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A Modular Synthesis of Teraryl-Based α-Helix Mimetics, Part 1: Synthesis of Core Fragments with Two Electronically Differentiated Leaving Groups

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Dedicated to Professor Bernhard Kräutler

Abstract: Teraryl-based α-helix mimetics have proven to be useful compounds for the inhibition of protein–protein interactions (PPI). We have developed a modular and flexible approach for the synthesis of teraryl-based α-helix mimetics. Central to our strategy is the use of a benzene core unit featuring two leaving groups of differentiated reactivity in the Pd-catalyzed cross-coupling used for terphenyl assembly. With the halogen/diazonium route and the halogen/triflate route, two strategies have successfully been established. The synthesis of core building blocks with aliphatic (Ala, Val, Leu, Ile), aromatic (Phe), polar (Cys, Lys), hydrophilic (Ser, Gln), and acidic (Glu) amino acid side chains are reported.

Keywords: inhibitors · peptide mimetics · protein–protein interactions · Suzuki coupling · teraryl

Introduction

Over the last two decades it has been realized that many proteins are regulated by binding interactions with one or several other proteins.[1] The establishment of protein–protein interaction matrices allows the complexity of these interaction processes to be increasingly better understood.[2] Protein–protein interactions (PPIs) play important roles in signal transduction and many other physiological processes. Moreover, the inhibition of such PPIs would present a potential target for pharmaceutical intervention.[3] However, it has been realized that the inhibition of PPIs with small molecules is an endeavor of considerable difficulty and complexity, as these PPIs are characterized by a multitude of many weak interactions over a typically large surface area, which are difficult to mimic with low molecular weight organic compounds.[4] Additionally, it has been recognized that the surface of proteins can undergo significant reorganization upon binding to other proteins.[5] Fortunately, careful thermodynamic analysis and mutation studies of PPIs have revealed that among the many contacts within an interaction area, quite frequently only a few amino acids are responsible for a significant amount of the overall binding energy ("hotspots").[6] A considerable number of PPIs involve the interaction of an α-helix (or helices) in which side chains of the α-helix are positioned to the hotspots of the surface of a second protein.[7,8] As short peptides have limitations as drugs due to their conformational lability, their poor proteolytic stability, and bioavailability, strategies have been pursued to overcome these limitations by using stapled peptides,[9] β-peptides,[10] β-hairpin,[11] or α-helix mimetics.[12]

The most prominent strategy for α-helix mimetics follows Hamilton's proposal that the i, $i+3$ (or $i+4$) and $i+7$ amino acid side chain of an α-helix can be mimicked if these side chains are positioned at the 2′,3,3″-position of a terphenylic scaffold (Figure 1).[13]

Hamilton and his group have demonstrated that this approach indeed successfully leads to inhibitors of several

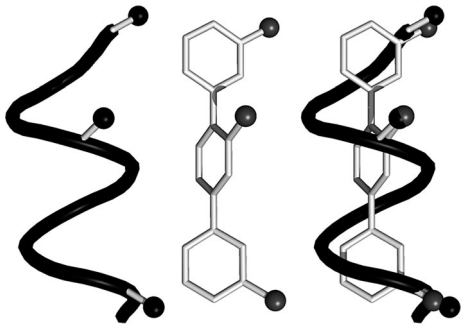

Figure 1. Schematic depiction of terphenylic scaffold **1** mimicking an α-helix.

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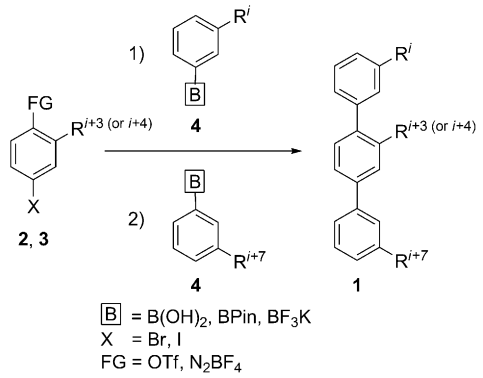
PPIs of physiological relevance.[12e,14] They have developed variants of their structural design, and improved upon the solubility and synthetic accessibility of their original terphenyl scaffold, which are assembled by linear synthesis involving protected building blocks.[13b] As this approach has turned out to be successful for several very specific problems, we reasoned that this design principle of teraryl α-helix mimetics might be so universal, that one can envision the synthesis of a comprehensive set of teraryls featuring all conceivable amino acid side chain permutations. But before such an endeavor can be pursued, one has first to find a more efficient synthetic access to this compound class, as the so far reported linear way of teraryl assembly would not be efficient enough due to its high step count and less than optimal synthetic efficiency.

Here we report a solution to this synthetic challenge by introducing a highly convergent strategy for the assembly of terphenyl-based α-helix mimetics **1** by exploiting the differentiated reactivity of core units **2**, **3** with two different leaving groups competent in the Pd-catalyzed cross-coupling with phenyl boronic acid derivatives **4** representing the top and bottom fragment. With this strategy it should be possible to synthesize a library featuring any possible α-helix teraryl mimic from two sets of 18 building blocks each, representing the proteinogenic amino acids in core units **2**, **3** and the top/bottom fragments **4** (Scheme 1).

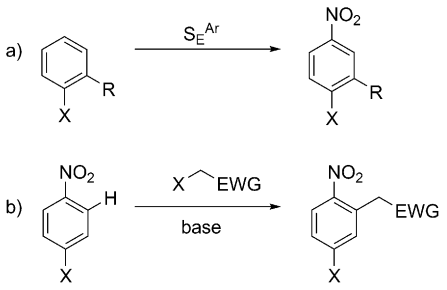


Scheme 1. Synthetic strategy for assembly of terphenyls **1** by using a set of core units **2** (FG = N_2BF_4, X = Br), **3** (FG = OTf, X = I) and boronic acid derivatives **4**.

Results and Discussion

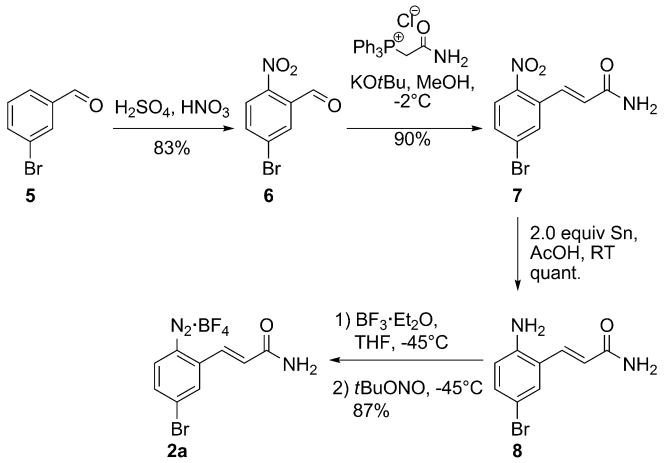
Our design of the core fragments **2** and **3** was guided by the following requirements. First, we were aiming for core building blocks featuring two different leaving groups for the Pd-catalyzed cross-coupling chosen as the fragment condensation reaction. The sequential Suzuki coupling of building blocks featuring different forms of boron species, such as boronic esters, MIDA-boronates, or BF_3 salts has been described by Burke and others.[15] Being aware that the synthesis of functionalized core fragments with two boron species of differentiated reactivity would impose an effort of considerable synthetic complexity, it appeared to us more convenient for our synthetic plan to use core building blocks with two different leaving groups, which participate in the first step of the catalytic cycle of Pd-catalyzed cross-coupling—the oxidative addition, for which the sequence of reactivity is known to be in the order $-N_2^+ > -I > -OTf \sim -Br > -Cl$.[16] We planned to use one halogen and either a diazonium tetrafluoroborate (core fragment **2**) or a triflate functional group (core fragment **3**) for these purposes (Scheme 1). The well-established literature for arene functionalization reactions motivated our plan for the introduction of these functional groups with the use of the precursor units $-NO_2$ and −OH as convenient directing groups to introduce the amino acid side chains at the desired positions. As a consequence of our synthetic strategy, it will be necessary to provide the top and bottom ring as boronic acid derivative building blocks **4**. As this set of building blocks requires only two functional groups (compared to three for the core unit) the introduction of the boronic acid moiety will definitely be less challenging on **4** than on **2** or **3**. An additional positive aspect of our approach is that only a set of 18 building blocks (excluding Pro and Gly, which are not relevant for α-helix PPI interaction sites) will be necessary for the top and bottom ring moiety **4** (Scheme 1).

In our first strategy we used the combination bromine/diazonium as leaving groups for our core fragment **2a**,**b**. Over the last decade the diazonium group has received increasing attention as a very reactive leaving group for Pd-catalyzed cross-coupling.[17] Typically the corresponding diazonium tetrafluoroborates are used as stable and (most often) crystalline reagents. The diazo compounds can be conveniently prepared by diazotation of aniline derivatives, which itself is accessible through hydrogenation of a suitably substituted nitrobenzene. We envisioned the following two strategies for the introduction of the amino acid side chains into the nitrobenzene: 1) electrophilic nitration (S_E^{Ar}) to introduce substituents in the *meta*-position (Scheme 2a); 2) vicarious nucleophilic substitution (VNS) of nitrobenzenes to introduce substituents in the *ortho*-position (Scheme 2).[18] As an example for the first variant, we used an S_E^{Ar} approach for the introduction of a glutamine side chain (Scheme 3).



Scheme 2. Introduction of the nitro group under: a) electrophilic conditions, or b) introduction of the amino acid side chain under vicarious nucleophilic substitution (VNS).

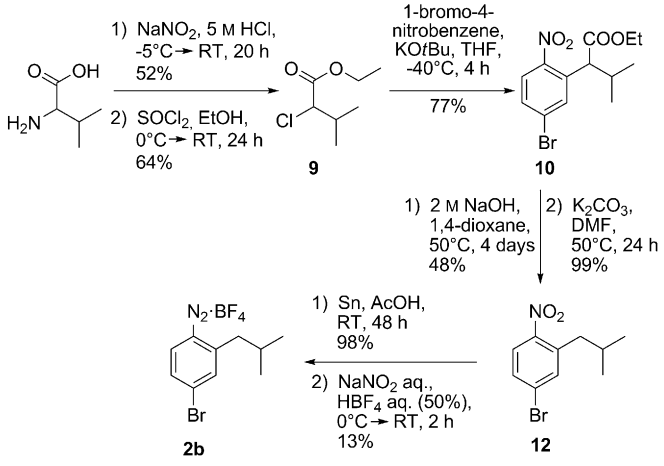
Nitration of 3-bromobenzaldehyde (**5**) with nitric and sulfuric acids produced 5-bromo-2-nitrobenzaldehyde (**6**) in



Scheme 3. Synthesis of diazonium tetrafluoroborate salt **2a**, starting from 3-bromobenzaldehyde (**5**).

83% yield. The aldehyde moiety served as an anchor to install the side chain fragment to product acrylamide **7** in 90% yield under Wittig conditions. The reduction of acrylamide **7** succeeded with Sn powder in acetic acid at room temperature in quantitative yield without interfering with the bromo substituent, which turned out to be sensitive to other reducing agents.[19] Finally, the diazonium salt **2a** was formed by treatment of amine **8** with $BF_3{\cdot}Et_2O$ and *t*BuONO in absolute THF producing the crystalline and air stable diazonium salt **2a** in 87% yield (Scheme 3).

As an example for the second route by vicarious nucleophilic substitution (VNS) towards a diazonium-based core unit (**2b**) we used a protocol developed by Bull and coworkers for nucleophiles prepared from amino acids.[20] L-Valine was converted to the α-chloroester **9** by using the well-established diazonium route followed by esterification with $SOCl_2$/EtOH (Scheme 4).[21] VNS of α-chloroester **9** with 1-bromo-4-nitrobenzene produced intermediate **10** in 77%. For decarboxylation, compound **10** had to be first saponified by treatment with NaOH solution (2 M) in 1,4-dioxane in disappointingly low yield of 48%. Gratifyingly, the actual decarboxylation of the isolated carboxylic acid **11** by heating in DMF in the presence of K_2CO_3 at 50 °C produced intermediate **12** quantitatively. Finally, the nitro group was reduced by Sn powder in AcOH at room temperature allowing diazotation of amine **13** with HBF_4 and $NaNO_2$.[22] However, compound **2b** was isolated in only 13% yield as the isolation of the product **2b** by precipitation turned out to be challenging (Scheme 4).

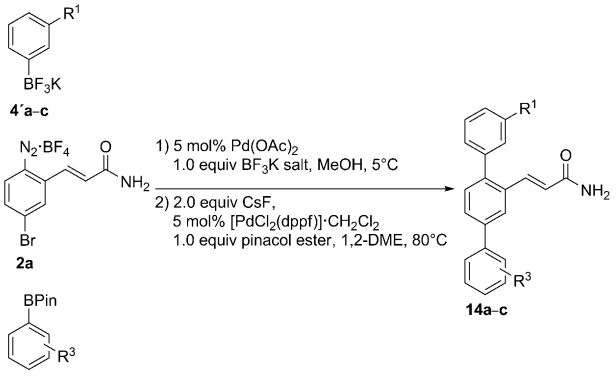


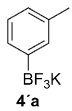
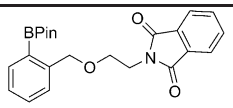
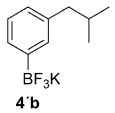
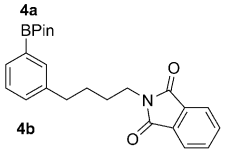
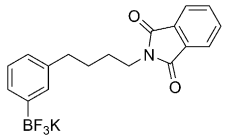
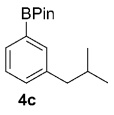
Scheme 4. Synthesis of second diazonium core unit **2b**.

In our teraryl assembly strategy the diazo core fragments **2a**,**b** will react first with the $-N_2BF_4$ group under Suzuki coupling conditions due to its high intrinsic reactivity. After considerable optimization we identified $Pd(OAc)_2$ (5 mol%) in MeOH at 5 °C as suitable conditions to couple the bottom fragment as its BF_3K salts **4′a–c** (Table 1).[23] The isolated biphenylic bromide derivatives were then coupled with boronic acid pinacol ester **4a–c** with $[PdCl_2(dppf)]{\cdot}CH_2Cl_2$ (5 mol%) and CsF as a base to furnish the corresponding acrylic terphenyls **14a–c** in 41–47% overall yields for this two-step process (Table 1).

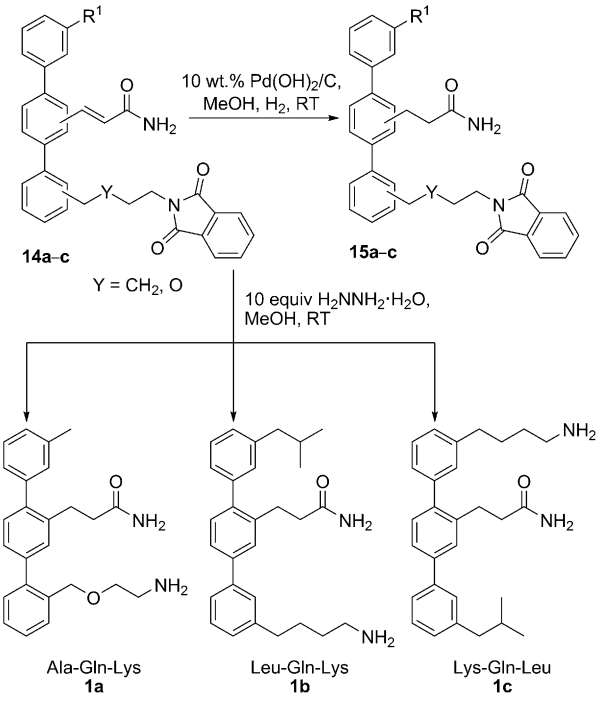
As the resulting acrylic terphenyls **14a–c** contained some of the amino acid side chains only in masked form, reduc-

Table 1. Synthesized terphenyls **1a–c** by using the diazonium core unit **2a**.[a]



Entry	BF_3K salt[b]	Pinacol ester[b]	Yield [%][c]
1	 4′a	 4a	43
2	 4′b	 4b	41
3	 4′c	 4c	47

[a] After $Pd(OAc)_2$-catalyzed cross-coupling with BF_3K salts **4′a–c**, the resulting biphenylic intermediates were coupled under Suzuki conditions. [b] For detailed synthetic procedures see the Supporting Information. [c] Yield of isolated product over two steps.

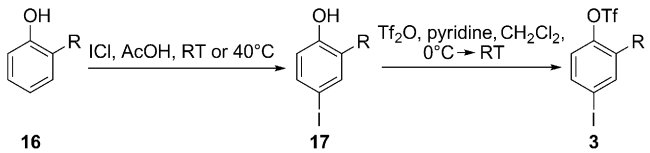


Scheme 5. Reduction and deprotection of acrylic terphenyls **14a–c** leads to the corresponding final α-helix mimetics **1a–c**.

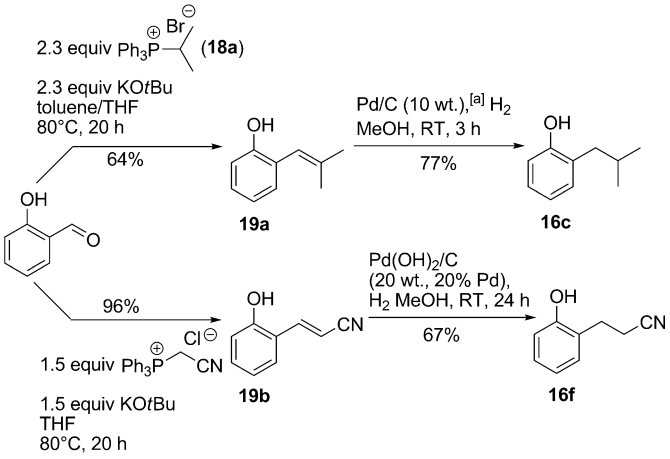
tion with $Pd(OH)_2/C$ and hydrazinolysis of the phthalimide-protected amino function of intermediate **15a–c** was necessary to produce the Ala-Gln-Lys (**1a**), Leu-Gln-Lys (**1b**) and Lys-Gln-Leu (**1c**) terphenyls (Scheme 5).

Although the diazonium route enabled the assembly of the desired terphenyls in a highly convergent manner in decent yields, the synthesis of several of the core fragment required many steps with only poor overall yields. Therefore, we explored an iodine/triflate strategy as an alternative to the diazonium route discussed above. We were attracted to this approach by the ready accessibility of phenol starting materials with different substitution patterns either from commercial sources or by simple modifications by electrophilic substitution (S_E^{Ar}) introducing substituents in the *ortho*/*para* position due to the activated character of phenols for this type of reactions. In the ideal case we would have to only perform iodination of the phenol derivatives **16** followed by treatment with Tf_2O in the presence of pyridine to produce the triflate ester **3** (Scheme 6).

Although for several amino acid side chain analogues the suitable phenol starting materials were commercially available, we had to synthesize the phenol starting materials **16**



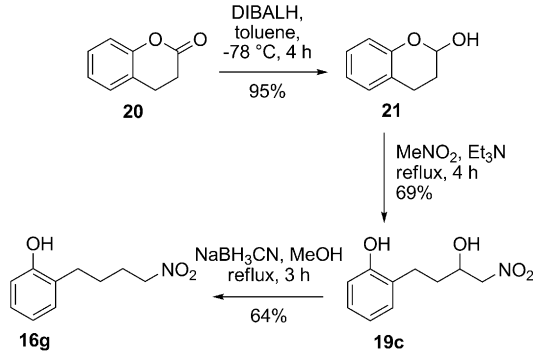
Scheme 6. General reaction scheme for synthesizing the triflate-based core units **3**.



Scheme 7. Introduction of the different side chains; [a] 5% Pd (based on dry substance).

for others from advanced intermediates. For the "Leu", "Glu" and "Gln" building blocks phosphonium salts **18a**,**b** were synthesized and coupled under Wittig conditions with salicylaldehyde (Scheme 7). The formed double bond of compounds **19a**,**b** was reduced by catalytic hydrogenation by using Pd catalysts like Pd/C or $Pd(OH)_2/C$. Any attempts by us to provide the "Glu" and "Gln" side chain as an ester, amide or free acid moiety in the presence of unprotected phenol-OH resulted in spontaneous lactonization under acidic conditions. Therefore, we masked the carboxyl moiety as a nitrile, which allowed us to produce the desired carboxyl or carboxamide functionality after teraryl assembly.

For the "Lys" side chain we started from chroman-2-one (**20**). Reduction with DIBALH in toluene produced the corresponding lactole **21** in 95% yield (Scheme 8).[24] Chain ex-

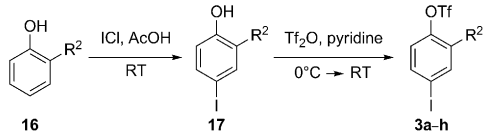


Scheme 8. Synthesis of "Lys" side chain precursor **16g**.

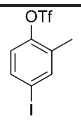
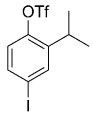
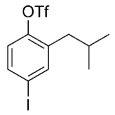
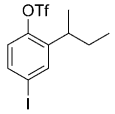
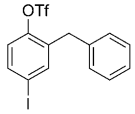
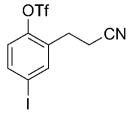
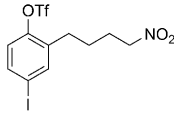
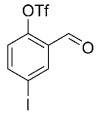
tension was accomplished by Henry reaction with nitromethane in 69% yield.[25] Reduction of **19c** with $NaBH_3CN$ selectively reduced the olefin leaving the nitro group intact as desired, since an amino group would interfere with the planned subsequent iodination and triflation reactions.

With the various phenol derivatives **16** now in hand, we pursued the iodination of these substrates using ICl/AcOH (96%) at room temperature, which produced *para*-iodinated phenols **17** in 69–93% yield.[14b] In the case of the "Ser" analogue **3h** these conditions did not lead to full conversion, but with glacial AcOH instead and by increasing the reaction temperature to 40°C produced pure **17h** in 93% isolated yield (Table 2, entry 8).[26] In the final step of the synthesis of core fragments **3** the −OH group was converted to a triflate with Tf_2O/pyridine.[27] Again for the "Ser" analogue these conditions had to be adapted to improve the yields. With CH_2Cl_2 as solvent and pyridine (1.5 equiv) as base 71% yield was achieved (Table 2).[28] In total eight iodine/triflate core structures **3a**–**h** could be produced in 46–77% yields over two steps from starting materials **16a**–**h**.

Table 2. Reaction conditions for iodination and introduction of triflate.

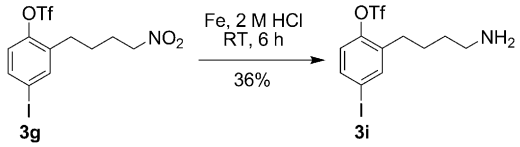


16 17 3a–h

Entry	Product	Side chain	Compound	Yield [%][a]
1		"Ala"	**3a**	71
2		"Val"	**3b**	59
3		"Leu"	**3c**	77
4		"Ile"	**3d**	59
5		"Phe"	**3e**	69
6		"Gln", "Glu"	**3f**	46
7		"Lys"	**3g**	57
8		"Ser"	**3h**	66[b,c]

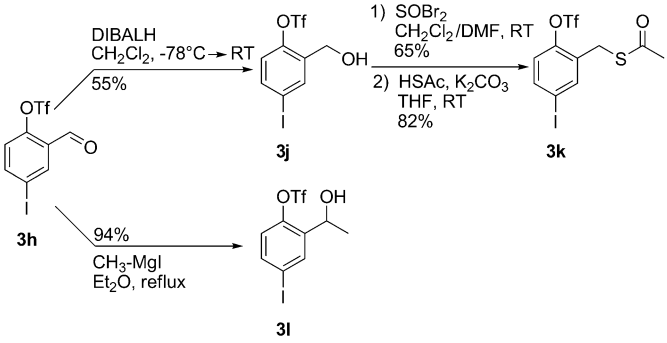
[a] Yields of isolated products over two steps. [b] Improved yields could be obtained by using glacial acetic acid and heating to 40°C during the iodination process. [c] Pyridine (1.5 equiv) and CH_2Cl_2 as solvent was used.

As has been mentioned above, for the "Lys" analogue **3g** it would have been impossible to introduce the iodine and the triflate group in the presence of the free amine. Conveniently, the corresponding nitro group was an ideal surrogate, perfectly compatible with these reaction conditions. By reduction with Fe in 2 M HCl the corresponding amine was furnished, producing the "Lys" building block **3i** in 36% yield (Scheme 9).



3g 3i

Scheme 9. Reduction of the nitro group.



3j 3k 3l

Scheme 10. Production of "Ser", "Cys" and "Thr" analogues.

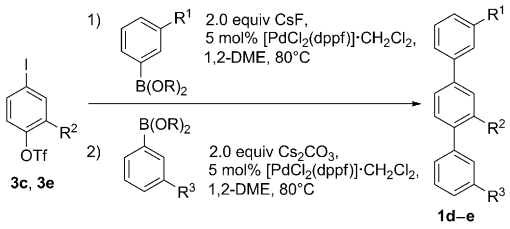
Starting from the aldehyde intermediate **3h** the "Ser", "Cys" and "Thr" analogues were accessible (Scheme 10). The reduction of the formyl group in the presence of the iodine and the triflate proved to be challenging. With DIBALH in CH_2Cl_2 the "Ser" analogue **3j** could be produced in 55% yield.[29] Two additional steps, bromination and introduction of a thioacetate group converted the "Ser" analogue **3j** into the acetyl-protected "Cys" analogue **3k** in 53% overall yield.[30] The "Thr" analogue **3l** was produced by chemoselective treatment with MeMgI in 94% yield.

The iodine/triflate strategy towards building block **3a**–**l** turned out to be of considerable flexibility involving only a few, typically high yielding reaction steps. We could prepare core building blocks **3** featuring aliphatic (Ala, Val, Leu, Ile), aromatic (Phe), polar (Ser, Thr) and basic (Lys) residues in unprotected form, and the S-containing amino acid side chain Cys and acidic/polar side chains (Gln, Glu) in protected form.

In order to demonstrate the suitability of our iodine/triflate building blocks for α-helix mimetic assembly, we synthesized a few representative terphenyls. In our optimization studies with core fragments **3** we identified [$PdCl_2$(dppf)]·CH_2Cl_2 as a suitable Pd precursor able to activate both leaving groups. As expected, the iodine reacted first. We found that with CsF as a base we could obtain very

good selectivity for Suzuki coupling with the iodine functionality. The less reactive triflate leaving group was then reacted smoothly by using Cs_2CO_3 as a base. Having the same solvent and catalyst in common for both Suzuki coupling reactions, we were intrigued by the possibility to perform the teraryl assembly in a one-pot reaction controlled by the sequence of addition of the bases. Indeed, in the case of Ile-Phe-Ala this proposition worked. However, the 79% yield of product is accompanied by a considerable amount of homocoupling and other products. Although careful reaction optimization might have improved the yield and purity for this reaction, we found it more opportune to come up with a flexible approach, which is in accordance with our main objective of this research: the assembly of a comprehensive library of teraryl mimetics, which makes it necessary to have reaction conditions available that should work for any building block combination. We were pleased to see, that the following in situ two-step synthesis protocol offers a good compromise between experimental simplicity and synthetic success. In a Schlenk tube, the first Suzuki coupling with the iodine moiety and the first building block was performed with $[PdCl_2(dppf)]\cdot CH_2Cl_2$ with CsF in 1,2-DME. After complete conversion the reaction mixture was filtered through silica, concentrated in vacuo, and the crude material was used in the second Suzuki coupling under similar conditions but with the second boronic acid building block and Cs_2CO_3 as base. Using this protocol the Ile-Phe-Ala terphenyl **1d** was produced in 59% overall yield, and the Phe-Leu-Val terphenyl **1e** in 54% overall yield (Table 3).[31]

Table 3. Synthesized terphenyls **1d,e** by using the triflate core units **3c** and **3e**.



$B(OR)_2 = B(OH)_2$, BPin

Entry	R^1	R^2	R^3	Compound[a]	Yield [%][b]
1	"Ile"	"Phe"	$-CH_3$ "Ala"	**1d**	59
2	"Phe"	"Leu"	"Val"	**1e**	54

[a] R^1 represents the *i* position, R^2 the $i+3$ (or $i+4$) and R^3 the $i+7$ position of an α-helix. [b] Yields of isolated products over two steps.

Conclusion

The inhibition of protein–protein interactions has become one of the big challenges and areas of research within drug discovery. Although this field is still in its nascency, recent results allow the conclusion that the use of α-helix mimetics has emerged as a successful paradigm in this area. Especially Hamilton's insight, that the teraryl moiety is an excellent scaffold to position the *i*, $i+3$ (or $i+4$) and $i+7$ residues of a folded α-helix has already been successfully applied into practice. Our new modular approach for the assembly of such terphenyls using either our halogen/diazonium or halogen/triflate strategy represents a synthetic bonanzafor the convenient synthesis of such α-helix mimetics. In contrast to previous efforts it allows the assembly of teraryls by sequential coupling of preset building blocks without intermittent protection or deprotection steps. In fact the teraryl assembly by sequential Suzuki couplings can be performed by sequential addition of the boronic acid building blocks for the top and bottom rings. With only a set of 18 core building blocks **2**, **3** and 18 substituted aryl boronic acid derivatives **4**, any representative of the 5670 permutations of α-helix mimetics featuring the proteinogenic amino acids could be prepared within a day. We are currently working on the synthesis of such a comprehensive tool box of building blocks, featuring all proteinogenic amino acids complemented by some non-natural ones.[32]

Experimental Section

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

Representative procedure for the iodination of phenol derivatives 16 to the corresponding *para*-iodo phenol derivatives 17: In a one-neck round-bottom flask (25 mL) the corresponding phenol derivative **16** (1.0 equiv) was dissolved in acetic acid and iodine monochloride (ICl; 1.0 equiv) was added at room temperature. In some cases additional ICl was added to ensure quantitative conversion. The reaction mixture was quenched with $NaHCO_3$ solution (100 mL, 0.5 M) and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with $Na_2S_2O_3$ solution (25%, 3×100 mL) followed by saturated NaCl solution (1×100 mL). After being dried over $MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography.

Representative procedure for synthesis of the triflate derivatives 3 from the corresponding *para*-iodo phenol derivatives 17: In a flame-dried and argon-flushed Schlenk-flask the corresponding *para*-iodo phenol derivative **17** (1.0 equiv) was dissolved in pyridine. After cooling the solution to 0°C trifluoromethanesulfonic anhydride (Tf_2O) was carefully added. After being stirred for 5 min at 0°C, the solution was allowed to warm to room temperature and stirred until quantitative conversion was detected by TLC. Et_2O (60 mL) was added and the organic phase was washed with H_2O (3×30 mL) followed by the extraction of the combined aqueous layers with Et_2O (2×30 mL). The organic phases were washed with HCl (1 M, 2×60 mL) and saturated NaCl solution (1×60 mL), dried over $MgSO_4$ and concentrated, in vacuo. The crude product was purified by flash column chromatography.

Representative procedure for the synthesis of terphenyls 1d,e by consecutive double Suzuki coupling: A flame-dried two-neck round-bottom flask with argon-inlet was charged with the corresponding boronic acid derivative **4** (1.0 equiv), CsF (2.0 equiv), and $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (5 mol%). After being dried, in vacuo, a solution of trifluoromethanesulfonate **3** (1.0 equiv) in absolute, degassed 1,2-DME was added. After additional degassing, the reaction mixture was stirred at 80°C until full conversion was detected by TLC. The typically brown suspension was filtered through a pad of SiO_2 (3×2 cm, eluents are denoted) and the filtrate was concentrated to dryness by using a rotary evaporator.

Another flame-dried two-neck round-bottom flask with argon-inlet was charged with the second pyridine-based boronic acid derivative **4** (1.0–1.2 equiv), cesium carbonate (Cs_2CO_3; 2.0–3.0 equiv), and [$PdCl_2$-(dppf)]•CH_2Cl_2 (5 mol%). After being dried, in vacuo, a solution of the previously prepared crude intermediate (4-(pyridin-3-yl)phenyl trifluoromethanesulfonate derivative, **22**) in 5 mL absolute, degassed 1,2-DME, was added. After additional degassing, the reaction mixture was stirred at 80 °C, overnight. The typically black suspension was filtered through a pad of SiO_2 (3×2 cm, eluent: 100 mL MeOH) and after being concentrated to dryness, the crude product was purified by flash column chromatography. To obtain highly pure substrate, products **1d**, **e** can be purified by semi-preparative HPLC.

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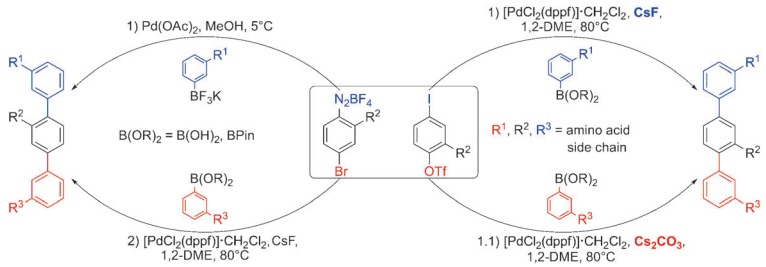

Turn on: Teraryl-based α-helix mimetics can be effectively produced by sequential Suzuki coupling of a central core fragment featuring electronically differentiated leaving groups with aryl boronic pinacol esters (see scheme). With a set of only 2×18 building blocks, all permutations of α-helix mimetics can be produced.

Peptidomimetics

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A Modular Synthesis of Teraryl-Based α-Helix Mimetics, Part 1: Synthesis of Core Fragments with Two Electronically Differentiated Leaving Groups