subsequent Suzuki coupling assembly and purification step. The masked "Lys" surrogates (**2e**, Table 2, entry 5) can easily be hydrogenated to the corresponding native structure at the teraryl stage, by using Raney nickel in an ammonia/MeOH mixture, as we demonstrated later (vide infra).

In order to highlight our convergent teraryl synthesis strategy, we prepared representative pyridine-based teraryls **1** with a phenylic core unit **3**. According to the established procedure, it is possible to obtain teraryls **1** in a convergent, in situ two-step synthesis.[15] The selective differentiation of the two leaving groups is based on the different reactivity of the leaving groups, the steric accessibility, and strength of the applied bases during the Suzuki coupling with $PdCl_2$-(dppf)·DCM catalyst (dppf = 1,1′-bis(diphenylphosphino)ferrocene).

The pyridine-based Leu-Val-Phe mimetic (**1a**) was assembled in 47% (Table 3, entry 1) and the Naph-Ile-Phe (**1b**) mimetic in 66% overall yields (entry 2). For the synthesis of the Leu-Val-Lys mimetic the second Suzuki coupling was performed with boronic ester **2e** to deliver compound **1c** in 46% yield (Table 3, entry 3). The lysine side chain in its latent form of a nitrile in compound **1c** can be easily reduced to the primary amine under reductive conditions by using Raney nickel in an H-Cube™ flow reactor to deliver the desired Leu-Val-Lys mimetic **1d** in 86% yield (Scheme 5). Already these three examples convincingly show that the combination of pyridine boronic acid ester building blocks **2** and the convergent assembly by electronically differentiated functional core units **3** provides an effi-

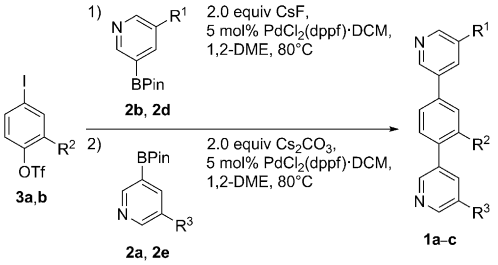
Table 2. Overall yields for the synthesis of building blocks **2** with representative residues (or a latent form; entries 5 and 6) for all groups of amino acids (nonpolar/hydrophobic, basic, acidic and polar/neutral or even non-natural).

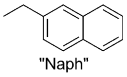
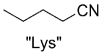


Entry	Product	Amino acid side chain	Overall yield [%][a]
1		"Phe", nonpolar/hydrophobic	76
2		"Leu", nonpolar/hydrophobic	45
3		"Ile", nonpolar/hydrophobic	24[b]
4		non-natural/nonpolar/hydrophobic	27
5		"Lys", basic	52
6		"Asp", acidic	55
7		"Asn", polar/neutral	37[c]

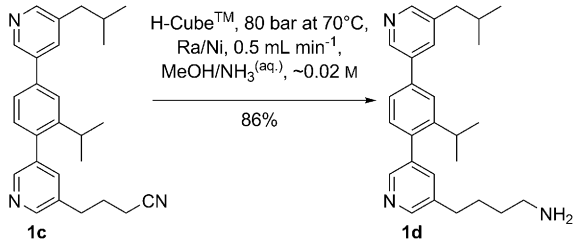
[a] Isolated yields over four steps starting from 3,5-diiodopyridine (**4b**). [b] The elimination product of compound **9c** (Table 1, entry 3) was reduced with 10% Pd/C, after borylation.[25] [c] Compound **2g** was prepared from compound **2f** by aminolysis with catalytic amounts of KCN in a 7 M ammonia/MeOH mixture at 50 °C.[25]

Table 3. Synthesized pyridine-based teraryls **1a–c** using the convergent two-step synthesis without purification approach.



Entry	R^{1}[a]	R^{2}[a]	R^{3}[a]	Teraryl	Yield [%][b]
1				**1a**	47
2				**1b**	66
3				**1c**	46[c,d]

[a] Residues for the corresponding amino acids that are mimicked by these residues. [b] Isolated yields. [c] Lys side chain (R^3) in its latent form of a nitrile. [d] The primary nitrile was reduced to the corresponding amine with Raney nickel in ammonia/MeOH solution.[25]



Scheme 5. Reduction of primary nitrile **1c** to the corresponding amine **1d**.

cient and general solution to the synthesis of polar teraryl-based α-helix mimetics as potential inhibitors of PPIs.

Conclusion

The interaction of small molecules with biologically active targets is the central focus of drug discovery. The field of inhibition of protein–protein interactions has become one of the big challenges and this area of research is still in its nascency. Our new modular approach for the assembly of more water soluble teraryls, based on integrating pyridinic building blocks with our strategy of electronically differentiated bifunctional core units **3**, represents an important synthetic advance for the convenient synthesis of libraries of such α-helix mimetics. With only a set of 18 core building blocks **3** and 18 3,5-disubstituted pyridine boronic acid pinacol esters **2**, any permutations of α-helix mimetics featuring all relevant proteinogenic amino acids (excluding Pro and Gly) could be prepared. We are currently working on the synthesis of such a comprehensive set of building blocks, featuring all 18 proteinogenic amino acids complemented by some non-natural ones, like compound **2d**.

Experimental Section

General methods, additional information and further experimental procedures are given in the Supporting Information.

Isopropyl magnesium chloride lithium chloride (*i*PrMgCl·LiCl) (13): A flame-dried two-neck round-bottom flask (250 mL) with reflux condenser (with argon inlet) charged with magnesium turnings (7.34 g, 0.30 mol, 1.2 equiv) was heated, in vacuo, with a heat gun for 5 min at maximum power level. After being cooled to room temperature, absolute, degassed THF (30 mL) was added and the suspension was sonicated for 10 min. 2-Chloropropane (23.20 mL, 19.93 g, 0.25 mol, 1.0 equiv) was added via syringe under inert conditions. After activation by heating, the strong exothermic reaction was kept between 55 and 60 °C by intensive ice-cooling. If the reaction did not start by heating, a small crystal of iodine was added, without stirring, to initiate the activation at a localized position. After the Grignard formation had started, the suspension was diluted with absolute, degassed THF (85 mL; overall 115 mL, $c_{calcd}=2.2$ M). After decay of the exothermic reaction, the mixture was heated for approximately 1 h at 80 °C and stirred, overnight, at room temperature. The Grignard suspension was filtered under argon by using an inert filtration funnel, and titration according to the procedure described below was performed to determine the concentration of the isopropyl magnesium chloride. The pale gray/brown filtered Grignard solution was added to ground and vacuum dried (120 °C/6 h) lithium chloride (9.93 g, 0.23 mmol, 1.0 equiv, based on the formed Grignard). After being stirred for 12 h at room temperature, the *i*PrMgCl·LiCl solution (**13**) was titrated again by using the following procedure.[20]

Titration of isopropyl magnesium chloride lithium chloride solution (*i*PrMgCl·LiCl) (13): A flame-dried amber glass Schlenk flask was charged with absolute, degassed toluene (200.0 mL) and absolute 2-butanol (20.0 mL).[26] This stock solution was stored under argon over 3 Å molecular sieves (stable over months). The calculated concentration of this stock solution ($c_{calcd}=0.99$ M) was used as reference for the titration of *i*PrMgCl·LiCl solution (**13**). *N*-Phenyl-4-phenylazoaniline (~2–5 mg) as indicator and the Grignard solution were added dropwise, under inert conditions, to the stock solution (2.0 mL). The equivalence point was indicated by a sharp color change from yellow–orange to deep red. To ensure a precise titration a triple determination was performed. The titration was carried out before every use of the Grignard solution.[27]

3,5-Diiodopyridine (4b): In a flame-dried Schlenk flask (250 mL) 3,5-dibromopyridine (**4a**; 7.27 g, 30.7 mmol, 1.0 equiv), copper(I) iodide[28] (585 mg, 3.1 mmol, 10 mol%) and sodium iodide (18.41 g, 0.13 mol, 4.0 equiv) were suspended in absolute, degassed 1,4-dioxane (50 mL). After adding *N,N'*-dimethylethylenediamine (330 μL, 270 mg, 3.07 mmol, 10 mol%), the pale yellow suspension was stirred for approximately 20 h at 120 °C until complete conversion ($R_f=0.68$, cyclohexane/EtOAc, 9:1). After filtration, the reddish brown suspension was quenched with saturated NH_4Cl solution (50 mL) and the deep blue aqueous phase was extracted with DCM (4×70 mL). The combined yellow organic layers were dried over Na_2SO_4, filtered and concentrated to dryness. The golden yellow crude product (9.23 g, 91%) was recrystallized from EtOH (235 mL; 8.72 g, 86%, pale golden shavings). As an alternative purification method, small amounts could be sublimated at 110–120 °C and 0.01 torr.[29] M.p. 166–168 °C; sublim. = 100–110 °C, 0.01 torr; ^{1}H NMR (300 MHz, [D]CHCl$_3$): $\delta=8.75$ (d, ^4J(H,H) = 1.3 Hz, 2H; H-2, H-6), 8.35 ppm (t, ^4J(H,H) = 1.8 Hz, 1H; H-4); ^{13}C NMR (76 MHz, [D]CHCl$_3$, APT): $\delta=154.3$ (C-2, C-6), 151.7 (C-4), 94.0 ppm (C$_q$; C-3, C-5); GC-MS (EI, 70 eV): *m/z* (%): 331 (100) [M^+], 204 (46) [M^+−I], 77 (17) [M^+ −2I].

2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (PinBO*i*Pr) (11): A flame-dried and argon-flushed two-neck round-bottom flask (100 mL), equipped with argon inlet, was charged with pinacol (6.92 g, 58.6 mmol, 1.0 equiv) and triisopropyl borate (13.50 mL, 11.00 g, 58.5 mmol, 1.0 equiv). After being stirred for 2 h at 68 °C, the formed 2-propanol was removed under inert conditions, in vacuo, at room temperature (~15 mbar). Compound **11** was isolated by fractionated distillation (b.p.$_{1.4}$ 30 °C) as a colorless liquid (4.75 g, 44%);[20a,30] b.p. 30 °C, 1.4 torr; ^{1}H NMR (300 MHz, [D]CHCl$_3$): $\delta=4.32$ (sept, ^3J(H,H) = 6.1 Hz, 1H; CH), 1.24 (s, 12H; CH_3^{BPin}), 1.19 ppm (d, ^3J(H,H) = 6.1 Hz, 6H; CH_3); ^{13}C NMR (76 MHz, [D]CHCl$_3$, APT): $\delta=82.6$ (C$_q$; C^{BPin}), 67.5 (CH), 24.7, (CH_3^{BPin}), 24.5 ppm (CH_3); GC-MS (EI, 70 eV): *m/z* (%): 186 (1) [M^+], 171 (100) [M^+-CH_3], 129 (33) [$M^+-C_4H_9$].

Representative procedure for the first iodine–magnesium exchange for synthesizing 3-(hydroxymethyl)-5-iodopyridine derivatives 9: A flame-dried and argon-flushed two-neck round-bottom flask (100 mL), equipped with argon inlet, was charged with 3,5-diiodopyridine (**4b**; 1.0 equiv) and absolute, degassed THF was added until a clear solution was obtained at room temperature ($c\approx0.2$ M). The colorless solution was cooled to −78 °C and *i*PrMgCl·LiCl solution (**13**; 1.05 equiv) was added in one portion. After being degassed, the pale yellow solution was stirred at −78 °C until full conversion (~1.5–2 h). The iodine–magnesium exchange was monitored by GC-MS. The GC samples were prepared by quenching a small aliquot of the reaction mixture with saturated NH_4Cl solution followed by extraction with DCM. After quantitative conversion, the corresponding electrophiles **8a–f** were added and the reaction mixture was allowed to warm to room temperature after 30 min at −78 °C, and stirred until full conversion. The reaction mixture was quenched with saturated NH_4Cl solution, extracted with DCM (5×20 mL) and dried over Na_2SO_4. After filtration, the solvent was removed, in vacuo, by using a rotary evaporator and the yellow or orange oil was purified by flash column

chromatography (short SiO_2 column, 4×4 cm, eluents are described in the Supporting Information).[20a]

Representative procedure for the formation of 3-(chloromethyl)-5-iodopyridine derivatives 10 from the corresponding 3-(hydroxymethyl)-5-iodopyridine derivatives 9: A round-bottom flask (50 mL) with reflux condenser was charged with the corresponding 3-(hydroxymethyl)-5-iodopyridine derivative **9** (1.0 equiv). After being cooled to −12 °C, freshly distilled $SOCl_2$ was added, and the mixture was stirred at the indicated temperature. In some cases, DCM was added to ensure complete dissolution of the formed pyridinium salt. Chlorination was monitored by GC-MS. The GC samples were prepared by quenching a small aliquot of the reaction mixture with saturated Na_2CO_3 solution followed by extraction with DCM. After quantitative conversion, the $SOCl_2$ was distilled off and the crude product was quenched with saturated Na_2CO_3 solution. The aqueous phase (pH ~8) was extracted with DCM (4×20 mL) and the combined organic layers were washed with brine (1×15 mL). The pale yellow or reddish organic phase was dried over Na_2SO_4, and after filtration, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (short SiO_2 column, 4×4 cm; vide infra).

Representative procedure for the second iodine–magnesium exchange for synthesizing 3-(chloromethyl)-5-BPin-pyridine derivatives 12: A flame-dried and argon-flushed two-neck round-bottom flask (50 mL), equipped with argon inlet, was charged with the corresponding 3-(chloromethyl)-5-iodopyridine derivative **10** (1.0 equiv) and absolute, degassed THF ($c \approx 0.2$ M) was added. The solution was cooled to −78 °C, and *i*PrMgCl·LiCl (**13**; 1.1 equiv) was added in one portion. After being degassed, the solution was stirred at −78 °C until full conversion was detected by GC-MS (~2 h). The GC samples were prepared by quenching a small aliquot of the reaction mixture with saturated NH_4Cl solution and extracted with DCM. PinBO*i*Pr (**11**; 1.15 equiv) was added and the reaction mixture was allowed to warm to room temperature and stirred until full conversion (~1 h). The reaction mixture was quenched with saturated NH_4Cl solution and extracted with DCM (4×25 mL). The combined organic layers were washed with brine (1×15 mL) and dried over Na_2SO_4. After filtration, the solvent was removed, in vacuo, by using a rotary evaporator and the crude product was used in the next step without further purification due to instability on SiO_2.[20a]

Representative procedure for the dechlorination of 3-(chloromethyl)-5-(BPin)-pyridine derivatives 12 to the corresponding 3,5-disubstituted pyridine-based boronic acid pinacol esters 2: In a round-bottom flask (250 mL) the corresponding 3-(chloromethyl)-5-(BPin)pyridine derivative **12** (1.0 equiv) was dissolved in approximately 1.0 M DCM/glacial acetic acid (21 equiv) solution. After addition of zinc dust (<10 μm, equivalents are denoted in the Supporting Information), the green suspension was stirred until full conversion was detected by GC-MS analysis. The GC samples were prepared by quenching a small aliquot of the reaction mixture with saturated Na_2CO_3 solution followed by extraction with DCM and filtration through a plug of cotton. The reaction mixture was quenched with saturated Na_2CO_3 solution, extracted with DCM (4× 20 mL) and washed with brine (1×20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The crude product was concentrated to dryness and the pale yellow or orange crude oily product was purified by Kugelrohr distillation (temperature and pressure are mentioned).

Representative procedure for the synthesis of linear pyridine-type teraryls 1a–c by consecutive double Suzuki coupling: A flame-dried two-neck round-bottom flask with argon inlet was charged with the corresponding 3,5-disubstituted pyridine-based boronic acid pinacol ester **2** (1.0 equiv), caesium fluoride (CsF; 2.0 equiv) and $PdCl_2$(dppf)·DCM (5 mol%). After being dried, in vacuo, a solution of the corresponding core unit **3** (1.0 equiv) in absolute, degassed 1,2-dimethoxyethane (DME, 4 mL) was added. After being degassed, the reaction mixture was stirred at 80 °C until full conversion was detected by TLC (~7 h). The brown suspension was filtered through a pad of SiO_2 (3×2 cm, eluent: 100 mL EtOAc) and the filtrate was concentrated to dryness by using a rotary evaporator. A second flame-dried two-neck round-bottom flask with argon inlet was charged with the second corresponding 3,5-disubstituted pyridine-based boronic acid pinacol ester **2** (1.05 equiv), caesium carbonate (Cs_2CO_3; 2.0 equiv) and $PdCl_2$(dppf)·DCM (5 mol%). After being dried, in vacuo, a solution of the previously prepared crude intermediate in absolute, degassed 1,2-DME (5 mL) was added. After being degassed, the reaction mixture was stirred at 80 °C, overnight. The quantitative conversion was confirmed by TLC, and after filtration of the black suspension through a pad of SiO_2 (3×2 cm, eluent: 100 mL MeOH) the filtrate was concentrated to dryness under reduced pressure and was purified by flash column chromatography.

Acknowledgements

We thank Prof. Reza Ahmadian (University of Düsseldorf) and Dr. Radovan Dvrosky (MPI for Molecular Physiology, Dortmund) for helpful discussions and continuous collaboration in the field of protein–protein interactions. This research was funded by grants of the Volkswagenstiftung, Hannover, and the PLACEBO (Platform for Chemical Biology) project as part of the Austrian Genome Project GEN-AU funded by the Forschungsförderungsgesellschaft (FFG) and Bundesministerium für Wissenschaft und Forschung (BMWF). We gratefully acknowledge Elisabeth Fuchs, Stefan Velikogne and Lukas Omann for skillful assistance in the laboratory.

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Received: August 23, 2012
Revised: November 13, 2012
Published online: December 23, 2012

