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Expanding the Diversity of Polycyclic Aromatics Through a Suzuki–Miyaura Cross-Coupling Strategy

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In recent years, Pd-catalyzed Suzuki–Miyaura (SM) cross-coupling reactions have revolutionized approaches to carbon–carbon bond formation. We have studied the application of SM coupling with several (ca. 16) complex molecular structures of particular relevance to scientists working at the interfaces of chemistry, biology, and materials sciences. In this regard, various structurally or biologically important polycyclic molecules (e.g., benzocrowns, C_3-symmetric molecules, 9,10-disubstituted anthracenes, and sulfones) and unusual amino acid derivatives have been modified by this reaction, while it has also been shown that allylation of aromatics through the use of a commercially available boronic acid ester by SM coupling under CsF/Pd^0 conditions is feasible.

1. Introduction

Biaryl compounds have widespread uses in many fields of organic chemistry.[1a] One of the most practical processes for the formation of aryl–aryl (or carbon–carbon) bonds involves Pd-catalyzed reactions between aryl halides, triflates, phosphates, or diazonium salts and various organoboron compounds in the presence of a base. Suzuki and co-workers[1b–1c] first reported this reaction in 1979, and it is usually referred to as the "Suzuki coupling reaction" or the "Suzuki–Miyaura (SM) reaction".[2]

Thanks to a fairly small difference in the electronegativities of boron (2.0) and carbon (2.5), organoboron compounds exhibit a high degree of functional group tolerance and also display exceptional stability (relative to other organometallic reagents) to heat, air, and moisture. With reference to "mainstream" methods,[3a] the SM reaction is regarded as a "clean cross-coupling" for carbon–carbon bond formation because the byproducts are nontoxic and can easily be removed from the reaction mixture. Of the various other available options for carbon–carbon bond formation, the Stille coupling also tolerates a wide variety of functional groups,[3b] but the tin byproducts formed during the reaction are toxic and difficult to purify, while Grignard-based coupling strategies cannot tolerate polar functional groups.

The SM reaction is usually carried out in a variety of solvents in the presence of diverse bases under the influence of Pd^{II} or Pd^0 catalysts. With the less reactive aryl chlorides, and also with electron-rich aryl bromides, the presence of electron-rich and sterically demanding phosphanes, imidazole carbenes, and palladacycles is useful,[4] while arenediazonium tetrafluoroborates, together with the aryl halides and triflates, are known to be more reactive towards palladium-catalyzed cross-coupling reaction with boronic acids.[5] The catalytic cycle for Pd^0-mediated cross-coupling between arylboronic acids and organic halides is shown in Figure 1 ("Ar′MY" in the catalytic cycle signifies arylboronic acid). Though aryl-/alkylboronic acids or boronate esters are widely used in the SM reaction, these regents very

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often suffer from a few limitations associated with their preparation, purification, and handling. To avoid this problem, there are a few reports in which potassium aryl/alkenyl trifluoroborates are used as coupling partners with arenediazonium tetrafluoroborates, aryl halides, and tosylates under palladium catalysis conditions.[6]

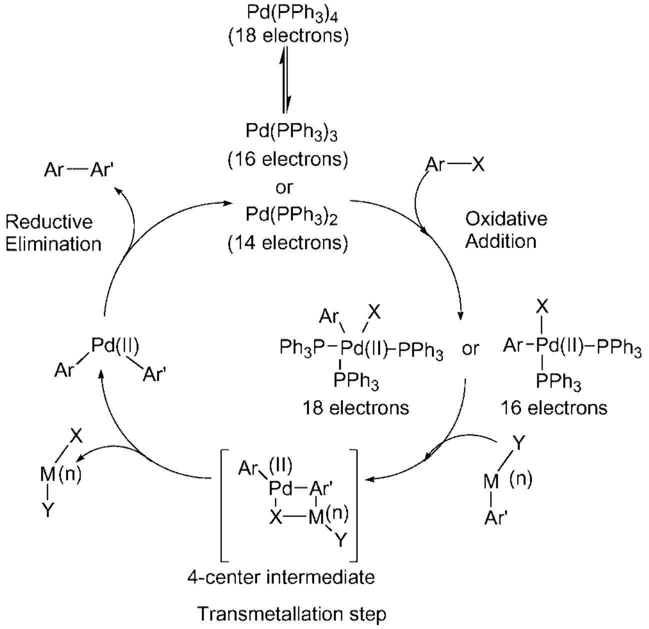


Figure 1. Catalytic cycle for the SM cross-coupling reaction.

The growth of the SM reaction can be broadly classified into three different fields: *i*) application of the SM reaction as a key step in the total synthesis of complex targets,[7] *ii*) the search for greener reaction conditions or catalyst improvement,[4] and *iii*) utilization of the SM reaction to synthesize biologically important molecules or to design compounds relevant to materials science applications.[2] Generally, the catalyst development work focuses on variation of metal and ligands, and the substrates tested are usually very simple and routine. To expand the scope and limitations of any new reaction it is also necessary to study its applicability with complex substrates, and to this end several novel molecular entities suitable for SM reactions have been identified. Our strategy is based on a "Building Block Approach",[8] a useful methodology for diversity-oriented synthesis. Recently, synthetic organic chemists have increasingly been shifting their attention from target-oriented synthesis to diversity-oriented synthesis, in which a large number of compounds are produced in a minimum number of steps. Suitable synthetic methodologies to expand molecular diversity are now widespread in the pharmaceutical and biotechnology industries and the diversity-oriented approach now constitutes an additional armament in the arsenal of synthetic organic chemistry.[9]

2. Synthesis of Polycycles by the SM Reaction

In this section we have chosen several intricate molecular structures to demonstrate the utility of the SM reaction (Figure 2). The criteria for the selection of an individual structural unit are its established, or sometimes projected, utility in biological, medicinal, and materials sciences. In most instances the parent compound (or simple derivative) is the only one available and extension of known methodology to provide highly functionalized derivatives requires more demanding synthetic procedures. Since the SM reaction is known to tolerate the presence of several polar functional groups, we have taken advantage of this aspect and have successfully and easily introduced various heterocyclic rings (e.g., furans and thiophenes) into the chosen target molecules. Intriguingly, in some instances we have been able to perform the SM reaction in a stepwise manner, thereby generating unsymmetrical molecules starting with symmetrical dihalo aromatics. These heterocyclic appendages provide additional handles for further exploration. Allylation methodology,[10] in combination with ring-closing metathesis (RCM),[11] as reported on in the following section, should open up new routes to various intricate cyclophane derivatives, while the production of the elaborate building blocks required for the design of intricate cyclophanes can be envisioned with the SM coupling reaction as a key step.

2.1. Synthesis of C_3-Symmetric Molecules by the SM Reaction

C_3-symmetric molecules are widely used in electrochemistry, coordination chemistry, and crystal engineering,[12] are useful components in the design of organic electroluminescent devices and three-dimensional molecular wires, and are also valuable as core units in diverse dendritic frameworks. Chiral C_3-symmetric molecules have been identified as helpful ligands known to induce high degrees of stereocontrol in various transition metal-catalyzed asymmetric transformations in which nonchelating or unfunctionalized substrates are involved.[13]

We therefore sought a general and simple methodology[14] for their synthesis, based on the utilization of acid-catalyzed trimerizations of carbonyl compounds followed by SM reactions. To this end, 1,3,5-tris(4-iodophenyl)benzene (**1**, Scheme 1) was prepared from 4-iodoacetophenone in a $SiCl_4$-mediated trimerization reaction based on classical cyclocondensation chemistry. Subsequently, SM reactions between compound **1** and various aryl and heteroarylboronic acids under $Pd(PPh_3)_4$ catalyst conditions were attempted, and the polyphenyl derivatives **2a**–**f** were obtained in 47–78% yields.[14] Since substituted thiophenes are valuable building blocks in electronic devices,[15] mixed aryl/heteroaryl C_3-symmetric derivatives such as **4a**–**b** (Scheme 2) are likely to be useful intermediates for further investigation. Initially a SM reaction between thiophen-2-ylboronic acid and the tribromo derivative **3** was attempted, and the coupling product **4a** was obtained in 14% yield along with mono- (13%) and bis-coupled (67%) derivatives. Since

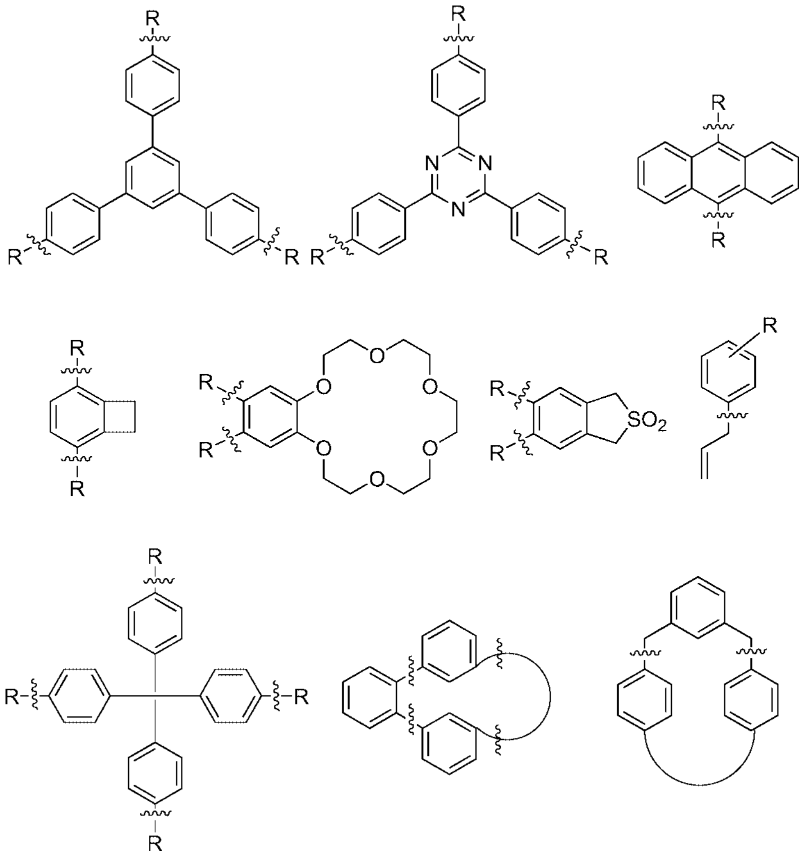
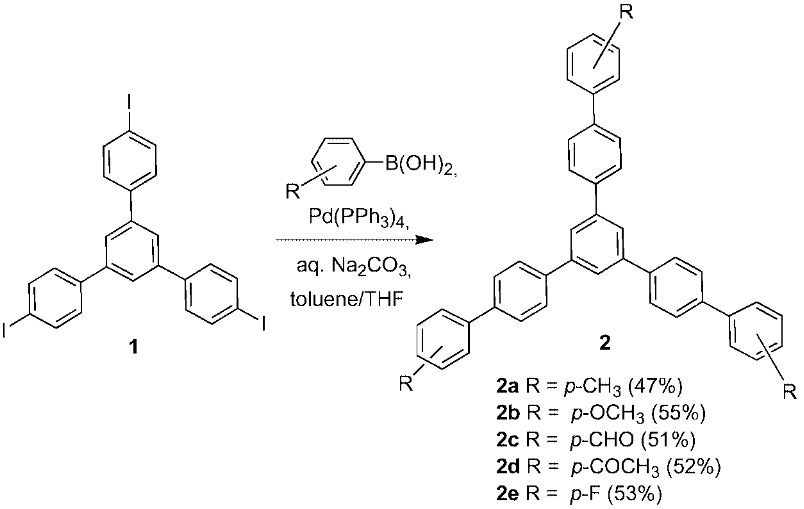


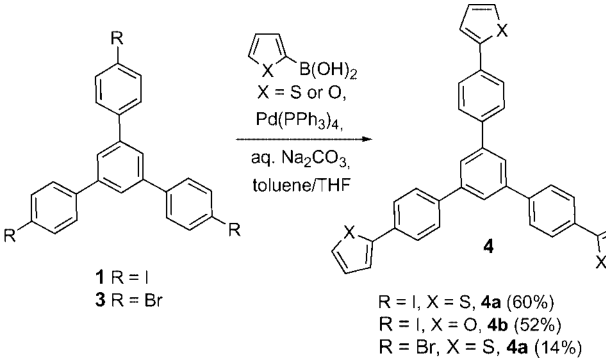
Figure 2. Several intricate molecular structures demonstrating the utility of the SM reaction (the wavy lines indicate the position of the formation of C–C bond by SM reaction).

iodoaromatics are better partners in SM cross-coupling reactions, the above reaction was also tried with triiodo compound **1** and thiophene- and furanboronic acids, with the coupling products **4a** (60%) and **4b** (52%) being obtained in good yields.

Compound **4a** was also prepared by an independent route: a SM reaction followed by a trimerization reaction (Scheme 3). The required thiophene derivative **6**, prepared in 92% yield by means of a Pd-catalyzed SM reaction between thiopheneboronic acid and 4-bromoacetophenone



Scheme 1.

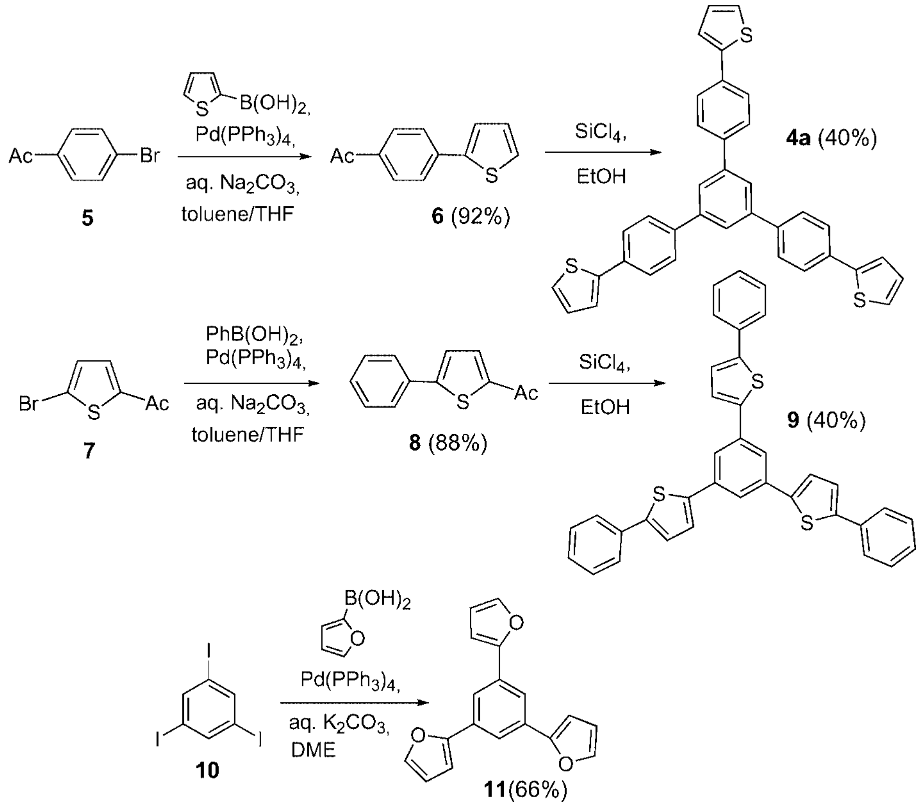


Scheme 2.

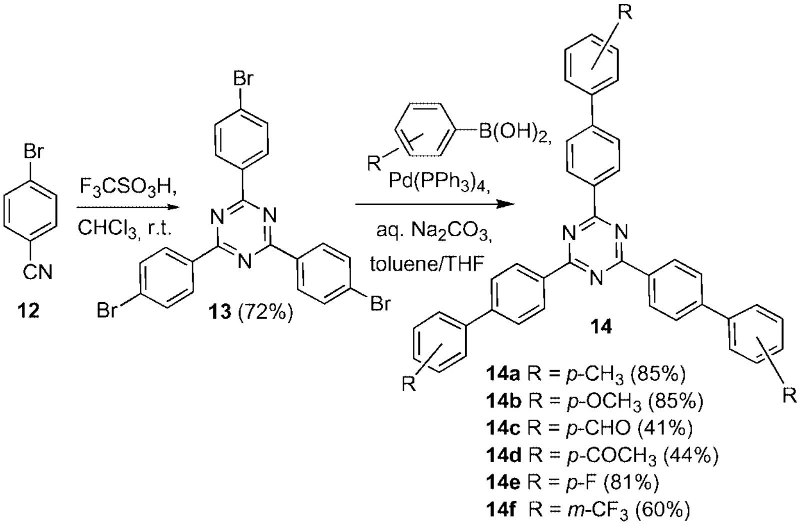
(**5**), underwent trimerization with $SiCl_4$ to give **4a**. Similarly, compound **9**, in which the thiophene units are situated in the inner core of the star-shaped molecule, has been prepared starting from **7**. In an extension of this idea to furan derivatives, triiodobenzene **10** was treated with furanboronic acid under SM reaction conditions to give compound **11** (66%); the $SiCl_4$-mediated trimerization route starting from 2-acetylfuran to give the C_3-symmetric molecule **11** was not accomplished. Later, the structural and conformational details of these star-shaped molecules were explored by semiempirical molecular orbital theory by use of the AM1 method.[14b] These studies indicated that the desired conformational rigidity can be finely tuned by modulating the aromatic rings.

Triazine-related compounds are also equally important in materials sciences and crystal engineering studies, and the synthesis of the C_3-symmetric 2,4,6-triphenyl-1,3,5-*s*-triazine derivatives **14a**–**f** was planned along similar lines (Scheme 4). Most of the known methods for the synthesis of this class of compounds have started with cyanuric chloride as a starting material, but our method involves trimerization of 4-bromobenzonitrile (**12**) in the presence of trifluoromethanesulfonic acid to provide the tribromo derivative **13** (72% yield),[16] with SM reactions between **13** and various arylboronic acids under palladium catalysis conditions then affording the cross-coupling products **14a**–**f** in moderate to good yields (41–85%).

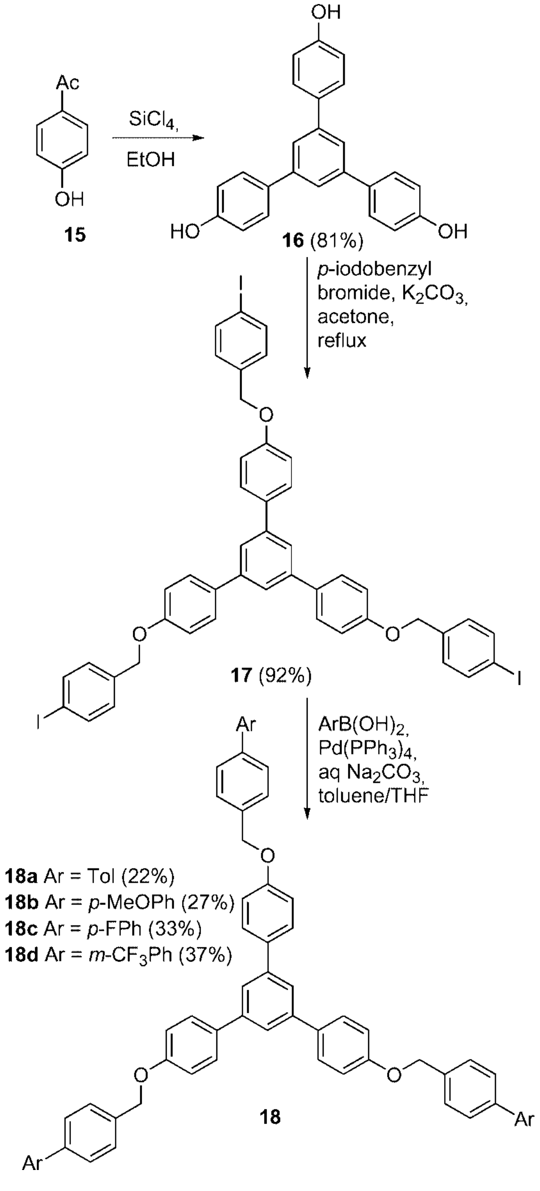
From our experience with polyaromatics, preparations of C_3-symmetric macromolecules such as **18** were undertaken (Scheme 5). 4-Hydroxyacetophenone (**15**) was trimerized to afford **16** in 81% yield, and to demonstrate the *O*-alkylation strategy, compound **16** was coupled with 4-iodobenzyl bromide, thus generating the C_3-symmetric aryloxy derivative **17**. The iodo functionality present here served as a useful handle for the synthesis of biphenyl-based macromolecules **18a**–**d** through SM reactions.[17]



Scheme 3.



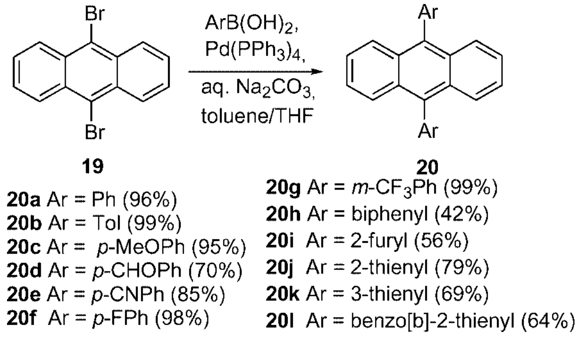
Scheme 4.



Scheme 5.

2.2. Synthesis of 9,10-Diarylanthracene Derivatives by Double SM Reaction

9,10-Diarylanthracene derivatives are valuable starting materials for Diels–Alder (DA) reactions,[18] but these derivatives are also very expensive and most of the synthetic methods for their preparation involve multi-step synthetic sequences, so the development of a cross-coupling strategy to functionalized 9,10-diarylanthracenes from inexpensive 9,10-dibromoanthracene (**19**) by a one-step procedure was an attractive option. We found that it is possible to couple the dibromide **19** with various boronic acids in the presence of $Pd(PPh_3)_4$ catalyst (Scheme 6),[19,20] with 42–99% yields of the coupling products **20a–l** typically being obtained. It may be relevant to mention that the substrate **20d** has also been prepared by a four-step sequence involving the Grignard coupling reaction as a key step.[21] Furthermore, the aldehyde functionality present in **20d** can be used for additional synthetic elaboration.



Scheme 6.

To prepare unsymmetrical 9,10-diarylanthracene derivatives,[20] compound **19** was treated with 1.5 equivalents of thien-2-ylboronic acid under the same reaction conditions to generate 9-bromo-10-(thien-2-yl)anthracene (**22**) in 79%

isolated yield (Figure 3). Selective SM reactions with other heteroarylboronic acids were attempted next, and typically 61–90% yields of the monocoupled products **21**–**25** were obtained. Thiophene-substituted anthracene derivatives are often incorporated in electroluminescent devices.

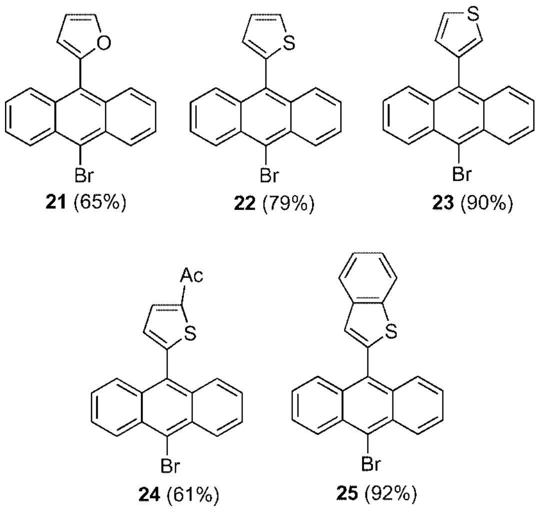
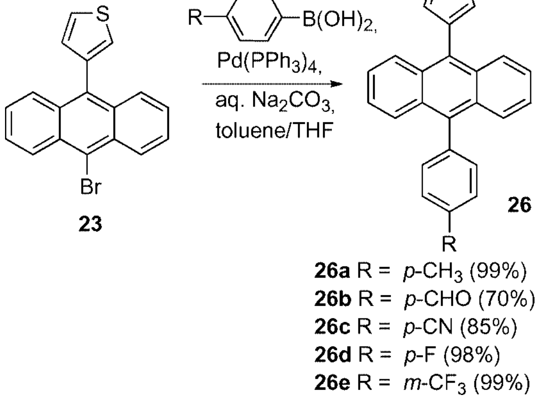


Figure 3. Examples of 9-bromo-10-aryl anthracene derivatives obtained by SM cross-coupling with **19**.

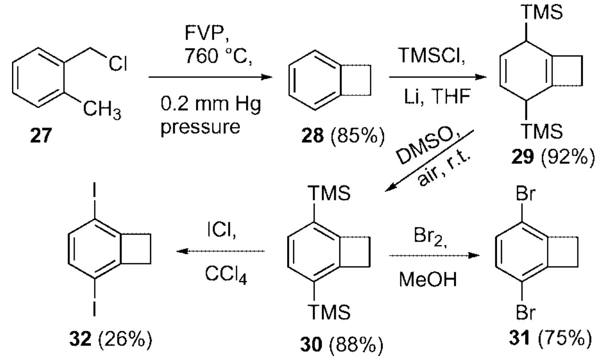
To begin with, the monobromo derivative **22** was treated with 4-methylphenylboronic acid in the presence of $Pd(PPh_3)_4$ catalyst to give the unsymmetrical 9,10-diarylanthracene derivative in 64% yield. Various arylboronic acids were also treated with **23** (Scheme 7) to generate the corresponding unsymmetrical 9,10-diarylanthracene derivatives **26a**–**e** in good yields. All the final products obtained from the SM reactions are crystalline solids and showed fluorescence behavior (TLC, visualization by short wavelength, 254 nm).



Scheme 7.

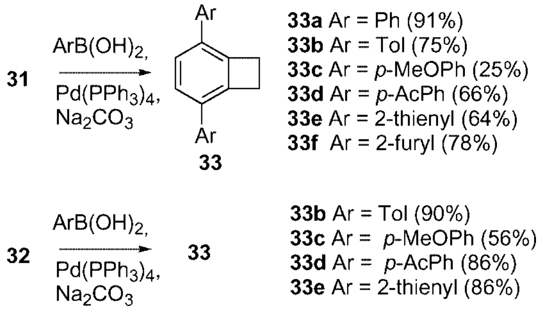
2.3. Synthesis of Highly Functionalized Benzocyclobutene Derivatives by SM Reaction

Benzocyclobutene (BCB) derivatives are attractive building blocks[22] because they participate in DA reactions with various dienophiles upon thermal activation. In view of the growing importance of BCB derivatives in polymer chemistry and materials science, we anticipated that the SM reaction could be a useful strategy. The required 3,6-dibromobenzocyclobutene (**31**) was prepared by a known procedure involving a four-step synthetic sequence starting from α-chloro-*o*-xylene (**27**, Scheme 8).[23]



Scheme 8.

To prepare highly functionalized BCBs, the dibromo BCB derivative **31** was treated with several boronic acids (Scheme 9) under $Pd(PPh_3)_4$ catalysis conditions.[24] Typically, 25–91% yields of the coupling products **33a**–**f** were obtained, with boronic acids containing electron-donating groups giving low yields of the cross-coupling products. To improve the cross-coupling yields, the diiodo BCB derivative **32** was prepared in 26% yield by treatment of the bis(trimethylsilyl) derivative **30** with iodine monochloride in CCl_4 at room temperature. (Scheme 8), and various arylboronic acids were coupled with **32** to generate the corresponding BCB derivatives **33b**–**e** with better yields (56–90%) than had been obtained with the bromo derivative **31** (Scheme 9).



Scheme 9.

Some of the BCB derivatives prepared here warrant special comment, as substrates such as **33e** are suitable precursors for the preparation of highly substituted BCB derivatives by manipulation of the thiophene moiety. BCB units containing thiophene components open up new possibilities in the design of conducting polymers.[15] Similarly, the furan building block present in **33f** can also be synthetically manipulated to generate highly functionalized BCB derivatives.

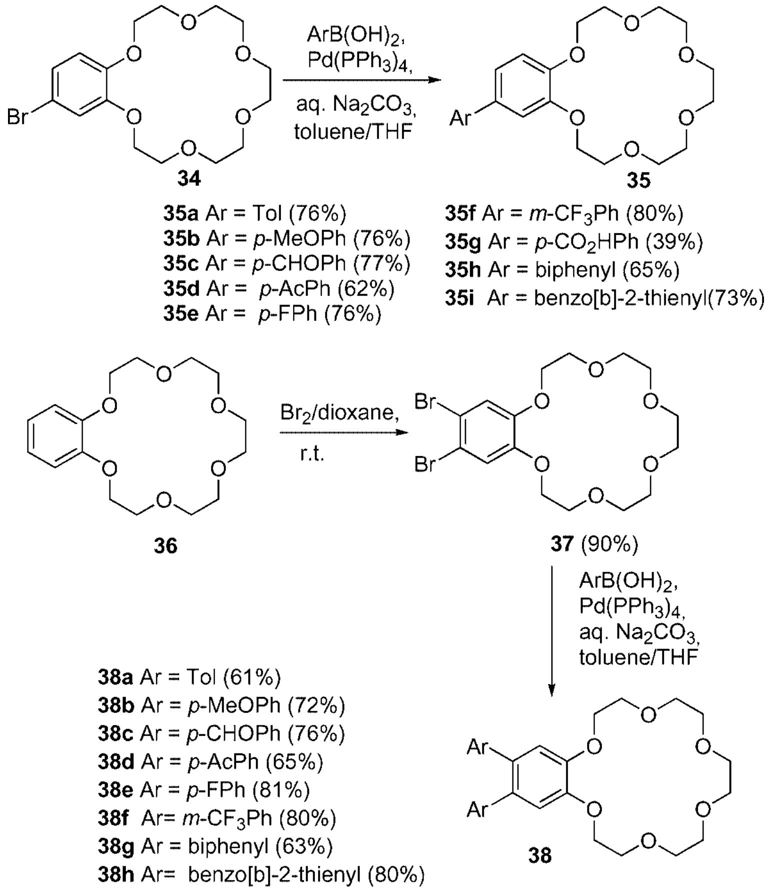
2.4. Synthesis of Functionalized Benzo-18-crown-6 Compounds by the SM Reaction

The complexing abilities of benzocrowns with different metal ions depend on ring size, the natures of the hetero atoms, and also on the natures of the substituents present on the benzene ring.[25] Benzocrown compounds are also used as versatile building blocks for supramolecular assemblies. Although these compounds have found interesting applications in analytical and pharmaceutical chemistry, their preparation by the SM reaction is a less explored field.[26] Encouraged by our earlier success with different molecular entities, 4′-bromobenzo-18-crown-6 (**34**) was subjected to SM reaction conditions in the presence of various arylboronic acids to give the biphenyl-based crown ethers **35a–i** in reasonably good yields (Scheme 10).[27] Later, 4′,5′-dibromobenzo-18-crown-6 (**37**) was prepared (Scheme 10) and was subjected to standard SM reaction conditions to give the symmetric 4′,5′-diaryl-substituted benzo-18-crown-6 compounds **38a–h** in good yields. These disubstituted benzocrown compounds may serve as precursors to phenanthrene-based crown ethers when subjected to photochemical irradiation under UV light in the presence of iodine.[28]

2.5. Highly Functionalized Tetraphenylmethane (TPM) Derivatives by the SM Reaction

A tetrahedral core with suitable functional groups at its vertices is an attractive motif for the construction of nanomaterials and dendrimers with spherical topologies.[29] Among tetrahedral structural motifs, tetraarylmethanes are of particular interest, with potential applications in the fabrication of organic crystals with tailor-made crystallinity and improved solid-state properties, such as organic glasses and organic light-emitting diodes (OLEDs), so the preparation of various TPM derivatives with SM reactions as key steps has been undertaken. The tetraiodo derivative of TPM **43** (Scheme 11), prepared from triphenylmethyl chloride by a known procedure, undergoes SM reactions with various boronic acids to generate the cross-coupling products **44a–d** (34–68 % yields).[30]

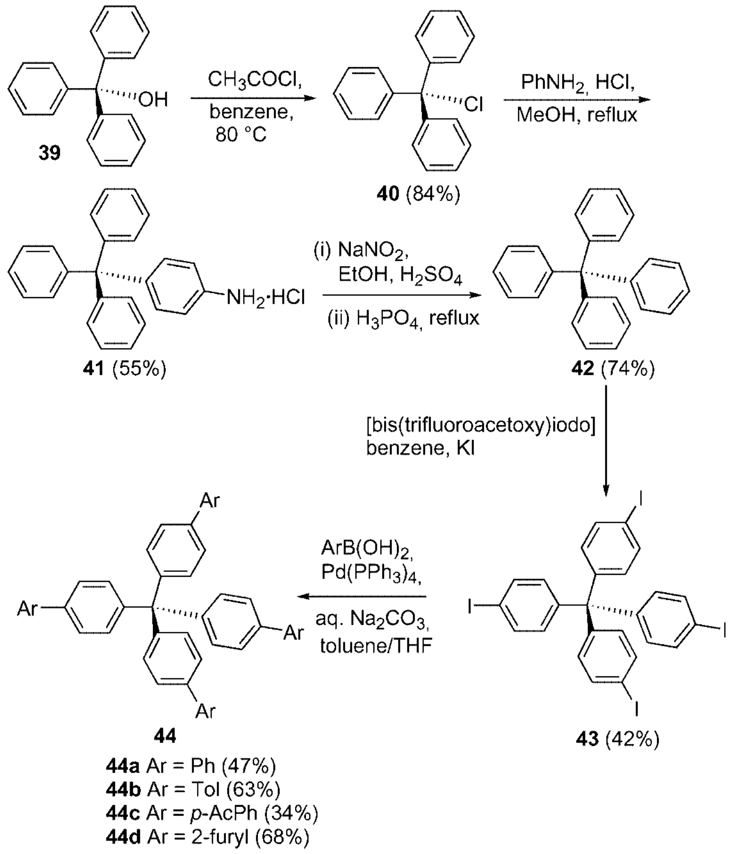
The preparation of the monoiodo TPM derivative **45** was based on 4-tritylanilium chloride (**41**) as a starting material (Scheme 12). SM reactions between compound **45** and various boronic acids gave the cross-coupling products **46a–d**, along with the self-coupled product **47**.[30] It is noteworthy to mention here that the self-coupling[31] product is a new and promising building block.



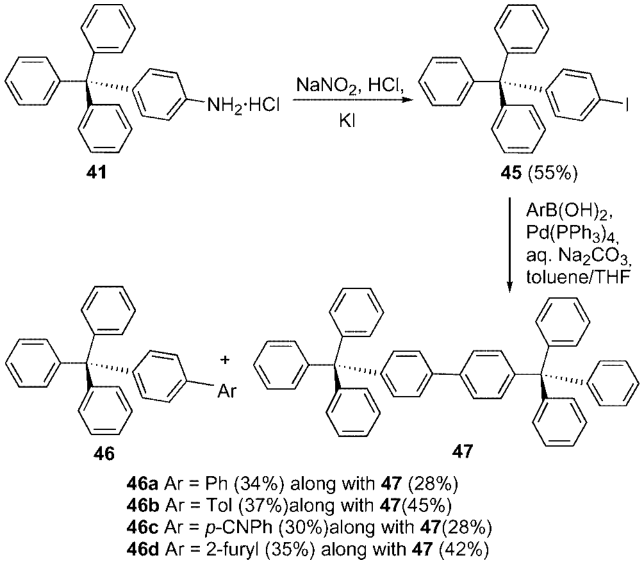
35a Ar = Tol (76%)
35b Ar = *p*-MeOPh (76%)
35c Ar = *p*-CHOPh (77%)
35d Ar = *p*-AcPh (62%)
35e Ar = *p*-FPh (76%)
35f Ar = *m*-CF_3Ph (80%)
35g Ar = *p*-CO_2HPh (39%)
35h Ar = biphenyl (65%)
35i Ar = benzo[b]-2-thienyl(73%)

38a Ar = Tol (61%)
38b Ar = *p*-MeOPh (72%)
38c Ar = *p*-CHOPh (76%)
38d Ar = *p*-AcPh (65%)
38e Ar = *p*-FPh (81%)
38f Ar= *m*-CF_3Ph (80%)
38g Ar = biphenyl (63%)
38h Ar= benzo[b]-2-thienyl (80%)

Scheme 10.



Scheme 11.



Scheme 12.

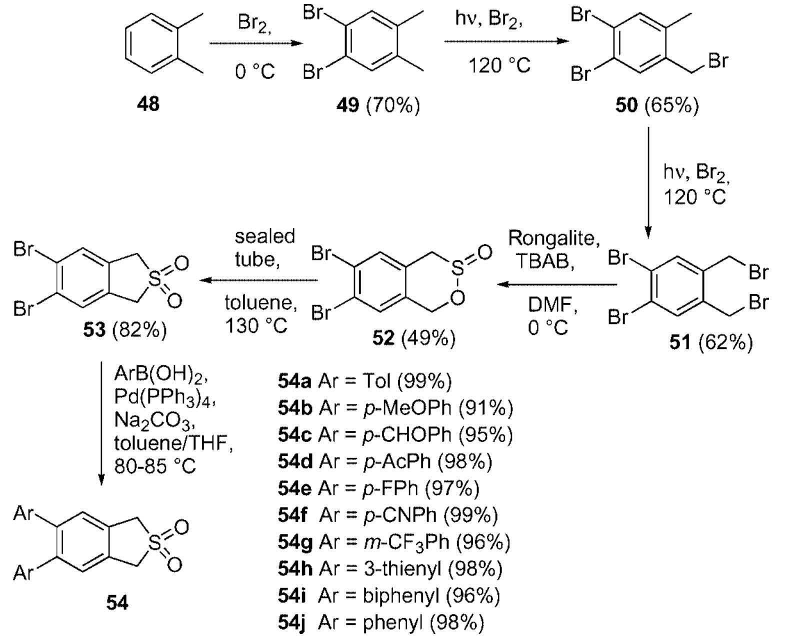
2.6. Synthesis of Functionalized Sulfone Derivatives by the SM Reaction

Sulfone derivatives are latent sources of conjugated dienes and are therefore valuable partners in DA reactions.[32] Thanks to the electron-withdrawing nature of the SO_2 moiety, the adjacent position can readily be alkylated with a variety of side chains containing some dienophile segment. Despite their extensive use in organic synthesis, though, only a handful of methodologies for the creation of highly functionalized sulfones are available.[33]

To generate the key sulfone building block **53**, the tetrabromo derivative **51** was prepared from *o*-xylene (**48**) by a three-step sequence (Scheme 13). Surprisingly, traditional conditions (NBS/AIBN) gave the required product **51** in only moderate yield. Subsequently, compound **51** was treated with Rongalite[34] to deliver the sultine derivative **52** in 49% yield, rearrangement of **52** under thermal conditions gave the corresponding sulfone **53**, and SM reactions between **53** and various boronic acids under Pd^0 catalyst conditions were examined, with the cross-coupling products **54a–j** being obtained in high yields.[35] Additional functional groups present in the cross-coupling products can serve as useful handles for further synthetic expansion, so this route is an attractive option for the combinatorial synthesis of sulfone derivatives.

2.7. Synthesis of Cyclophane Derivatives by SM Reaction

Cyclophanes are useful model systems for study of through-space interactions and have demonstrated their utility in molecular recognition and chiral catalysis.[36] In this regard, we designed a new and simple approach for the



Scheme 13.

synthesis of cyclophane derivatives, using SM coupling and RCM reactions[11] as key steps.[37] To test the key concept, various boronic acids were coupled with bis-armed benzyl bromide **55** in the presence of $Pd(PPh_3)_4$, and the cross-coupling products **56a–d** were obtained in good yields (Scheme 14). This methodology was also extended to the tris-armed benzyl bromide **57**. To prepare the target cyclophane **61**, the dialdehyde derivative **56c** was diallylated and the resulting diallyl compound was subjected to RCM in the presence of Grubbs' 2nd generation catalyst $[Ru(H_2IMes)(PCy_3)Cl_2(=CHPh)]$ (**A**) to deliver the cyclophane derivative **60** as a mixture of diastereomers (ratio 2:1) in 33% yield. Later on, oxidation of the diol mixture gave cyclophane **61**, and its structure was further confirmed by X-ray crystallographic data.[37]

The SM reaction has also been used to synthesize macrocyclic cyclophane-based α-amino acid (AAA) derivatives such as **67** (Scheme 15).[38] To this end, 1,2-dibromobenzene (**62**) was treated with *p*-tolylboronic acid in the presence of $Pd(PPh_3)_4$, and the cross-coupling product **63** was obtained in 86% yield. Benzylic bromination of **63**, followed by alkylation of the dibromide **64** with ethyl isocyanoacetate (**65**) in the presence of BEMP[39] (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine), gave the cyclophane derivative **66** as a mixture of diastereomers. Hydrolysis of **66** gave **67** as an isomeric mixture.

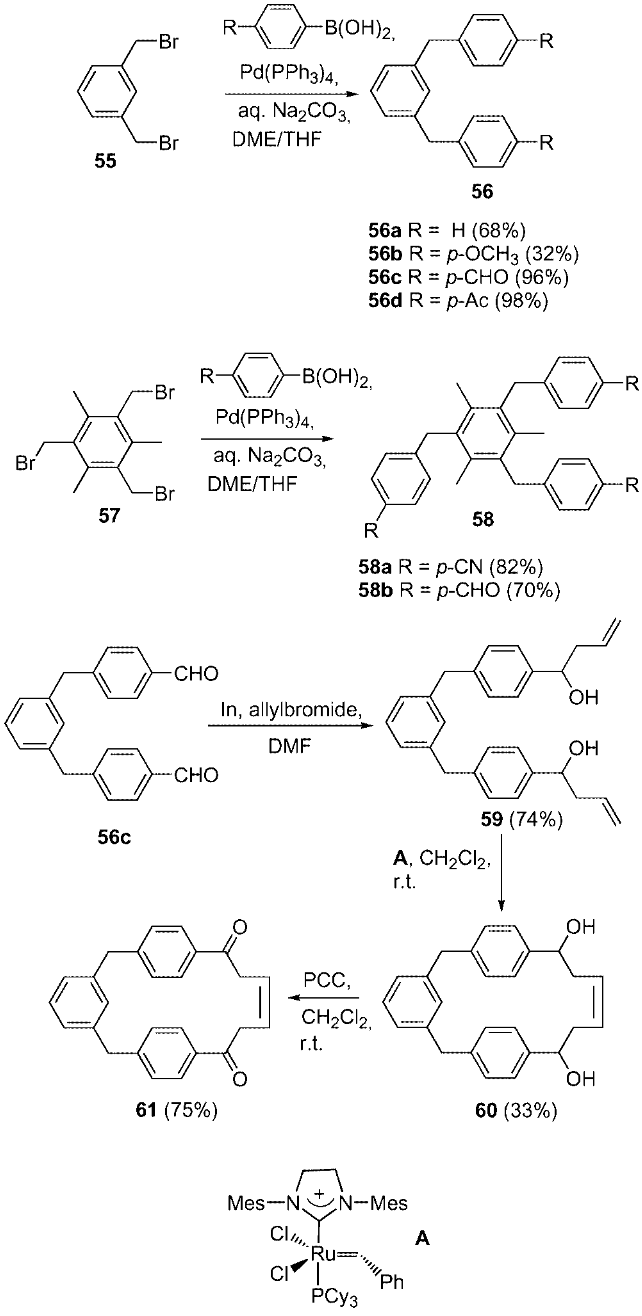
3. Synthesis of Unusual AAAs and Peptides by the SM Reaction

Unusual AAA derivatives play an important role in the design of peptidomimetics and peptide drugs.[40] Since only a limited number of synthetic methods (e.g., Bucherer–Berg, BB)[41] are available for their preparation, only simpler systems are used in this regard. We have selected several constrained analogues of phenylalanine (Phe) – known to be useful in medicinal and bioorganic sciences – for modification, and to demonstrate the utility of SM we have chosen the targets shown in Figure 4. The multi-armed AAA derivatives proposed here are useful core units for less explored peptide dendrimers.

3.1. Modification of Phenylalanine Derivatives and Peptides by the SM Reaction

Adverse pharmacological properties have restricted the usage of native peptides as drugs, and a general goal of peptide chemist is to aim for structural modifications that can improve the pharmacological profile of a target peptide. In several instances, non-proteinogenic AAAs have been used to modify conformational and stability aspects of native peptides.[40] Among proteinogenic AAAs, Phe is a crucial structural element present in several bioactive peptides, and there are numerous reports in which the replacement of Phe with a constrained analogue generates more effective therapeutics. SM reactions between various arylboronic acids and simple AAA derivatives such as the iodophenylalanine derivative **70** (Scheme 16), obtained from commercially available 4-iodo-L-phenylalanine (**68**), have therefore been attempted, and the modified AAAs **71a–g** have been obtained in good yields.[42]

For the modification of Phe peptides, tri- (**72a** and **72b**) and pentapeptides (**72c**) were prepared by application of a water-soluble carbodiimide-mediated peptide-coupling strategy, and a SM coupling technique with these peptides was carried out under the conditions developed for Phe-based AAA derivatives to provide good yields of the coupling products (Scheme 17).[42,43] The methodology delivered



Scheme 14.

a range of modified analogues that may be useful for the design of various biologically active peptides and may also be suitable for the development of combinatorial synthesis of peptidomimetics. Recently this methodology has been extended to proteins.[44]

3.2. Modification of Unusual Indane-Based AAA Derivatives by the SM Reaction

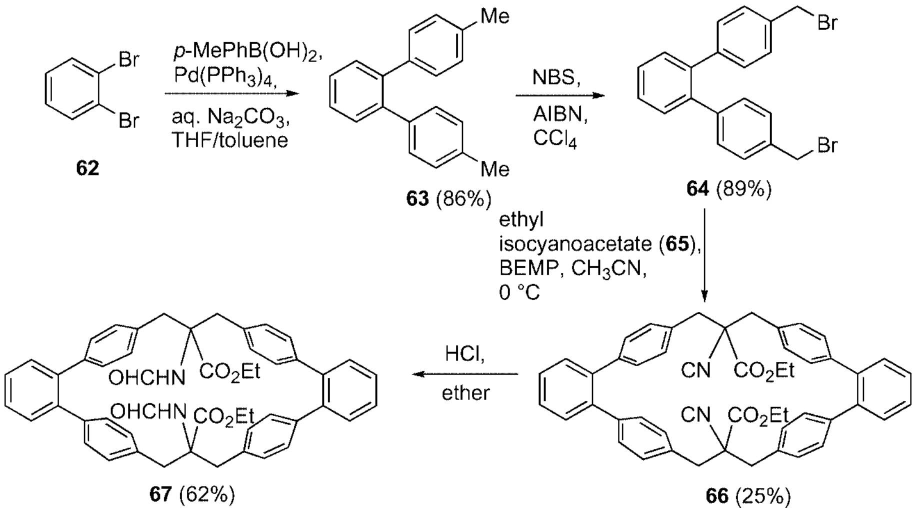
Indanylglycine (Ind) is a component of a potent ligand of the angiotensin-II receptor and has been extensively used in the synthesis of various biologically active peptides.[45] When the C-terminal Phe residue in the chemotactic agent HCO-Met-Leu-Phe-OH (FMLP) was replaced by Ind, the resulting modified analogue was shown to be highly active in superoxide production. Mash and co-workers have designed ladder-like molecules displaying intricate hydrogen-bonding patterns based on Ind precursors.[46]

The BB method[41] is generally used for the preparation of these Ind derivatives, but this methodology cannot be applied to sensitive substrates. In an attempt to overcome this we initially synthesized the indane-based α,α-disubstituted amino acid (αα-AA) derivative **79** (Scheme 18), but attempts to functionalize **79** through SM reactions were unfortunately unsuccessful.[47] Since aromatic substrates containing iodo substituents are better substrates for SM reactions, the corresponding iodo compound **83** was prepared by a [2+2+2] cycloaddition reaction as key step (Scheme 19),[48] but the overall yield of this compound was low and so an alternative route was explored, with the isocyanide derivative **86** (Scheme 20) being hydrolyzed to give the amino ester **87** in 72% yield. To increase the solubility of the AAA building block we prepared several derivatives with different protecting groups and found that pivaloyl derivatives are better candidates; this aspect is also critical for increasing the lipophilicities of indane-based AAA derivatives. SM reactions with several boronic acids under $Pd(PPh_3)_4$ catalyst conditions were then studied, and 62–99% yields of the cross-coupling products **89a**–**f** were typically observed (Scheme 21). Since ααAAs have been used as means of controlling secondary structures in de novo design of peptides, the ααAA derivatives prepared here are likely to find useful applications in peptidomimetics.

3.3. Modification of Unusual Tetralin-Based AAA Derivatives by the SM Reaction

A tetralin-based AAA (2-aminotetralin-2-carboxylic acid, Atc) is a constrained analogue of Phe that has been extensively used in the design of bioactive peptides, being incorporated in place of Phe into, for example, μ- and δ-selective opioid peptides. Recently, Aldrich et al. have synthesized analogues of the heptadecapeptide dynorphin A (Dyn A) by solid-phase synthesis and have performed modifications by incorporating (*S*)-Act and (*R*)-Act at the Phe[4] position in Dyn A.[49] Dynorphin analogues have been studied as potential analgesic, neuroprotective, and anticonvulsant agents and Atc is also a useful building block for the synthesis of modified antitumor antibiotics such as daunomycin and adriamycine.

The preparation of complex Atc derivatives requires much involved synthesis, so we have developed a new strategy to produce highly functionalized Atc derivatives by trapping of an *o*-xylylene intermediate with ethyl 2-acetamidoacrylate (**93**, Scheme 22).[50,51] In addition, we have also modified the diiodotetralin derivative **94** by application of the SM reaction, and the constrained AAA derivatives **95a**–**f** prepared by this methodology are valuable for designing peptidomimetics.



Scheme 15.

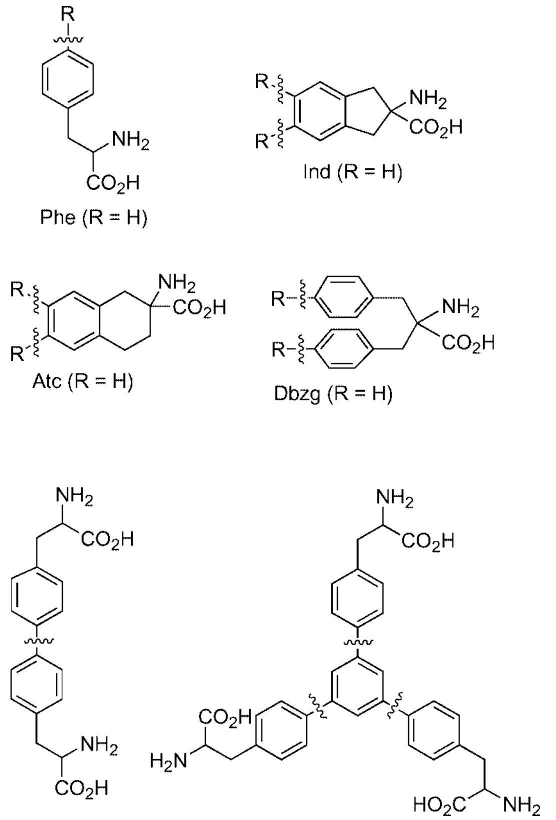
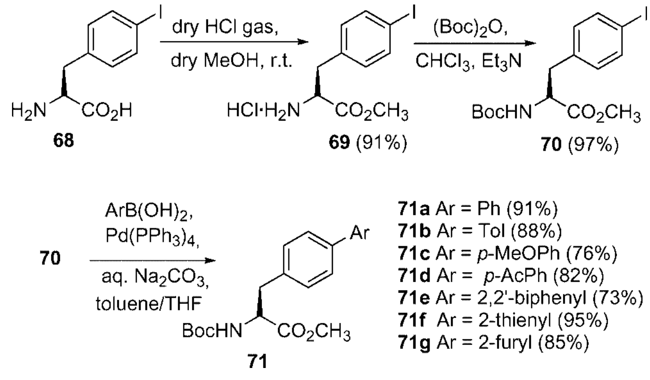


Figure 4. Proposed list of constrained analogues of phenylalanine (Phe) for modification by the SM reaction (the wavy lines indicate the position of the formation of the C–C bond by the SM reaction).

3.4. Modification of Dibenzylglycine (Dbzg) Derivatives by the SM Reaction

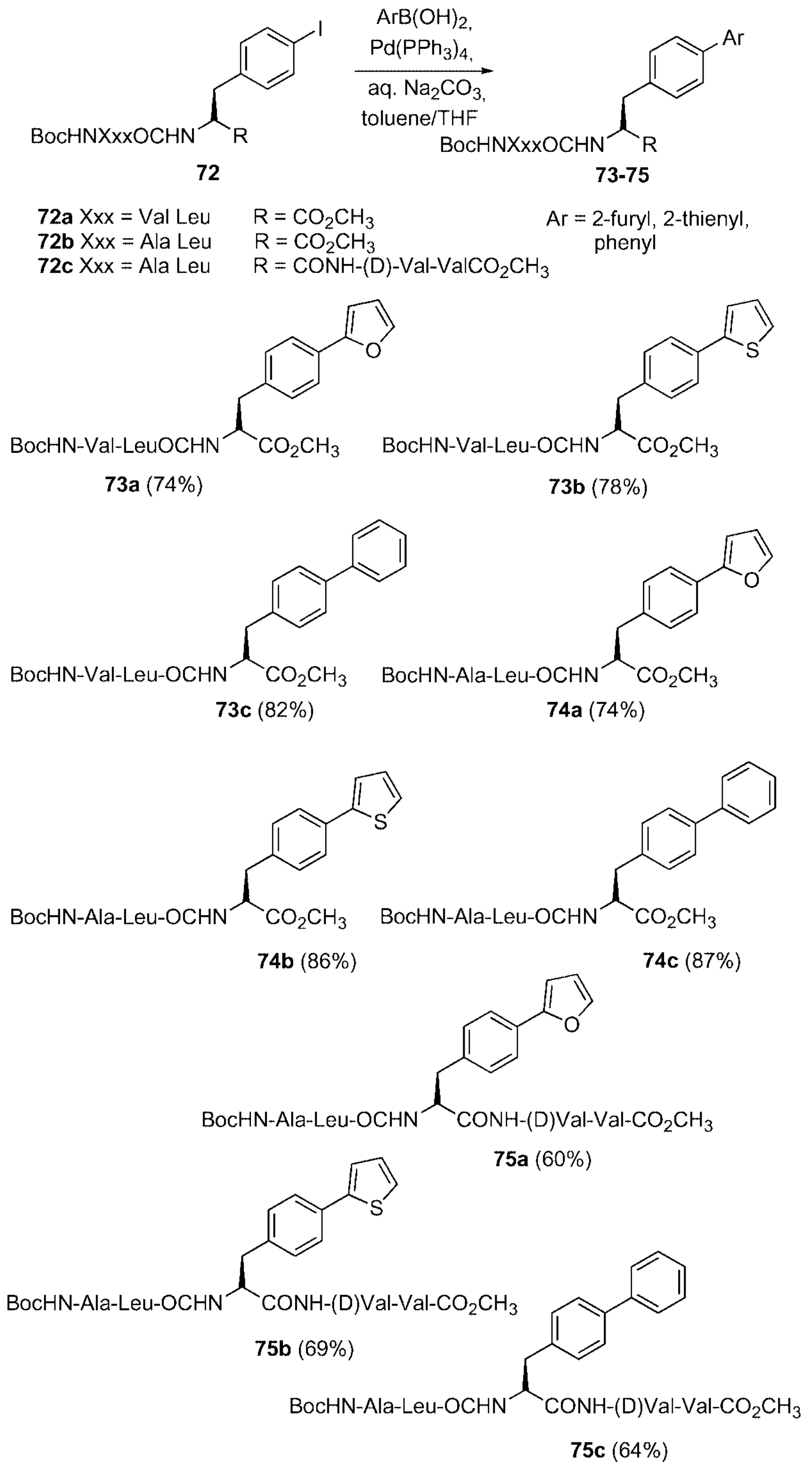
α,α-AAs are important members of the class of modified AAAs.[52] Dibenzylglycine (Dbzg) is an important structural variant of α-aminoisobutyric acid (Aib, a racemic amino acid), in which the two benzyl groups not only impart rigidity to the peptide backbone, but also provide compatibility for study of π–π interactions. Despite their importance, only limited numbers of synthetic methods for the synthesis of highly functionalized dibenzylglycines are available. To address these problems, iodo-substituted Dbzg derivatives suitable for SM reactions were designed.[53,54]



Scheme 16.

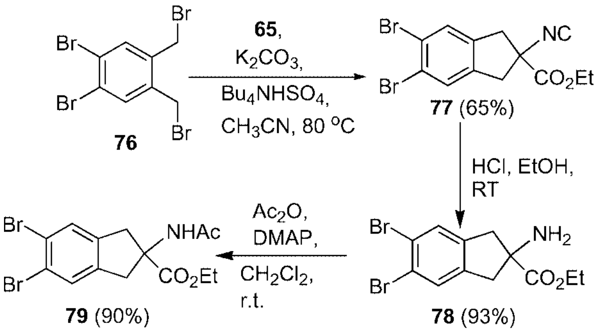
After considerable experimentation we found that **65** (ethyl isocyanoacetate) can be alkylated with 4-iodobenzyl bromide under phase-transfer catalysis (PTC) conditions to give the Dbzg derivative **96** in better yield (Scheme 23), with hydrolysis and acetylation of the free amino group subsequently giving the acetylated product **99**. Here the acetylated product was contaminated with *N*-formyl derivative. The formylated impurity is derived from the hydrolysis step and it is carried over into the subsequent steps. The problem was circumvented by converting the isocyanide derivative **96** into the *N*-formyl derivative **97** without the involvement of the amine intermediate. With the formyl derivative of Dbz available in pure form, efforts were directed towards the SM reaction, and the yields of the coupling products were good. Since Boc derivatives are useful in peptide arena, we have also prepared the *N*-Boc protected derivative **100** and have studied SM reactions with this derivative (Scheme 21).

Next, to prepare cyclophane-based AAA derivatives, the synthesis of diallyl AAA derivative **107** (Scheme 24) from

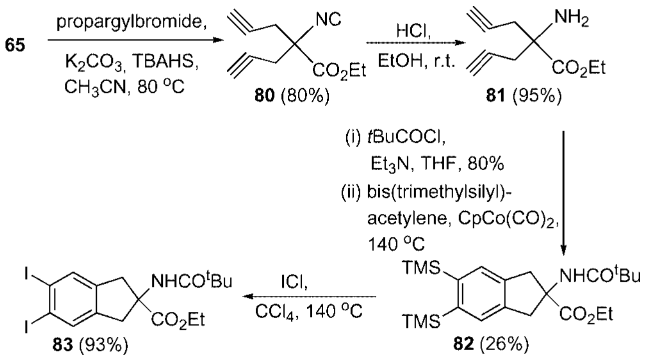


Scheme 17.

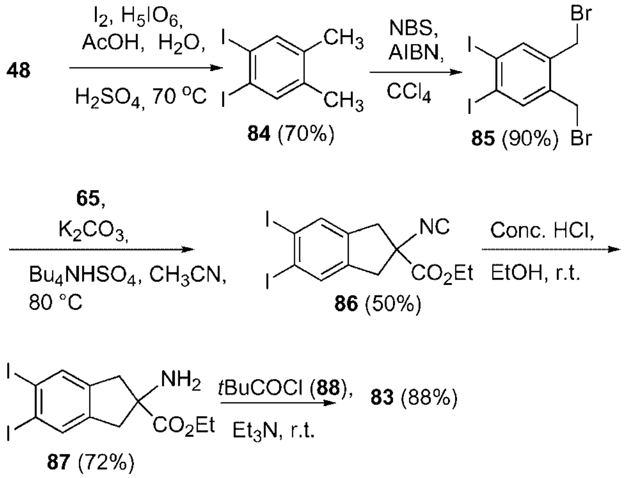
the diodo compound **97** was pursued. Since allylated aromatics are critical for advanced organic synthesis, methods based on SM reactions are highly desirable, and we found that Pd-catalyzed cross-coupling reactions between aromatic halides and the commercially available allylboronic acid pinacol cyclic ester (**103**) in the presence of CsF were useful to provide the allylated aromatics. It is worth mentioning that Stille coupling with allyltri-*n*-butyltin in the presence of Pd^0/THF was studied and that the diallylated product **107** was obtained along with some undesired tin impurities, which could not be removed completely by column chromatography. Use of the commercially available allylboronic ester **103** seems to avoid such problems. The presence of CsF appears to be crucial for the success of the SM reaction, the allylated compound **107** being obtained in 90% yield. The allylation methodology seems to be general



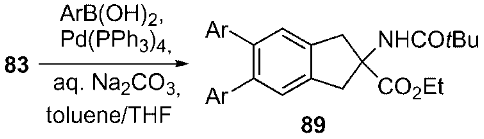
Scheme 18.



Scheme 19.

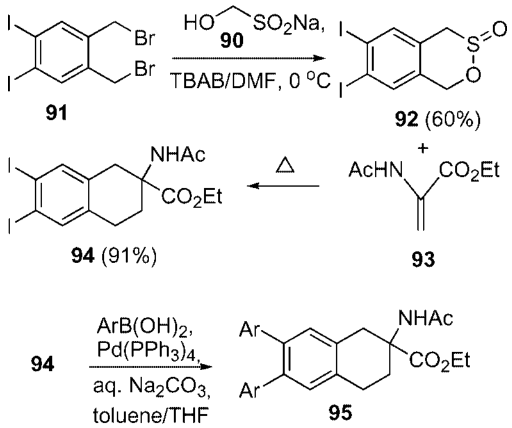


Scheme 20.



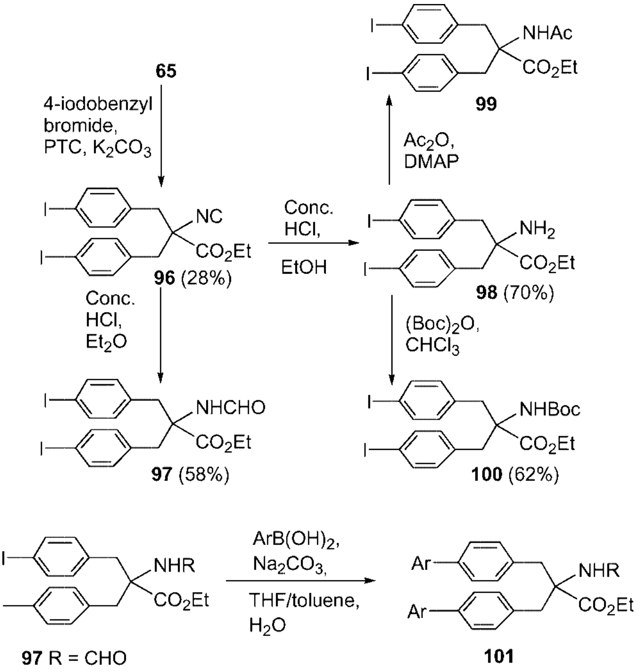
89a Ar = Ph (95%)
89b Ar = Tol (99%)
89c Ar = *p*-MeOPh (95%)
89d Ar = *p*-AcPh (87%)
89e Ar = 2-thienyl (62%)
89f Ar = 2-furyl (72%)

Scheme 21.



95a Ar = Tol (89%)
95b Ar = *p*-MeOPh (91%)
95c Ar = *p*-CHOPh (87%)
95d Ar = *p*-AcPh (65%)
95e Ar = 5-Ac-2-thienyl (78%)
95f Ar = benzo[b]-2-thienyl (79%)

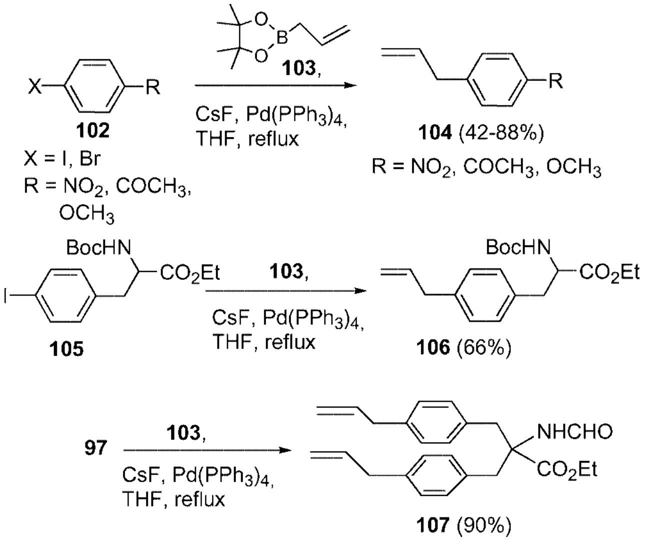
Scheme 22.



Ar = 4-MePh, R = CHO, **101a** (81%)
Ar = 4-MePh, R = Boc, **101b** (73%)
Ar = 4-MeOPh, R = CHO, **101c** (86%)
Ar = 4-MeOPh, R = Boc, **101d** (96%)
Ar = 4-AcPh, R = CHO, **101e** (68%)
Ar = 4-AcPh, R = Boc, **101f** (72%)
Ar = Ph, R = CHO, **101g** (72%)
Ar = 4-CHOPh, R = Boc, **101h** (54%)
Ar = 2-thienyl, R = CHO, **101i** (93%)
Ar = 2-furyl, R = CHO, **101j** (92%)
Ar = 2-benzothienyl, R = Boc, **101k** (79%)

Scheme 23.

with various aryl iodides and bromides[10] and we believe that this approach is a better alternative to the traditional B-alkyl SM reaction.[7b]



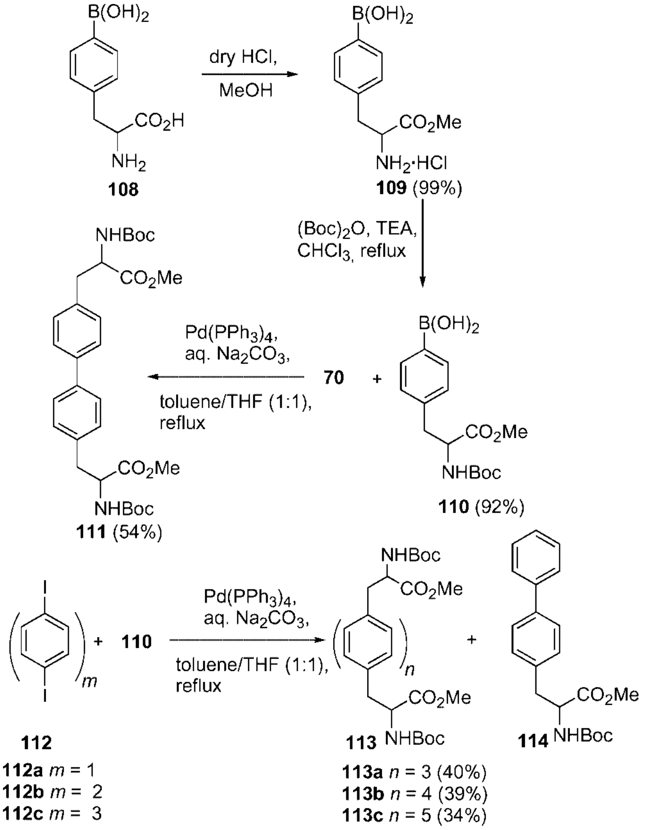
Scheme 24.

3.5. Synthesis of Multi-Armed AAA Derivatives by the SM Reaction

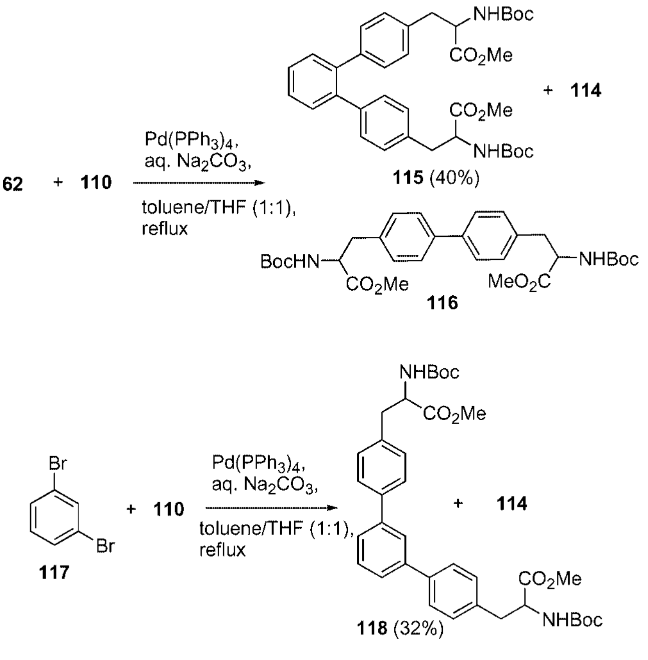
Bis-armed-α-amino acids (BAAAs) are key structural elements present in antibiotics, disrupting microbial cell wall synthesis and useful for stabilization of structural proteins in bacteria and plants.[55,56] Various BAAA derivatives are also used as helix-turn-helix (HTH) motifs in DNA-binding proteins[57] and are also known to be handy ligands for chelation with an appropriate metal, the complexes thus formed being useful as chiral catalysts in asymmetric synthesis.[58] We have therefore explored the synthesis of both bis- and multi-armed AAA derivatives.[59,60]

The commercially available DL-4-boronophenylalanine **108** (Scheme 25) would appear to be an appropriate coupling partner for the preparation of BAAA derivatives by SM reactions. The carboxylic group was protected as a methyl ester under acidic conditions to give the compound **109**, which was treated with Boc-anhydride to deliver the *N*-Boc-protected boronic acid derivative **110**. The 4-iodophenylalanine derivative **70** was coupled with the boronic acid **110** to generate the biphenyl derivative **111** in 54% yield, while when the boronic acid **110** was subjected to Pd^0-catalyzed SM reaction conditions with 1,4-diiodobenzene (**112a**, *m* = 1), the coupling product **113a** (*n* = 3) was obtained in 40% isolated yield along with the scrambled product **114**. Similarly, when 4,4′-diiodobiphenyl (**112b**, *m* = 2) and the diiodide **112c** were subjected to SM reaction conditions with **110**, the cross-coupling products **113b** (*n* = 4) and **113c** (*n* = 5) were isolated in 39% and 34% yields, respectively.

The methodology was then extended to the synthesis of angular BAAA derivatives (Scheme 26), 1,2-dibromobenzene (**62**) and 1,3-dibromobenzene (**117**) being coupled with the boronic acid derivative **110** to deliver the corresponding *o*-terphenyl BAAA derivative **115** and the *m*-terphenyl BAAA derivative **118** in 40% and 32% yields, respectively.

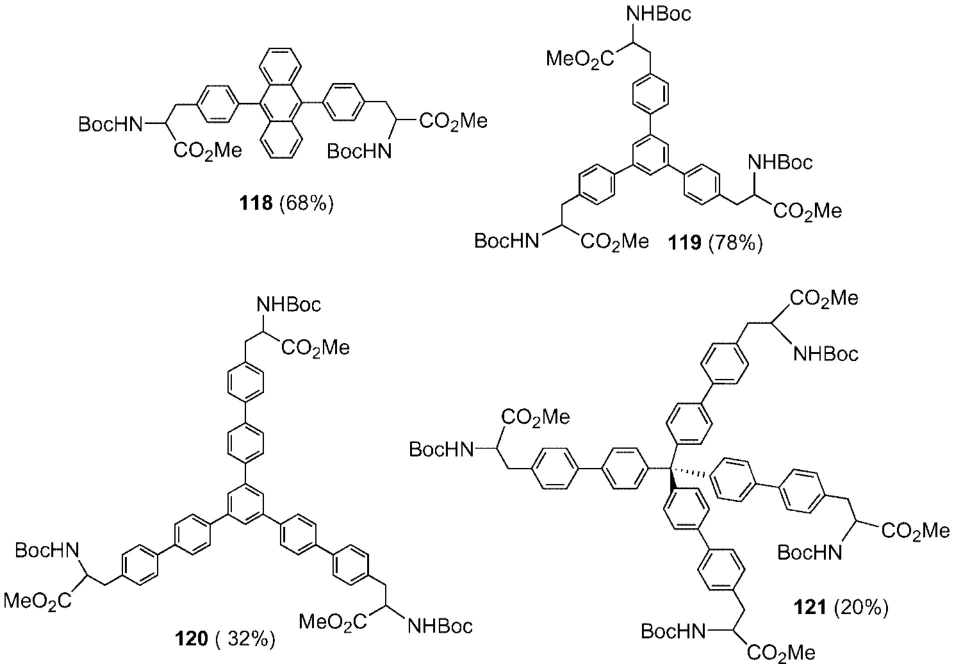


Scheme 25.



Scheme 26.

The Suzuki coupling methodology has also been extended to tris- and tetra-armed AAA derivatives (**119**, **120**, and **121**), which are useful building blocks (Figure 5). Along similar lines, the bis-armed anthracene-based AAA derivative **118** has also been prepared. It is interesting to



118 (68%)

119 (78%)

120 (32%)

121 (20%)

Figure 5. List of bis- and multi-armed AAAs prepared by the SM reaction.

note that these anthracene derivatives exhibit interesting fluorescent properties. The yields of the reactions are low, but in view of the multiple carbon–carbon bond formation in a single operation the overall yields are not that bad. The Suzuki reaction may be straightforward, but the substrates studied here are complex in nature.

4. Conclusions

Pd-mediated cross-coupling of organic electrophiles with organoboron compounds occupies a prominent place in organic synthesis. We have demonstrated that the application of SM coupling with various polycycles – such as C_3-symmetric molecules, BCB derivatives, 9,10-disubstituted anthracenes, benzocrown compounds, TPM derivatives, and sulfones – is useful for generation of molecular diversity. In addition, we have also utilized the SM reaction for assembling multi-armed AAA derivatives and to modify various highly constrained AAA derivatives and Phe peptides. Because of the limited availability of synthetic methods for the preparation of complex analogues of Aib, only simpler systems are reported in the literature,[52] and availability of synthetic methods capable of delivering various Aib analogues should encourage research in medicinal and structural biology. The design and synthesis of highly constrained racemic amino acid derivatives (e.g., Aib analogues or dialkylated amino acid derivatives) is also considered a task equally challenging as that of optically active amino acid derivatives. In some instances chiral auxiliaries are used to prepare racemic amino acid derivatives due to unavailability of synthetic methods. We believe that several opportunities will slowly open up when more of these methods are available in the literature. Furthermore, SM coupling is also used as a key step in the synthesis of cyclophane derivatives, while, finally, a simple methodology for allylation of aromatics with the aid of a commercially available boronic acid ester has been developed. Just like other well known reactions (e.g., DA and Grignard), the SM reaction is slowly becoming a routine tool for carbon–carbon bond formation. While we believe that our article is a minuscule drop in this ocean of knowledge, the methodologies developed here are extremely useful in organic synthesis as they meet an important goal: rapid increases in molecular diversity. They also have their own impact in delivering range of compounds useful to bioorganic, medicinal chemists, and materials scientists.

Acknowledgments

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