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A Retrospective on the Design and Synthesis of Novel Molecules through a Strategic Consideration of Metathesis and Suzuki–Miyaura Cross-Coupling

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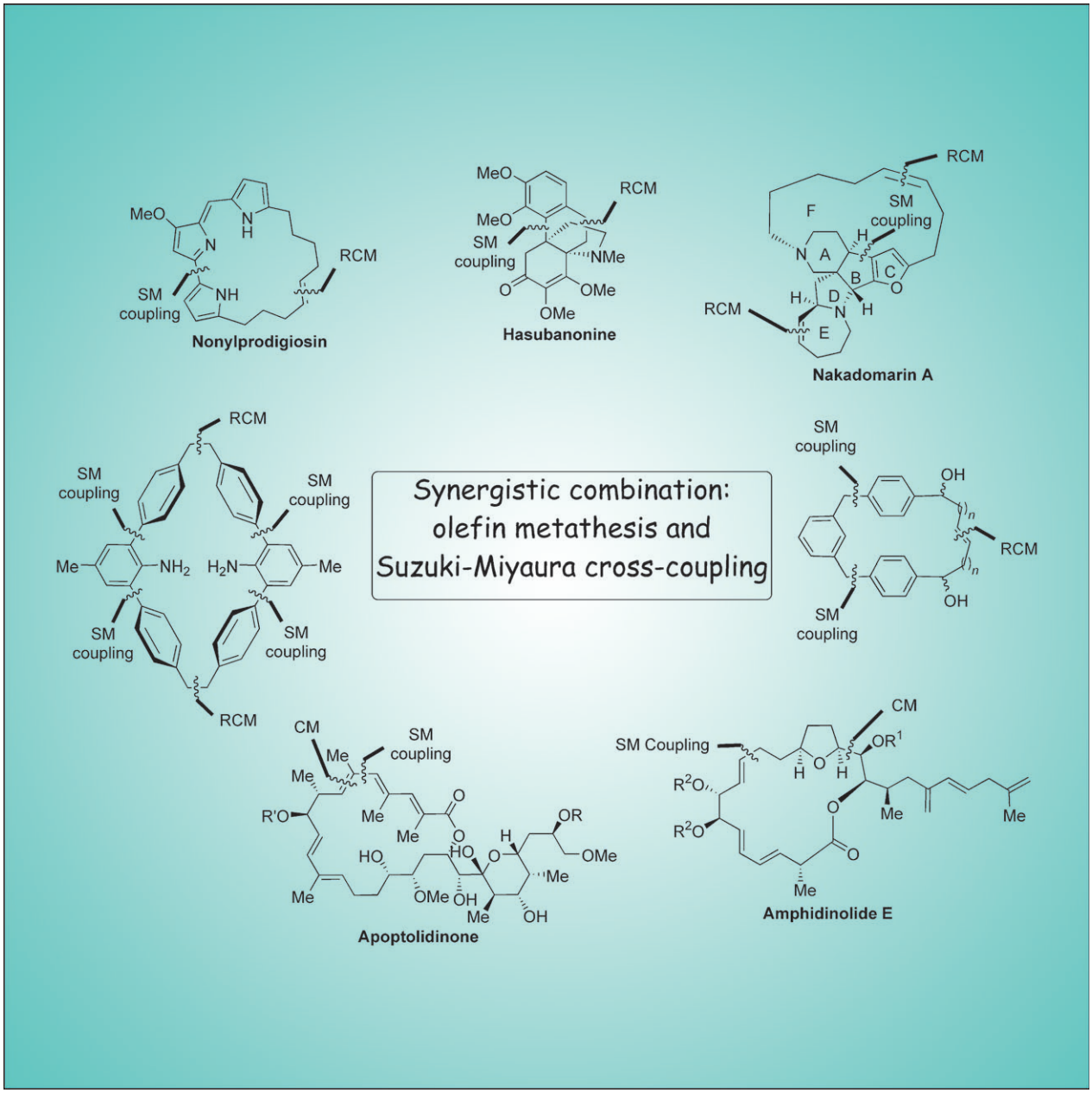

Abstract: In recent years, ruthenium-catalyzed metathesis and palladium-catalyzed Suzuki–Miyaura cross-coupling reactions have proven to be the most efficient tools for carbon–carbon bond formation in synthetic organic chemistry. This is mainly because of the stability and remarkable functional-group tolerance of these catalysts. Therefore, the strategic consideration of these two powerful reactions can eventually minimize the synthetic steps for the construction of complex target molecules. In this perspective we summarize the efforts of many research groups who have used the combination of these two powerful reactions (either together in concert or separated by a few multistep sequences) for the synthesis of supramolecular ligands, polyaromatic compounds, and complex natural products.

Keywords: cross-coupling · cross-metathesis · natural products · ring-closing metathesis

1. Introduction

Recently, ruthenium-based metathesis and Pd-catalyzed cross-coupling reactions have made a profound impact on carbon–carbon bond-formation processes. More specifically, with the advent of the commercially available and well-defined metal carbene complexes **1**, **2**, and **3**[1] (Figure 1), the

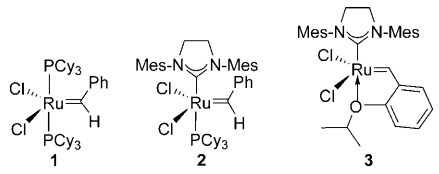

Figure 1. Ruthenium-based olefin-metathesis catalysts.

metathesis strategy has received a renewed interest and has been quickly accepted in the main stream of organic synthesis.[2] These catalysts function under mild reaction conditions and they exhibit a wide range of functional-group tolerance. These advances have opened up a completely new set of possibilities in organic synthesis. Among various modes of olefin metathesis, the intramolecular version, ring-closing metathesis (RCM), has become more popular than the intermolecular form, cross-metathesis (CM).

Similarly, among various Pd-catalyzed cross-coupling reactions, the Suzuki–Miyaura (SM) cross-coupling reaction is considered one of the most efficient methods for C–C bond formation.[3] The preference for the SM cross-coupling reaction over the other Pd-catalyzed cross-coupling reactions is not incidental. The key advantages of the SM cross-coupling reaction are the mild reaction conditions and the commercial availability of the diverse boronic acids that are environmentally safer than other organometallic reagents. Furthermore, handling and removal of boron-containing by-products is easy when compared with the other organometallic reagents, especially in a large-scale synthesis. Therefore, a unique combination of these two powerful strategies for C–C bond-formation processes should open up new and "green" synthetic routes to various complex targets.

A recent perusal of the literature indicated that a strategic consideration of these two well-established methodologies have made a profound impact in the design and synthesis of complex polyaromatic compounds and natural products. The details of this synergistic combination are covered in the following sections.

2. Synthesis of Supramolecular Hosts

Perhaps one of the most efficient routes to biaryls is the SM cross-coupling reaction. Therefore, after the formation of biaryls by SM cross-coupling reaction, judicious placement of olefinic handles on aryl group followed by RCM can eventually lead to macrocycles of desired topology, which in principle can act as supramolecular receptors.

In connection with the design of concave supramolecular ligands, Lüning and Fahrenkrug successfully used a combination of the SM cross-coupling and RCM to synthesize concave-shaped 1,10-phenanthroline ligands, suitable for complexation with transition-metal ions which also act as

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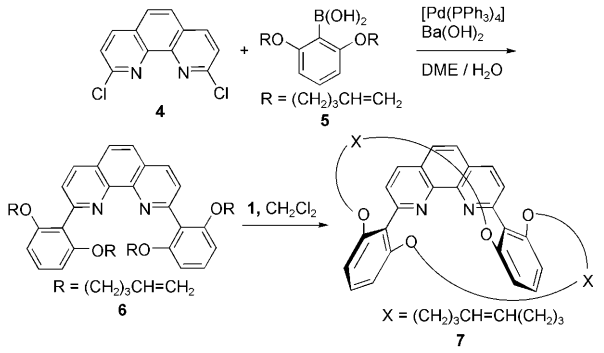
highly selective catalysts.[4] In a three-step sequence, two aryl bridges were introduced at the 2- and 9-positions of the 1,10-phenanthroline through the SM cross-coupling of bis-*ortho*-substituted boronic acids (Scheme 1). The successive



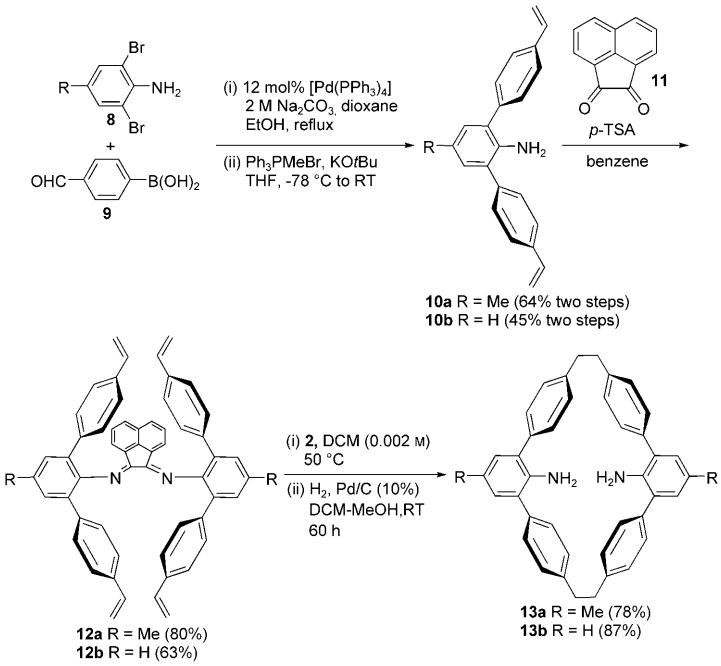
Scheme 1. Synthesis of concave 1,10-phenanthroline ligands.

RCM of the resulting diaryl 1,10-phenanthrolines, substituted with an alkene moiety, delivered (bi)macrocyclic 1,10-phenanthrolines (e.g., **7**) in good yields (73–96%). The authors speculated that the high selectivity stems from the concave shape of the ligand.

Sambasivarao Kotha *was born in Amarthalur, AP (India). He received his PhD degree under the supervision of Professor G. Mehta at the University of Hyderabad in 1985. After spending some time in the UK and USA, he joined IIT-Bombay in 1994 as an Assistant Professor and was promoted to Professor in 2001. He is a member of the editorial board of the Indian Journal of Chemistry, Section B, and J. Chem. Sci. Indian Academy of Science and has also been elected as a Fellow of the National Academy of Sciences. His current research interests include organic synthesis and the development of new synthetic methods.*

Kalyaneswar Mandal *was born in Birbhum, West Bengal in 1977 and studied chemistry at Visva Bharati University, Santiniketan, West Bengal. After completing his MSc in 1999, he worked as a research assistant for one year under the joint supervision of Professor Uday Maitra and Professor S. Chandrasekaran at the Indian Institute of Science, Bangalore. He completed his PhD in 2006 with Professor Sambasivarao Kotha at the Department of Chemistry, IIT-Bombay on the synthesis of polycyclics and unusual α-amino acid derivatives via olefin metathesis. Currently he is pursuing postdoctoral research with Professor Stephen B. H. Kent at the University of Chicago.*

In 2004, Camacho et al. reported an efficient use of the atom-economical Pd-catalyzed SM cross-coupling and template-mediated RCM for the synthesis of *m*-terphenyl-based cyclophane derivatives by using second-generation Grubbs catalyst **2** (Scheme 2).[5] The utilization of the *cis*-α-diimine as an organic labile template was crucial for the success of the RCM. Surprisingly, prolonged hydrogenation detached the template to deliver the cyclophane derivative **13**.



Scheme 2. Synthesis of *m*-terphenyl-based cyclophane derivatives by template-mediated RCM.

Albrecht et al. also adopted this approach and synthesized a 56-membered macrocycle using terephthalic di-aldehyde as an organic template in good overall yield (Scheme 3).[6] Use of second-generation Grubbs catalyst **2** was found to be superior to the first-generation Grubbs catalyst **1**. The authors also observed a drastic decrease of macrocyclization yield (21%) when the metathesis was performed without template assistance. The authors suggested, therefore, that the template-assisted RCM is superior to the nontemplated protocol owing to the avoidance of undesired oligomeric and polymeric side products.

We also demonstrated a simple and useful strategy for the synthesis of novel cyclophane derivatives through an integrated approach based on the SM cross-coupling reaction and RCM as shown in Scheme 4.[7a–b] The aromatic rings were assembled by means of a relatively little explored sp^2–sp^3 SM cross-coupling reaction.[7c–n] Different cyclophane derivatives of varying cavity size were prepared by modulating the length of the alkyl chain of the alkylating agents. The key macrocyclization was accomplished by RCM of the corresponding diolefinic precursors in the presence of second-generation Grubbs catalyst **2** under high-dilution conditions

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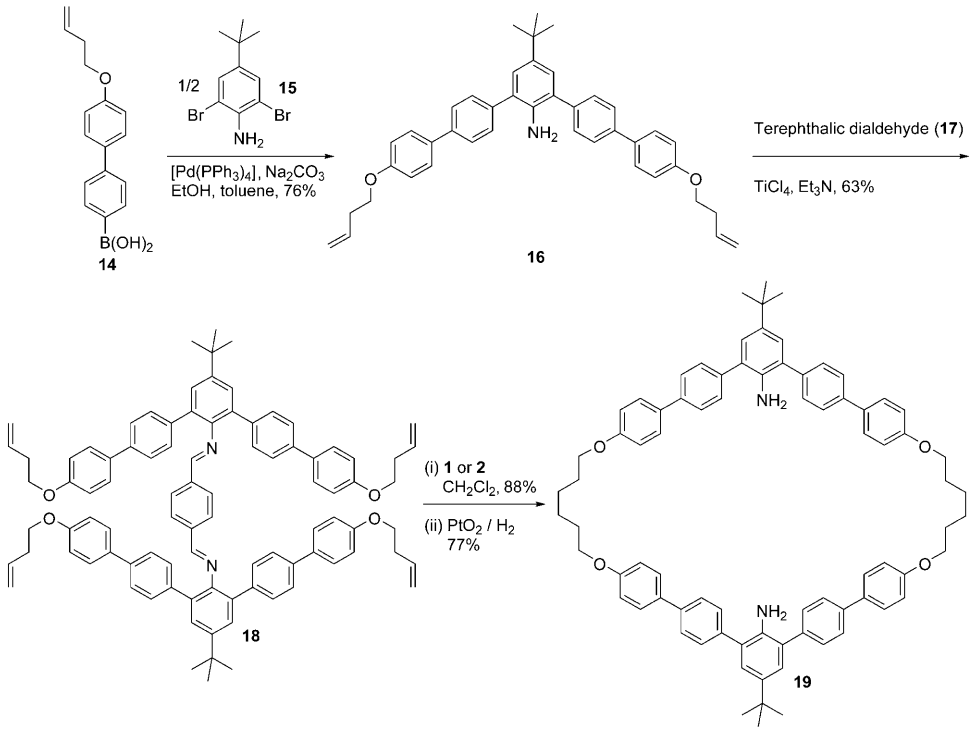
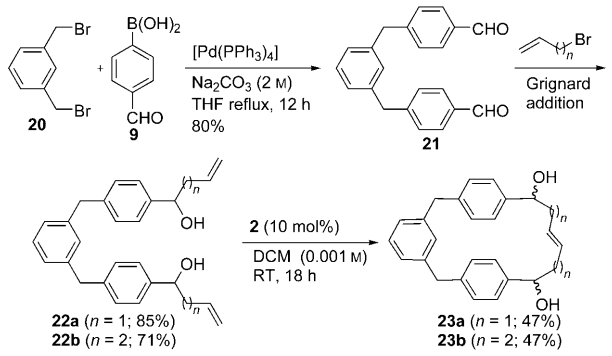


Scheme 3. Synthesis of 56-membered macrocycle through the combination of SM cross-coupling and organic-template-assisted RCM.



Scheme 4. Synthesis of cyclophane derivatives by SM cross-coupling reaction and RCM.

to minimize the oligomerized side-product formation. The unsymmetrical cyclophane **25** was obtained as a minor product along with the desired product **23b** from **22b** through the intermediacy of **24** by a tandem isomerization and subsequent RCM sequence (Figure 2).

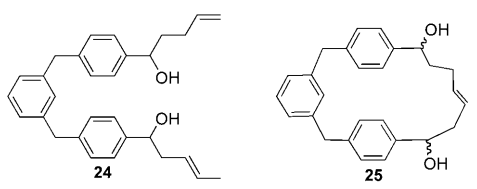
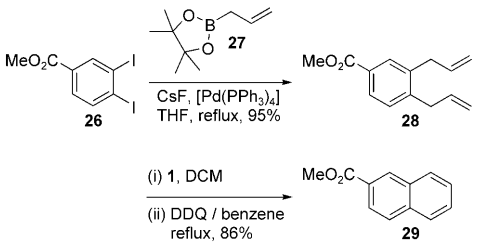


Figure 2. Unsymmetrical cyclophane derivative (**25**) and its precursor intermediate (**24**).

3. Construction of Aromatic Rings

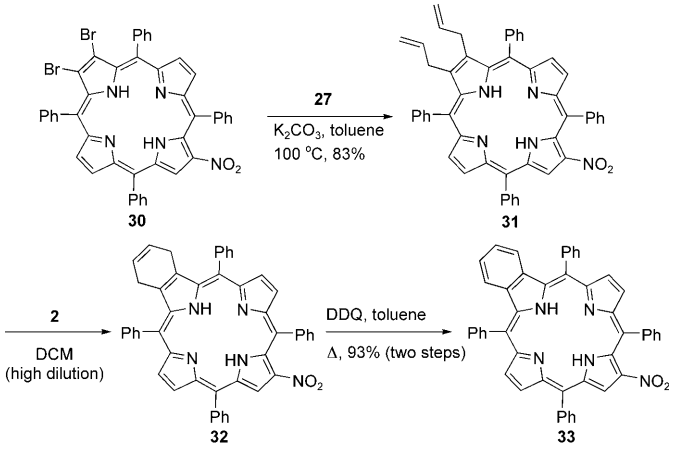
One of the classic synthetic strategies used for the construction of aromatic rings is the utilization of RCM in combination with SM cross-coupling reaction. We rationally designed a new and general approach for attaching a benzene ring on a pre-existing aromatic system through a sequential combination of allylboronate-mediated SM cross-coupling reaction and RCM (Scheme 5).[8a] We found that the substrates containing electron-withdrawing groups are better partners for the SM cross-coupling of aromatic halides with allyl boronate.[8b] Following this precedence, diiodobenzene or diiodonaphthalene derivatives containing electron-withdrawing substituents were chosen for diallylation.



Scheme 5. A new method of arene formation by SM cross-coupling and RCM.

RCM of these *ortho*-diallyl derivatives in the presence of first-generation Grubbs catalyst **1** followed by a one-pot DDQ oxidation sequence delivered benzo-annulated derivatives in good yields. The advantage of this methodology is that the benzene ring can be appended in both a linear as well as angular fashion depending on the position of the diiodo groups.

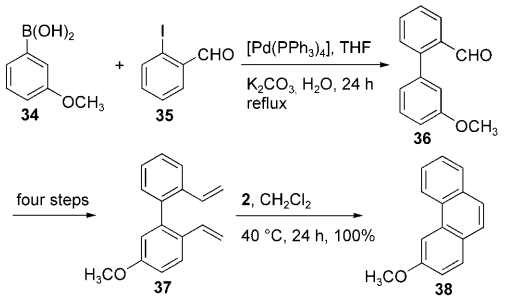
Smith and co-workers independently developed a similar strategy for the synthesis of extended π-conjugated porphyrin macrocycles involving a combination of allylboronate-mediated SM cross-coupling reaction and RCM (Scheme 6).[9] Thus, introduction of allyl groups at the β-position of a porphyrin macrocycle by SM cross-coupling for halogen-substituted porphyrin **30** with allylboronate **27** and subsequent RCM and oxidation with DDQ gave the corresponding benzoporphyrin **33** in good overall yield (Scheme 6). RCM was carried out at high dilution in di-



Scheme 6. Synthesis of benzoporphyrins by sequential SM cross-coupling and RCM.

chloromethane to avoid undesired cross-metathesis product formation.

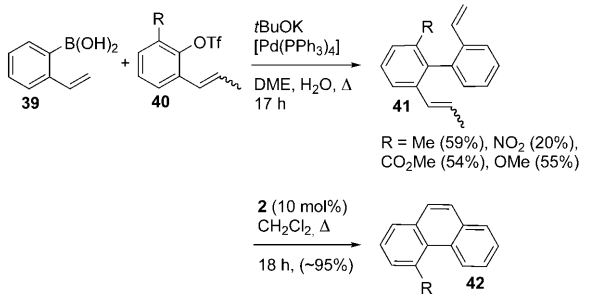
Differently functionalized biphenyls are readily accessible by aryl–aryl SM cross-coupling. In view of successful realization of the SM cross-coupling reaction in combination with RCM, Iuliano et al. demonstrated the synthesis of differently functionalized phenanthrene derivatives (Scheme 7).[10] The desired biphenyl unit **36** was prepared by the SM cross-



Scheme 7. Synthesis of differently functionalized phenanthrene derivatives.

coupling of 3-methoxyphenylboronic acid and 2-iodobenzaldehyde. The two vinyl groups were introduced in a four-step sequence starting with the biphenyl derivative **36**. RCM of the corresponding divinylbiphenyl derivative **37** in the presence of second-generation Grubbs catalyst **2** gave the functionalized phenanthrene derivative **38** in quantitative yield.

Barrett and co-workers reported a useful approach for the synthesis of the phenanthrene core by adopting the SM cross-coupling and RCM protocols (Scheme 8).[11] They found that various orthosubstituted triflates could be coupled with boronic acid **39** using $[Pd(PPh_3)_4]$ as catalyst to deliver the required biphenyl derivatives in good yields. Surprisingly, attempts to couple these triflates using $Pd(OAc)_2$ and PCy_3 were unsuccessful. When the RCM was attempted with catalyst **2** at room temperature, poor conversion was observed. However, RCM in dichloromethane at reflux tem-

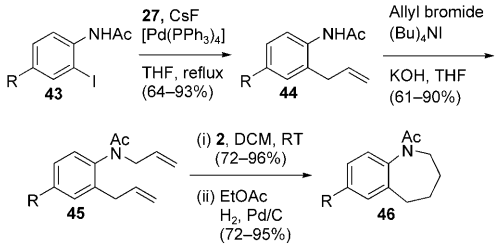


Scheme 8. Phenanthrene derivatives by SM cross-coupling of aryl triflates and RCM.

perature furnished the desired phenanthrene derivatives **42** ($\geq$95 % yield).

4. Synthesis of Benzazepine Derivatives

Benzazepine is an important structural element present in various biologically active molecules. In our own ongoing efforts towards the synthesis of 1-benzazepine derivatives we successfully utilized the strategic combination of SM cross-coupling and RCM for the construction of benzo-fused N-heterocyclic units (Scheme 9).[12] *o*-Allyl acetanilide derivatives were prepared from the corresponding *o*-iodo acetani-



Scheme 9. Substituted benzazepines by SM cross-coupling of aryl iodides and RCM.

lides through an allylboronate SM cross-coupling reaction. *o*-Allyl acetanilides, upon N-allylation under phase-transfer catalysis conditions, provided diallyl derivatives as suitable precursors for RCM. These diallyl derivatives upon treatment with second-generation Grubbs catalyst **2** furnished the 1-benzazepine derivatives in moderate to good yields. However, the RCM product containing the electron-withdrawing substituent at the 7-position was found to be highly unstable, and hence immediately after purification (at some instances in a one-pot reaction) Pd/C-catalyzed hydrogenation was performed to deliver the stable saturated derivative **46** in good yield.

5. Application in Natural Product Synthesis

SM cross-coupling and metathesis reactions are often used as key steps in the total synthesis of many complex natural

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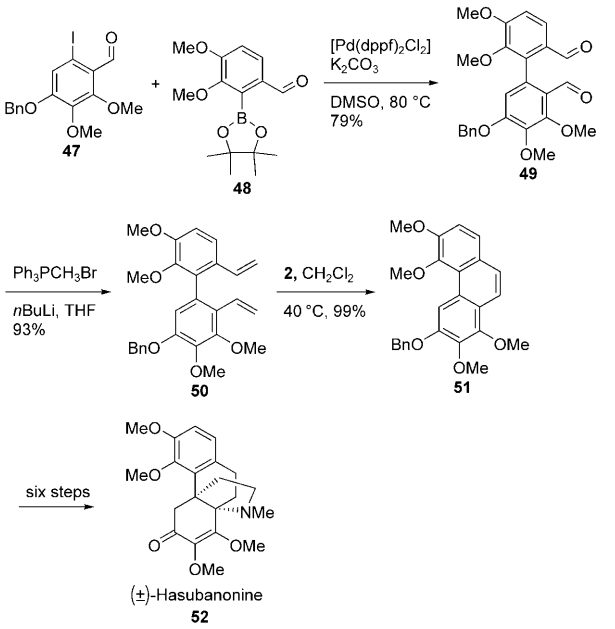
products. In some cases both reactions work together in concert, or they are separated by a few multistep sequences.

Castle and co-workers reported the total synthesis of the alkaloid (±)-hasubanonine by using a strategic combination of SM cross-coupling and RCM reactions as shown in Scheme 10.[13] The key phenanthrene intermediate **51** was

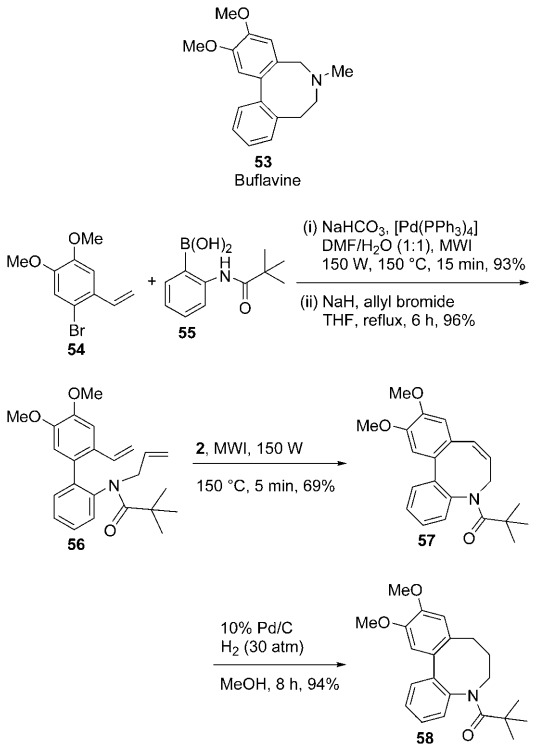


Scheme 10. Total synthesis of (±)-hasubanonine.

assembled through a combination of SM cross-coupling, Wittig olefination, and RCM reaction. SM coupling of **47** with **48** furnished a highly hindered biaryl system **49**, which upon Wittig olefination gave the divinyl derivative **50**. Subsequent RCM of **50** in the presence of second-generation Grubbs catalyst **2** delivered highly functionalized phenanthrene intermediate **51** in good yield. The synthesis of the target natural product **52** was achieved in a six-step sequence starting with phenanthrene derivative **51**. The novelty of this approach is that several other functionalized hasubanone alkaloids can be accomplished by simply choosing the suitable starting reaction partners.

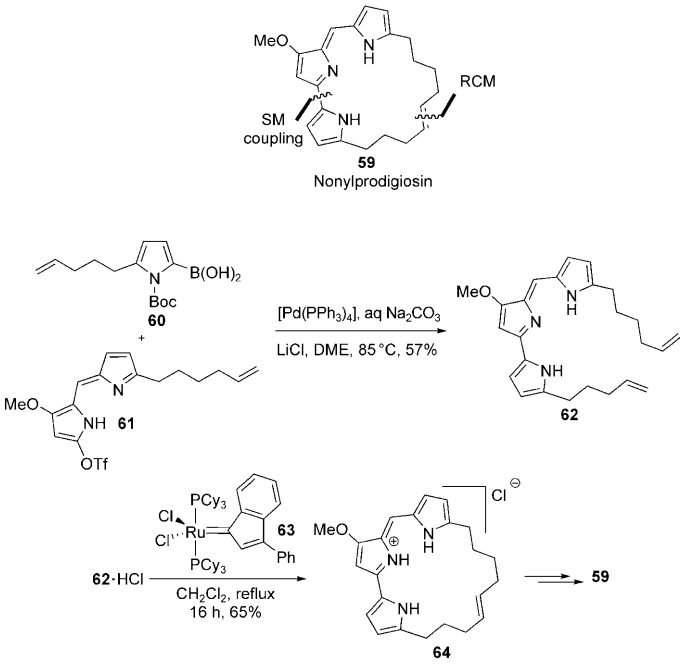
Eycken and co-workers demonstrated the synthesis of N-shifted buflavine analogues (**58**) using a SM cross-coupling and RCM protocol (Scheme 11).[14] The key feature of this approach is the utilization of microwave irradiation (MWI) for realization of the SM cross-coupling as well as RCM steps. Generally, electron-rich substituents tend to react in a sluggish manner during oxidative addition of the Pd catalyst to the C–Br bond. However, application of MWI was found to accelerate the SM cross-coupling reaction of highly electron-rich substrates such as **54** and also enhanced the efficacy of the RCM reaction to generate otherwise inaccessible biaryl-based, eight-membered N-heterocyclic ring systems.

Fürstner and co-workers described the first total synthesis of the tripyrrole pigment nonylprodigiosin (**59**) where Pd-catalyzed SM cross-coupling and RCM worked together in



Scheme 11. Synthesis of N-shifted buflavine analogue **58**.

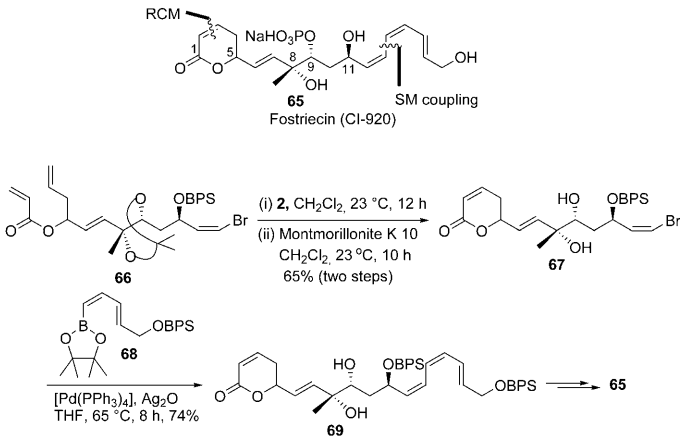
concert (Scheme 12).[15a] The RCM precursor was prepared by the SM cross-coupling of electron-rich triflate **61** with the unstable boronic acid derivative **60**. Here, owing to its labile nature, boronic acid **60** was used immediately in the next step. In spite of considerable experimentation only 57% yield of the desired cross-coupling product was obtained. To



Scheme 12. Total synthesis of the tripyrrole pigment nonylprodigiosin.

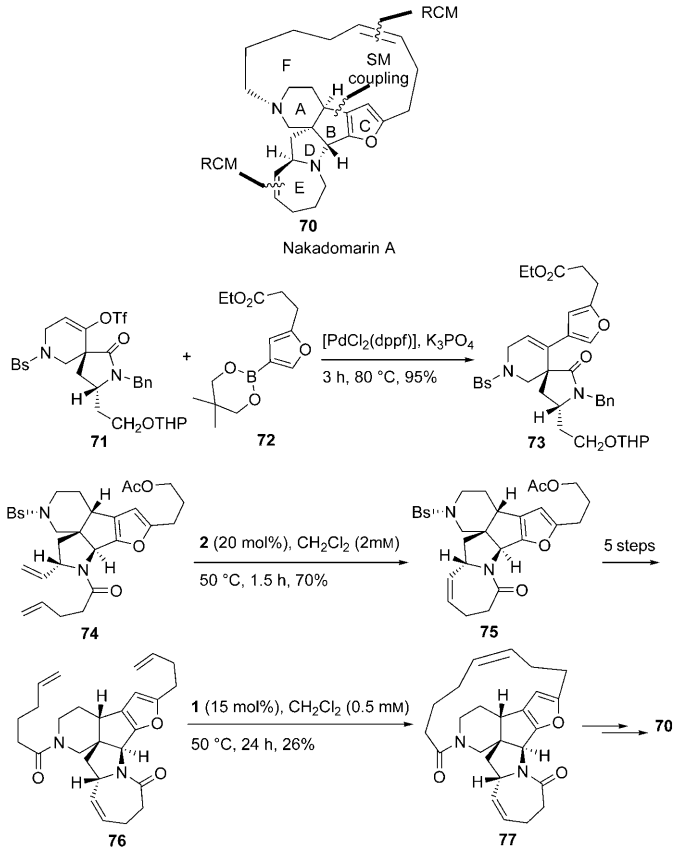
prevent the unwanted chelation of ruthenium with free amine groups, the RCM step was conducted with the hydrochloride salt of the substrate **62**. RCM reaction in the presence of second-generation Grubbs catalyst **2** furnished a moderate yield of the desired macrocycle **64**. However, an improved yield of the desired metathesis product was observed by using the modified ruthenium catalyst **63**.[15b]

Reddy and Falck realized a conceptually novel approach to a potent protein phosphatase inhibitor and anticancer agent, fostriecin (CI 920, **65**) through RCM and SM cross-coupling as key steps (Scheme 13).[16] The sensitive six-membered unsaturated lactone part in the C(1)–C(13) segment of the fostriecin skeleton was accomplished by RCM sequence and the remaining C(14)–C(18) unit of the carbon framework was appended by efficient SM cross-coupling of **67** and **68**.



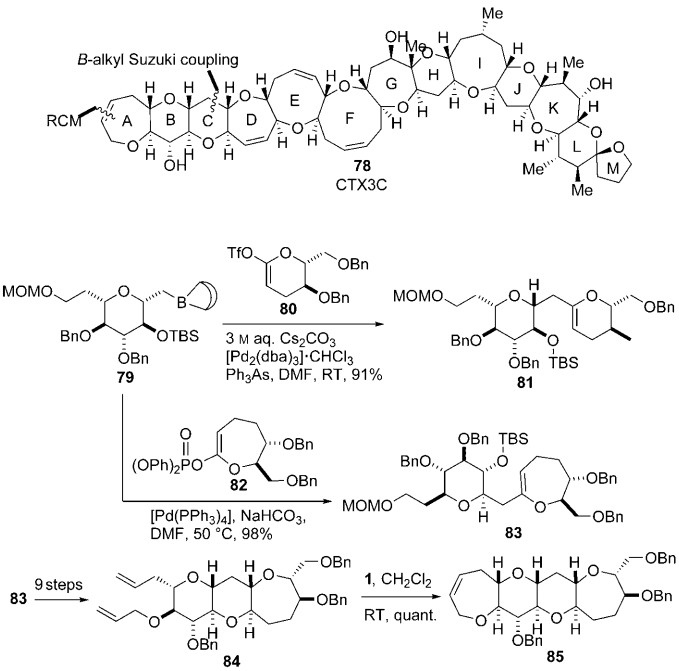
Scheme 13. A novel approach to fostriecin (CI 920).

The first total synthesis of nakadomarin A (**70**) was reported by Nishida and co-workers through SM cross-coupling and sequential RCM as key steps (Scheme 14).[17] Steric problems encountered owing to the presence of the hindered *N*-benzyl group in the spiro compound **71** necessitated the use of strong basic conditions for the SM cross-coupling with furan-3-boronic ester **72** using [$PdCl_2$(dppf)] as a catalyst. At a later stage, both eight- and 15-membered azacycles were obtained by sequential application of RCM protocols. RCM in the presence of second-generation Grubbs catalyst **2** furnished the desired eight-membered azocine lactum **75** in 70% yield. Surprisingly, the 15-membered heterocyclic compound **77** was easily realized by using first-generation Grubbs catalyst **1** to deliver a mixture of geometrical isomers (ca. 2:3 *Z*/*E*).



Scheme 14. Total synthesis of nakadomarin A (**70**). Bs = $-SO_2Ph$.

Sasaki et al. successfully used the *B*-alkyl SM cross-coupling and RCM as key synthetic steps for the construction of the ABCD ring fragment of ciguatoxin (Scheme 15).[18a] The convergent union of the B and D ring was achieved by Pd-catalyzed *B*-alkyl SM cross-coupling of lactone-derived enol triflates or phosphates. SM cross-coupling of alkylborane **79** with triflate **80** in the presence of $[Pd_2(dba)_3]\cdot CHCl_3$ and triphenyl arsine at room temperature gave the desired

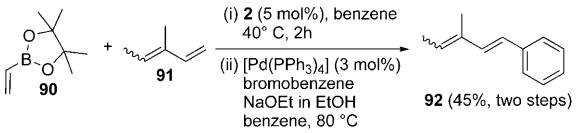


Scheme 15. Application of *B*-alkyl SM cross-coupling and RCM for the construction of ABCD ring fragment of a ciguatoxin congener (CTX3C).

product **81** in excellent yield, which upon ring expansion led to a seven-membered ketone. To reduce the synthetic steps the authors also investigated an alternative and more direct approach that used SM cross-coupling of seven-membered enol triflates. However, owing to the unstable nature of the seven-membered enol triflate in aqueous basic conditions, no product formation was observed. Since enol phosphates were found to be more stable and easier to handle than enol triflates, *B*-alkyl SM cross-coupling of lactone-derived enol phosphates was explored.[18b] After considerable experimentation it was found that use of two equivalents of enol phosphate in the presence of $[Pd(PPh_3)_4]$ using $NaHCO_3$ as base delivered the best results. With these optimized conditions, enol phosphate **82** gave the desired cross-coupling product **83** in 98% yield. Finally, the A ring was constructed by RCM of the diene **84** in the presence of Grubbs catalyst **1** to furnish the desired ABCD ring fragment of ciguatoxin.

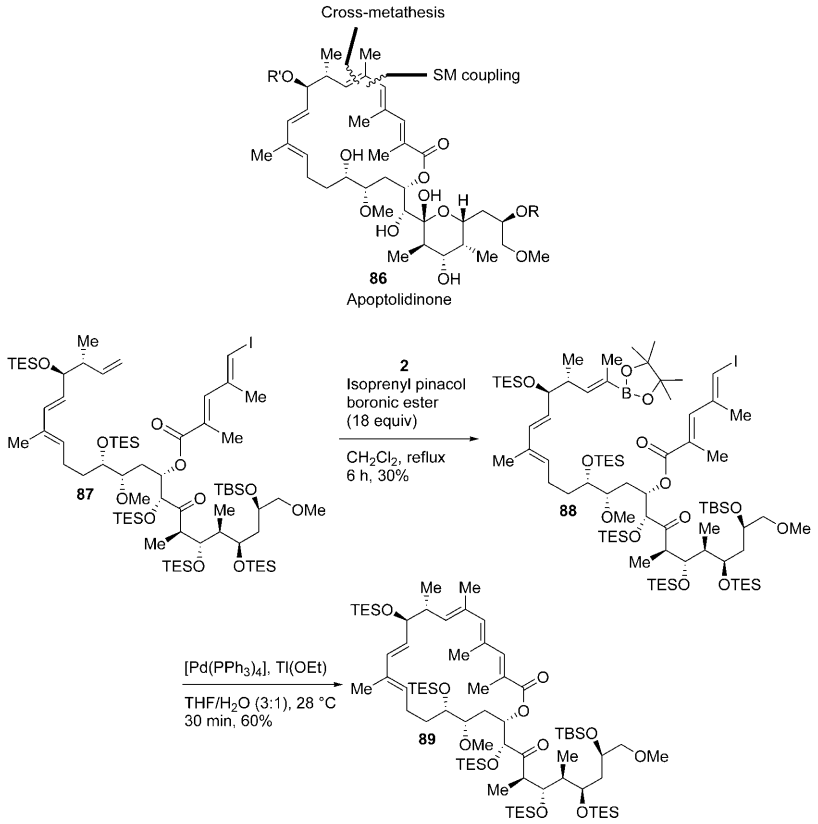
In addition to RCM, the CM strategy has also been employed in combination with SM cross-coupling for the synthesis of complex natural products. CM with vinylboronate followed by intramolecular SM cross-coupling was first utilized for the construction of the 20-membered macrocycle of the polyketide natural product apoptolidinone **86** (Scheme 16).[19] CM of **87** with second-generation Grubbs catalyst **2** with an excess amount of isopropenyl pinacol boronic ester furnished the vinyl boronate **88** as a single isomer in moderate yield. The final ring closure of the macrolactone **89** was achieved by a successive intramolecular SM cross-coupling reaction.

Along similar lines, Grubbs and co-workers disclosed an intriguing stereoselective one-pot cross-metathesis/SM cross-coupling strategy to deliver highly conjugated styrene derivatives (Scheme 17).[20] The authors reported that the yields were comparable with the analogous two-step procedure.



Scheme 17. Application of one-pot cross-metathesis/SM cross-coupling approach to conjugated styrenes.

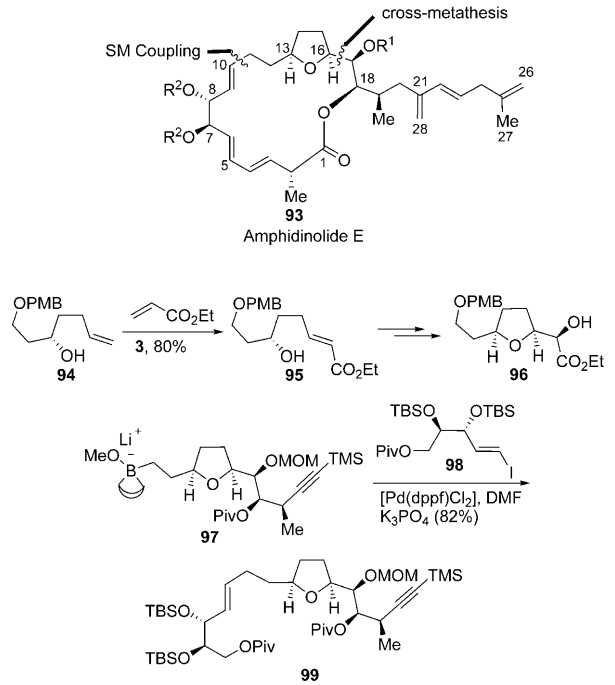
CM and sp^2–sp^3 SM cross-coupling reactions separated by a few multistep sequences were used by Marshall et al. as key steps in a promising synthetic approach to amphidinolide E (**93**), a polyketide containing an unusual 19-membered macrocyclic lactone embodying a tetrahydrofuran moiety (Scheme 18).[21] The required precursor for the construction of the tetrahydrofuran moiety was prepared through CM of alcohol **94** with ethyl acrylate in the presence of Hoveyda catalyst **3**. After a few synthetic manipulations based on previous findings, the authors successfully utilized the sp^2–sp^3 SM cross-coupling reaction for the construction of the C(6)–C(21) segment of the molecule. In situ generated 9-BBN derivative **97** was coupled with vinyl iodide **98** in the presence of $[Pd(dppf)Cl_2]$ to afford **99** in good yield.



Scheme 16. Application of CM followed by intramolecular SM cross-coupling for the construction of the 20-membered macrocycle of apoptolidinone.

Conclusions

Various examples described here clearly indicate that the SM cross-coupling in combination with the RCM or CM strategy has a synergetic value in accomplishing the total synthesis of complex targets.[22] Since achieving the total synthesis in a minimum number of steps is part of green synthesis, one may conceive various other such combinations for designing efficient synthetic routes. We anticipate that many more such new advances with new combinations in the near future will eventually en-



Scheme 18. Utilization of CM and sp^2–sp^3 SM cross-coupling reactions for the synthesis of amphidinolide E. PMB = *p*-methoxybenzyl.

hance the synthetic efficiency toward target compounds and thereby provide "green routes" to organic synthesis.

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