Synthetic Methods

Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis

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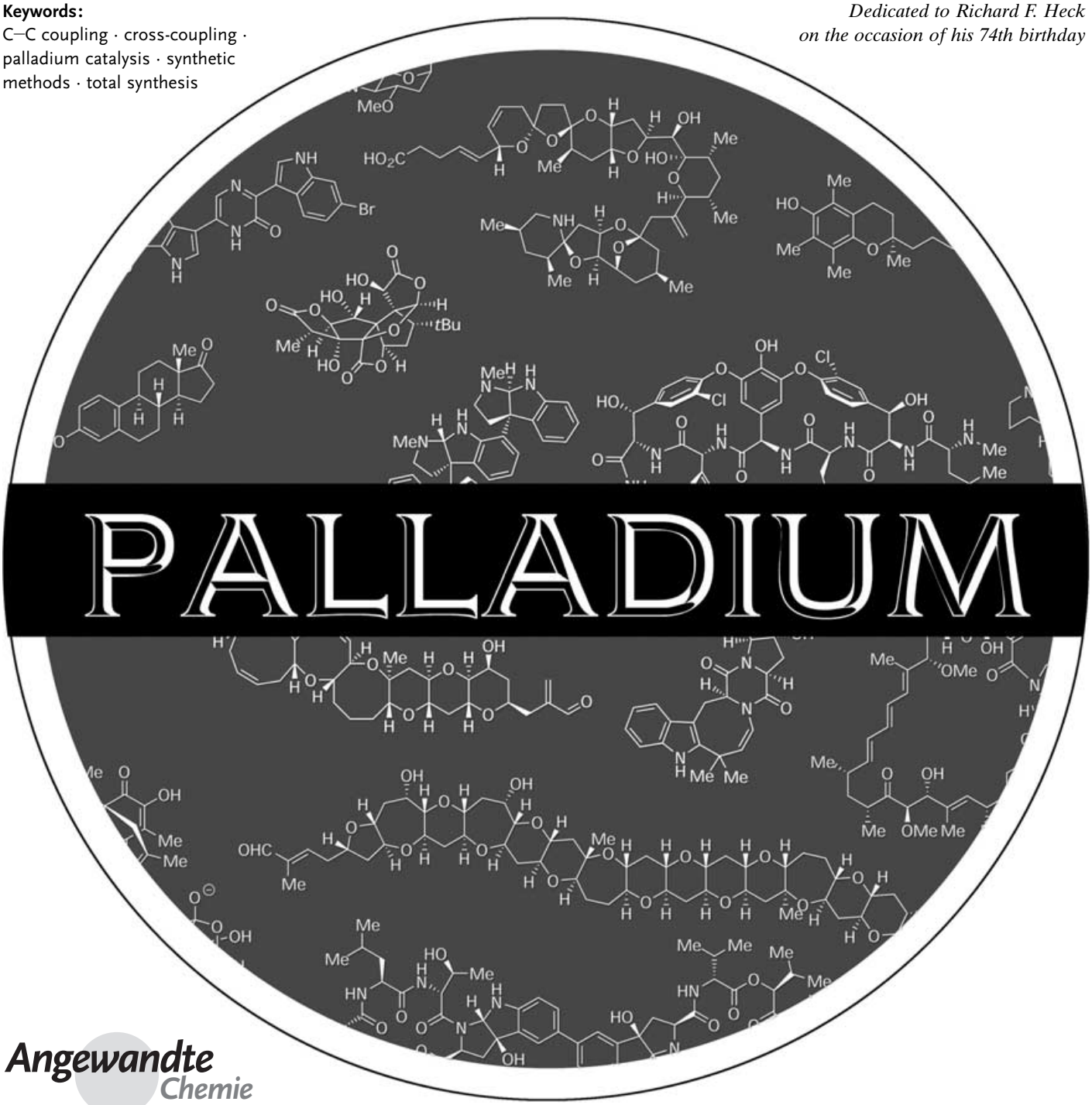
C–C coupling · cross-coupling · palladium catalysis · synthetic methods · total synthesis

Dedicated to Richard F. Heck on the occasion of his 74th birthday



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In studying the evolution of organic chemistry and grasping its essence, one comes quickly to the conclusion that no other type of reaction plays as large a role in shaping this domain of science than carbon–carbon bond-forming reactions. The Grignard, Diels–Alder, and Wittig reactions are but three prominent examples of such processes, and are among those which have undeniably exercised decisive roles in the last century in the emergence of chemical synthesis as we know it today. In the last quarter of the 20th century, a new family of carbon–carbon bond-forming reactions based on transition-metal catalysts evolved as powerful tools in synthesis. Among them, the palladium-catalyzed cross-coupling reactions are the most prominent. In this Review, highlights of a number of selected syntheses are discussed. The examples chosen demonstrate the enormous power of these processes in the art of total synthesis and underscore their future potential in chemical synthesis.

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1. Introduction

Ever since the first laboratory construction of a carbon–carbon bond by Kolbe in his historic synthesis of acetic acid in 1845, carbon–carbon bond-forming reactions have played an enormously decisive and important role in shaping chemical synthesis. Aldol- and Grignard-type reactions, the Diels–Alder and related pericyclic processes, and the Wittig and related reactions are but a few examples of such processes that have advanced our ability to construct increasingly complex carbon frameworks and, thus, enabled the syntheses of a myriad of organic compounds. In the last quarter of the 20th century, a new paradigm for carbon–carbon bond formation has emerged that has enhanced considerably the prowess of synthetic organic chemists to assemble complex molecular frameworks and has changed the way we think about synthesis. Based on transition-metal catalysis, this newly acquired ability to forge carbon–carbon bonds between or within functionalized and sensitive substrates provided new opportunities, particularly in total synthesis but also in medicinal and process chemistry as well as in chemical biology and nanotechnology.

Prominent among these processes are the palladium-catalyzed carbon–carbon bond-forming reactions. Because the historical, mechanistic, theoretical, and practical aspects of these processes have been amply discussed,[1] in this Review we focus only on selected applications of the most commonly applied palladium-catalyzed carbon–carbon bond-forming reactions in total synthesis, namely, the Heck, Stille, Suzuki, Sonogashira, Tsuji–Trost, and the Negishi reactions, with particular emphasis on the pioneering as well as some of the most recent and exciting examples. In doing so, we hope to illustrate the tremendous enabling ability of these modern synthetic tools.

The Heck reaction can be broadly defined as the palladium-catalyzed coupling of alkenyl or aryl (sp^2) halides or triflates with alkenes (Scheme 1) to yield products which formally result from the substitution of a hydrogen atom in the alkene coupling partner. The first examples of this reaction as we would recognize it today were reported independently by Mizoroki (1971)[2] and, in an improved form, by Heck (1972).[3] However, it would prove to be more than a decade before the broader applicability of this transformation began to be investigated by the wider synthetic organic community. The development of catalytic asymmetric Heck reactions in the late 1980s led to a further resurgence of interest in this field.[4] The Heck reaction now stands as a remarkably robust and efficient method for carbon–carbon bond formation, particularly in the generation of tertiary and quaternary stereocenters and intramolecular ring formation, and remains a flourishing area of research. Significantly, it inspired important variations that, with time, have assumed their own names, identities, and place in total synthesis.

The palladium-catalyzed cross-coupling of organic electrophiles with vinyl organotin compounds is today known as the Stille reaction (Scheme 1),[5] after the late Professor J. K. Stille who pioneered (1978)[6] and subsequently developed[7] this reaction, although the seeds of discovery were sown earlier by Kosugi and his group, who published the first reports of transition-metal-catalyzed carbon-carbon bond-forming reactions with organotin compounds a year earlier.[8,9] Nearly 30 years later the Stille reaction remains one of

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the most widely applied palladium-catalyzed carbon–carbon bond-forming reactions, in large part due to typically mild reaction conditions, the ease of preparation of a wide range of coupling partners, and the tolerance of a wide variety of sensitive functionalities in this transformation. In particular, the number of ingenious and daring applications of Stille couplings in the challenging proving ground of total synthesis bears testament to the faith placed in the robustness and versatility of this reaction by practitioners of this art. Notably, the Stille reaction can be viewed as a variation of the Heck reaction in which a hydrogen atom is replaced by a tin-bearing substituent.[10]

Another extraordinarily useful palladium-catalyzed carbon–carbon bond-forming reaction involves the palladium-mediated coupling of organic electrophiles, such as aryl or alkenyl halides and triflates, with organoboron compounds in the presence of a base (Scheme 1),[11] a process known today as the Suzuki reaction. The first examples of this protocol were reported by the Suzuki group in 1979[12]

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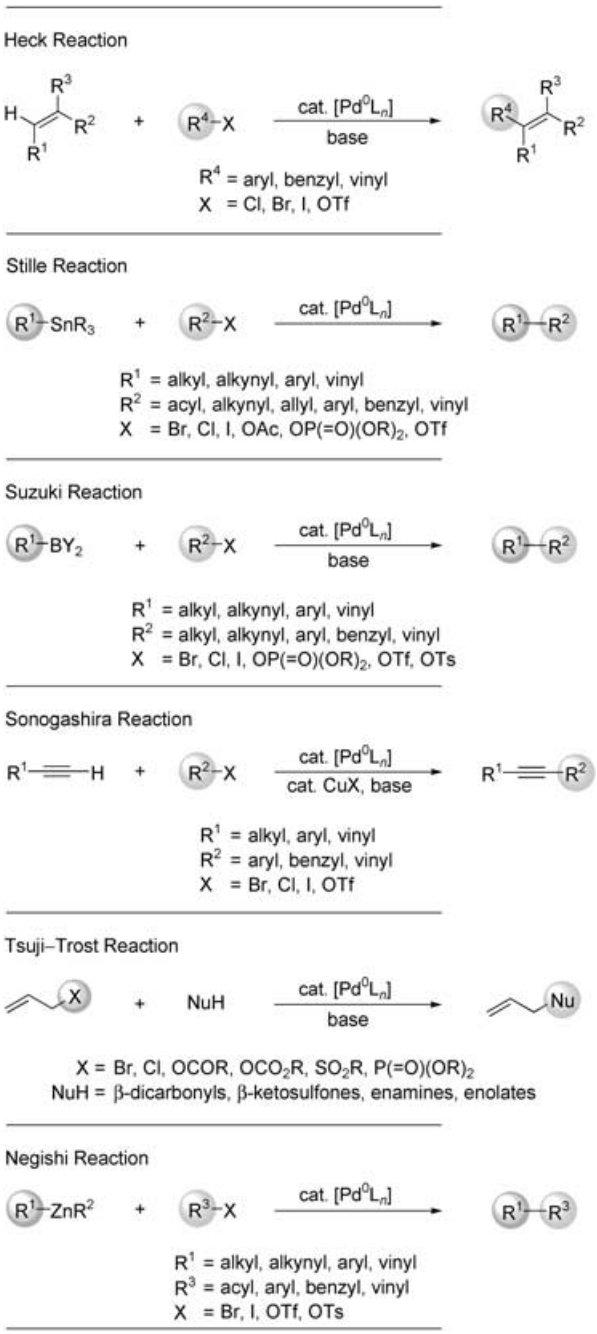
David Sarlah was born in Celje, Slovenia in 1983. He is currently student in the Faculty of Chemistry and Chemical Technology, University of Ljubljana (Slovenia). Since 2001, he has been a research assistant at the Laboratory of Organic and Medicinal Chemistry at the National Institute of Chemistry (Slovenia) where he carried out research on asymmetric catalysis under the direction of Dr. B. Mohar. During the summer of 2004, he was engaged in total synthesis endeavors as a member of the azaspiracid team under Professor K. C. Nicolaou.



Scheme 1. The most commonly utilized palladium-catalyzed cross-coupling reactions.

although, again, the inspiration or the seeds of this development can be found in earlier work by others, in this case the groups of Heck (1973)[13] and Negishi (1977).[14] The ensuing quarter of a century saw remarkable developments in the field. Amongst its manifold applications, the Suzuki reaction is particularly useful as a method for the construction of conjugated dienes and higher polyene systems of high stereoisomeric purity, as well as of biaryl and related systems. Furthermore, tremendous progress has been made in the development of Suzuki coupling reactions of unactivated

alkyl halides, enabling $C(sp^2)$–$C(sp^3)$ and even $C(sp^3)$–$C(sp^3)$ bond-forming processes.[15,16] The ease of preparation of organoboron compounds (e.g. aryl, vinyl, alkyl) and their relative stability to air and water, combined with the relatively mild conditions for the reaction as well as the formation of nontoxic by-products, makes the Suzuki reaction a valuable addition to the armory of the synthetic organic chemist. Indeed, it has become one of the most reliable and widely applied palladium-catalyzed cross-coupling reactions in total synthesis, where it has found a prominent role.[17] It is, again, worth mentioning that the Suzuki reaction may be considered as a variation of the Heck reaction, in which a boron-containing group replaces a hydrogen atom in the olefinic partner of the cross-coupling.

The palladium-catalyzed coupling of terminal alkynes with vinyl or aryl halides was first reported independently and simultaneously by the groups of Cassar[18] and Heck[19] in 1975. A few months later, Sonogashira and co-workers demonstrated that, in many cases, this cross-coupling reaction could be accelerated by the addition of cocatalytic Cu^I salts to the reaction mixture.[20,21] This protocol, which has become known as the Sonogashira reaction, can be viewed as both an alkyne version of the Heck reaction and an application of palladium catalysis to the venerable Stephens–Castro reaction (the coupling of vinyl or aryl halides with stoichiometric amounts of copper(I) acetylides).[22] The Sonogashira reaction provides a valuable method for the synthesis of conjugated acetylenic systems, which are used in a diverse array of important applications from natural products and pharmaceuticals to designed molecules of interest in biotechnology and nanotechnology. Interestingly, the utility of the "copper-free" Sonogashira protocol (i.e. the original Cassar–Heck version of this reaction) has subsequently been "rediscovered" independently by a number of other researchers in recent years.[23]

The palladium-catalyzed nucleophilic substitution of allylic compounds, known as the Tsuji–Trost reaction (Scheme 1), is arguably one of the most synthetically useful carbon–carbon bond-forming reactions to emerge in the last quarter of the previous century.[24] Allyl acetates are by far the most commonly employed electrophiles, and soft anions such as those derived from β-dicarbonyl compounds are most routinely used as the nucleophilic coupling partner. However, a wide variety of substrate combinations is possible, which gives the reaction an exceptionally broad scope. The development of the palladium-catalyzed asymmetric allylic alkylation reaction over the last decade has considerably increased the enabling nature of this transformation.[25] A notable feature of the allylic alkylation reaction is its net reaction at sp^3-hybridized carbon atom centers, a feature common among the palladium-catalyzed coupling reactions only to the Fu modification of the Suzuki reaction. The asymmetric allylic alkylation reaction now provides a powerful method for ring formation, 1,3-chirality transfer, desymmetrization of *meso* substrates, the resolution of racemic compounds, and a plethora of other applications.

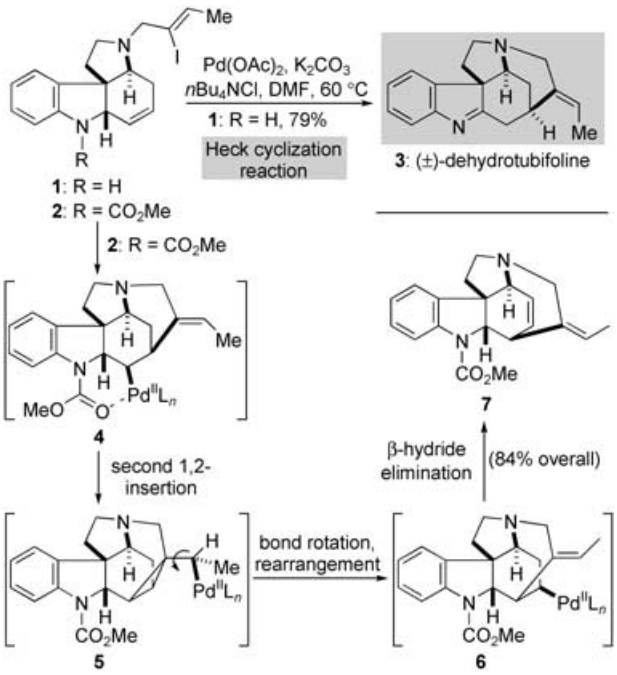
Historically, the use of organozinc reagents as the nucleophilic component in palladium-catalyzed cross-coupling reactions, known as the Negishi coupling (Scheme 1), actually predates the development of both the organostannane- (Stille, 1978)[6] and organoborane-based (Suzuki, 1979)[12] procedures, with the first such examples being reported in 1977.[26] Nevertheless, the rapid and widespread embracement of the latter two protocols by synthetic chemists during the 1980s led to the potential of organozinc reagents in cross-coupling processes being relatively underappreciated and underutilized during this time, particularly in total synthesis. However, recent years have witnessed a resurgent interest in the development and application of organozinc-mediated cross-couplings, largely fueled by the recognition that these reagents offer complementary modes of reactivity to those of the less electropositive metals species (e.g. B and Sn). Organozinc reagents exhibit a very high intrinsic reactivity in palladium-catalyzed cross-coupling reactions, which combined with the availability of a number of procedures for their preparation and their relatively low toxicity, makes the Negishi coupling an exceedingly useful alternative to other cross-coupling procedures, as well as constituting an important method for carbon–carbon bond formation in its own right.[27]

In the following sections, we discuss the contributions of these palladium-catalyzed carbon–carbon bond-forming reactions to the art and science of total synthesis and the new thinking that they have precipitated in the field.

2. The Heck Reaction

Total synthesis has benefited enormously from the Heck reaction, which has been widely applied in both its intermolecular and intramolecular variants.[28–30] The enabling attributes of this remarkable reaction manifest themselves in a plethora of ways, including appendage attachments, polyene construction, fragment couplings, and ring-closure reactions. In this section, we highlight a few examples that demonstrate the elegance and effectiveness of strategies based on the Heck reaction as the key step.

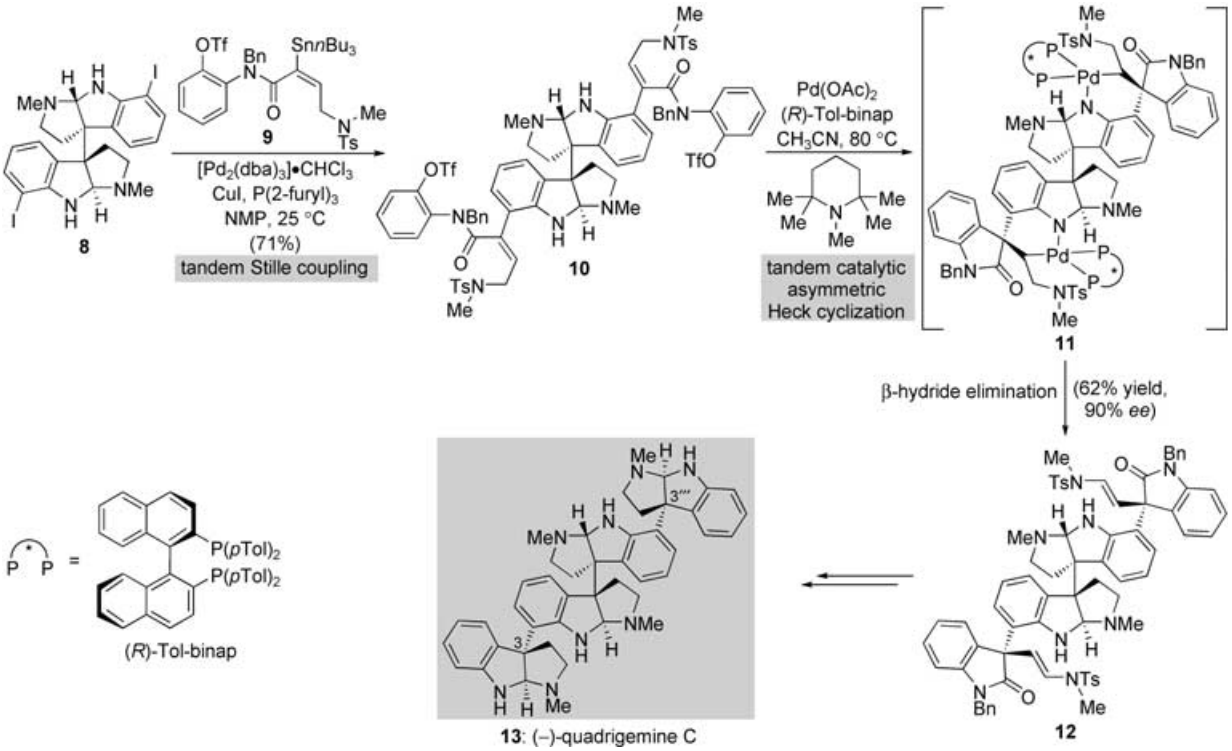
Among alkaloid total syntheses employing the Heck reaction, that of dehydrotubifoline (**3**) by Rawal and co-workers stands out (Scheme 2).[31] In this instance the palladium-catalyzed process was used to forge the final carbon–carbon bond and cast the final ring of the polycyclic structure of the target in 79% yield (**1**→**3**, Scheme 2). This effective operation, involving a 6-*exo*-palladation followed by β-hydride elimination and tautomerization of the resulting enamine species, would seem simple enough and certainly predictable, until one considers the different outcome observed with the corresponding *N*-carbomethoxy cyclization substrate **2**. In that initial attempt, the researchers noticed the exclusive formation of the unexpected compound **7**, the apparent product of a 7-*endo*-cyclopalladation reaction, in 84% yield. Moreover, close scrutiny of the spectroscopic data of pentacyclic compound **7** revealed that inversion of geometry of the exocyclic double bond had occurred, an outcome inconsistent with a direct 7-*endo* mode of ring closure. The proposed mechanistic explanation for the formation of **7** is both intriguing and illuminating. Thus, under the Jeffery modification[32] of the Heck conditions



Scheme 2. Intramolecular Heck reactions in the total synthesis of (±)-dehydrotubifoline (**3**) (Rawal et al., 1993).[31]

($Pd(OAc)_2$ cat., K_2CO_3, nBu_4NCl, DMF, 60 °C), the expected 6-*endo* cyclization occurs to yield initially σ-alkyl–palladium species **4** which, due to stabilization by intramolecular carbamate complexation, is prevented from undergoing a normally facile *syn*-β-hydride elimination, despite the presence of a β-hydrogen atom.[33] Instead, this intermediate is sufficiently long-lived to undergo a second cyclopalladation to form the cyclopropylmethyl palladium complex **5**, which is forced by steric congestion to undergo a 120° rotation about the σ bond. This then allows the proper alignment required for fragmentation of the other cyclopropane bond to give palladium complex **6**, which is no longer stabilized by carbamate complexation and undergoes the anticipated β-hydride elimination to provide the observed product **7**. Based on these mechanistic considerations, the Rawal group subjected the "carbamate-free" substrate **1** to the same reaction conditions realizing, much to their delight, the formation of the natural product dehydrotubifoline (**3**). This case serves to illustrate the fact that the "normal" mechanistic pathways of metal-catalyzed processes may be diverted, in certain cases, by the judicious placement of coordinating groups within the employed substrates.[34]

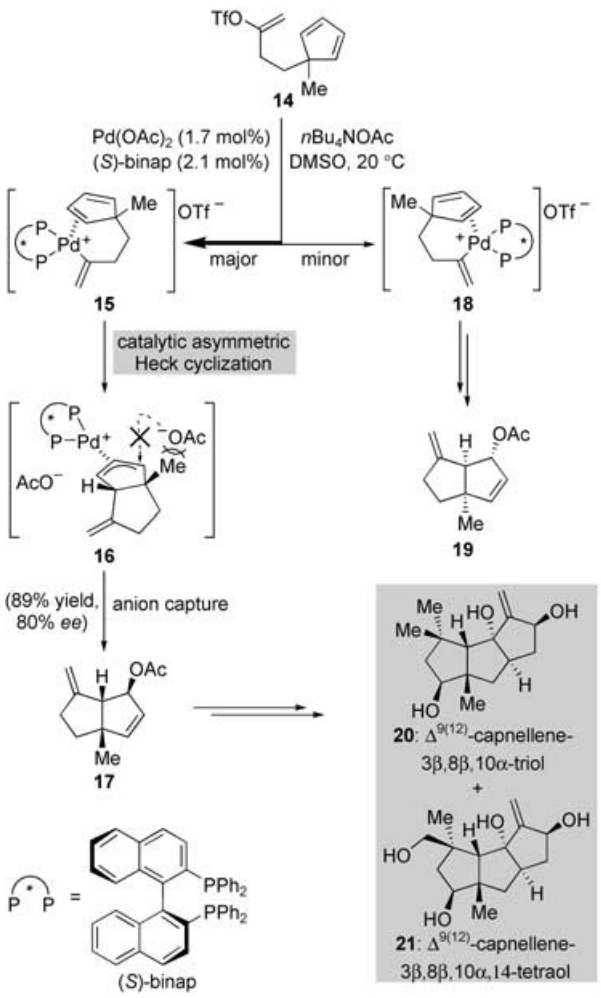
Palladium-catalyzed reactions abound in the spectacular synthesis of quadrigemine C (**13**, Scheme 3), a tetrameric member of the polypyrrolidinoindoline alkaloid family, by Overman and co-workers.[35] Noting that the quaternary C3 and C3‴ stereocenters within the target molecule **13** have the same absolute configuration, these researchers applied catalytic asymmetric Heck reactions[4] to effect the desymmetrization of an advanced *meso* intermediate **10**, formation of the two peripheral indoline residues, and installation of the final two quaternary stereocenters in a single step. This remarkable double cyclization (**10**→**11**→**12**) was preceded by another highly effective palladium-catalyzed carbon–carbon bond-forming reaction, namely a Stille coupling, which was used to assemble the required precursor **10** from its constituent



Scheme 3. Sequential tandem Stille couplings and asymmetric intramolecular Heck reactions in the enantioselective synthesis of (−)-quadrigemine C (**13**) (Overman et al., 2002).[35]

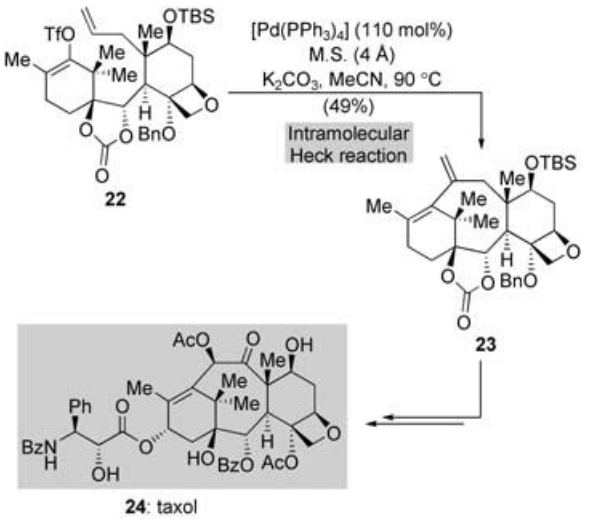
fragments, bisaromatic iodide **8** and stannane **9**. Thus, following assembly of **10** from **8** and **9** under Farina conditions[36] (note the selectivity of the cross-coupling of the vinyl stannane moiety with the aryl iodide groups in the presence of the aryl triflate groups, owing to the higher reactivity of aryl iodides relative to the corresponding triflates towards oxidative addition to Pd^0 species),[37] the crucial asymmetric Heck reaction was induced by treatment with $Pd(OAc)_2$ (100 mol%, precatalyst), (*R*)-Tol-binap (200 mol%, ligand), and 1,2,2,6,6-pentamethylpiperidine (base) in acetonitrile at 80°C to yield decacyclic system **12** in 62% yield with 90% *ee*, together with another two undesired stereoisomeric products in a combined yield of 21%. A few more steps then converted the advanced intermediate **12** into the targeted natural product **13** in good overall yield. This accomplishment stands as a powerful testament to the power of modern synthetic methods, most notably the catalytic asymmetric Heck reaction, to construct quaternary stereocenters[38,39] and crowded bonds.

These workers were not alone in developing the asymmetric Heck reaction. Shibasaki and his group also made pioneering contributions to the field at about the same time. Indeed, it was the Overman and the Shibasaki groups that independently reported the first examples of asymmetric Heck reactions in 1989.[40,41] The Shibasaki group applied their chemistry to the catalytic asymmetric synthesis of vernolepin and, subsequently, compound **17**, a key intermediate in the total synthesis of the complex triquinane sesquiterpenes $\Delta^{9(12)}$-capnellene-3β,8β,10α-triol (**20**) and $\Delta^{9(12)}$-capnellene-3β,8β,10α,14-tetraol (**21**), by making use of an asymmetric Heck reaction/anion-capture cascade sequence (Scheme 4).[42] Thus, starting with the prochiral vinyl triflate **14**, the team was able to prepare the diquinane derivative **17** in 89% yield with 80% *ee* by treatment with catalytic amounts of $Pd(OAc)_2$ (1.7 mol%) in the presence of (*S*)-binap (2.1 mol%) and nBu_4NOAc in DMSO at 20°C. The reaction presumably proceeds through a mechanism involving oxidative addition of the vinyl triflate to the initially formed Pd^0–binap complex, followed by coordination of the resulting vinyl–Pd^{II} species to, potentially, either enantiotopic double bond of the cyclopentadienyl system to give intermediates **15** or **18**. Intermediate **15** enjoys much less steric congestion as a result of the chiral environment created around the Pd^{II} ion than does intermediate **18** and is, therefore, energetically favored; rearrangement of **15** through 1,2-insertion of the coordinated alkene into the Pd–C(vinyl) σ bond is then followed by a rapid σ→π shift to generate the π-allylpalladium species **16**. Trapping of the latter intermediate with an acetate ion derived from nBu_4NOAc, whose presence proved to be essential for the reaction to occur, proceeded in both a regio- (attack at the least-hindered terminus of the π-allyl system) and stereocontrolled (attack from the face opposite to palladium) manner, leading to the key building block, diquinane **17**. Elaboration of this intermediate, and others like it, allowed the formal total syntheses of both natural products **20** and **21**. In addition to these pioneering examples, asymmetric Heck reactions have been successfully employed in several other total syntheses of a structurally diverse range of natural products, including alkaloids, terpenoids, and polyketides. For a fuller coverage of this topic, the reader is referred to a recently published review.[4a]

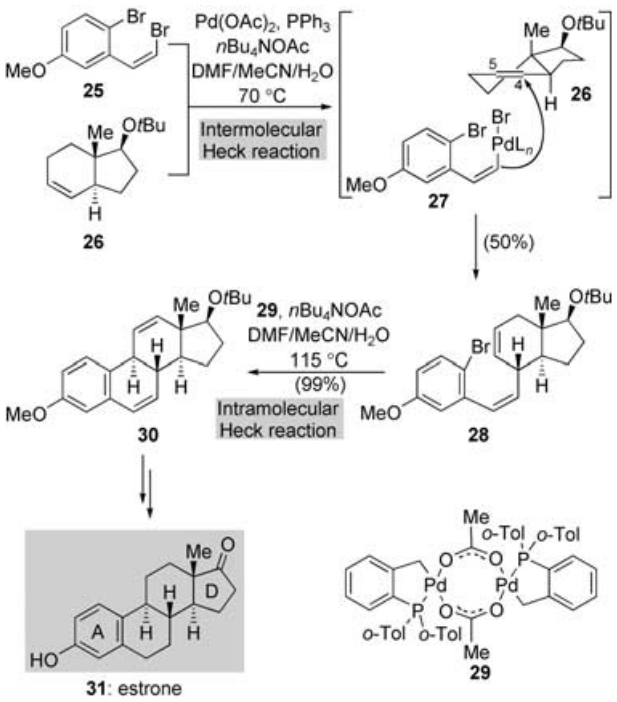


Scheme 4. Use of a catalytic asymmetric intramolecular Heck reaction to generate a key intermediate (**17**) in the total synthesis of $\Delta^{9(12)}$-capnellene-3β,8β,10α-triol (**20**) and $\Delta^{9(12)}$-capnellene-3β,8β,10α,14-tetraol (**21**) (Shibasaki et al., 1989).[42]

It can be seen from the previous two examples that, besides the customary halide species, the corresponding aryl and vinyl triflates also make excellent electrophilic coupling partners in the Heck reaction. One of the most breathtaking applications of vinyl triflates in the intramolecular Heck reaction was in the construction of the core tricyclic ABC ring system of taxol (**24**) by Danishefsky and co-workers, en route to their total synthesis of this famous natural product (Scheme 5).[43] The intramolecular cyclization of the cyclohexene moiety of triflate **22** onto the pendant terminal alkene was brought about by treatment with $[Pd(PPh_3)_4]$ and K_2CO_3 in refluxing MeCN, thus effecting the closure of the central eight-membered ring to generate the tetracyclic product **23** in 49% yield. It was found to be necessary to add a stoichiometric amount of the palladium "catalyst" in several portions over the course of the reaction to ensure its completion. Nonetheless, this transformation is astonishing for several reasons, not the least of which are the remarkable steric



Scheme 5. The intramolecular Heck cyclization of an enol triflate in the total synthesis of Taxol (**24**) (Danishefsky et al., 1995).[43]



Scheme 6. Sequential inter- and intramolecular Heck reactions in the enantioselective total synthesis of estrone (**31**) (Tietze et al., 1998).[50]

hindrance at the junction of ring closure that had to be overcome and the strained nature of the product thus formed, which contains a tetrasubstituted bridgehead double bond. Furthermore, the delicate oxetane ring was retained intact, together with the rest of the sensitive functionality, illustrating the mildness of this ring-closure method. The success of this reaction must be, in no small part, due to the presence of the cyclic carbonate 1,2-diol-protecting group. This protecting group restricts the rotational degrees of freedom available to the precursor **22**, thus making the ring closure less entropically unfavorable.[44]

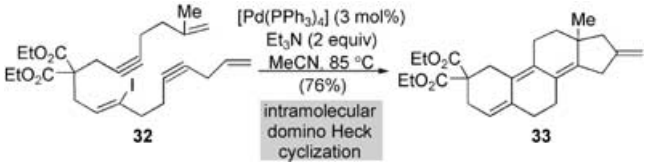
Steroid research can be regarded as one of the triumphs of 20th century science, from the story of their structure elucidation to their manifold pharmaceutical applications. No less significant is the impact this field has had on organic synthesis by providing inspiration for the development and application of a rich collection of novel synthetic methods.[45] Classic examples include the development of Robinson-type annulations,[46] the biomimetic olefin-cation cyclizations, as suggested by the Eschenmoser–Stork hypothesis[47] and pioneered by Johnson and his group,[48] and the cobalt-mediated alkyne cyclotrimerization/*ortho*-quinodimethane strategies introduced by Vollhardt and co-workers.[49]

An alternative approach to the steroid skeleton, based on palladium-catalyzed Heck reactions, has more recently been introduced by Tietze and his group and is exemplified by an elegant, enantioselective total synthesis of the female sex hormone estrone (**31**, Scheme 6).[50] The cornerstone of this strategy relies on the generation of the steroid ring B by the fusion of the functionalized aromatic compound **25** onto the enantiopure hydrindene derivative **26**[51] through consecutive inter- and intramolecular Heck reactions. Specifically, these researchers discovered that treatment of a mixture of **25** and **26** with catalytic amounts of $Pd(OAc)_2$ and PPh_3 in the presence of nBu_4NOAc in a mixed $DMF/MeCN/H_2O$ solvent system at 70 °C led to the selective formation of the intermolecular Heck reaction product **28**; when the latter was treated with a catalytic amount of the novel palladacycle **29**[52] in the same solvent system, but at a slightly higher temperature (115 °C), the desired intramolecular ring closure was effected, generating the estrone core structure **30** in quantitative yield. A few more steps then completed what amounted to a concise total synthesis of the natural product.

The overall conversion of **25** and **26** into tetracyclic structure **30** is indeed a remarkable transformation, several aspects of which warrant further discussion. First, it will be noted that the initial union of **25** and **26** involves selective reaction at the vinyl bromide moiety of compound **25**. The researchers expected this selectivity based on earlier investigative work which uncovered subtle reactivity differences between the two halogen atoms in dihalides such as **25**: the vinyl–bromine bond was found to be more susceptible to oxidative addition to Pd^0 complexes than the corresponding aryl–bromine bond. Second, whereas the diastereoselectivity of the 1,2-insertion of Pd^{II} complex **27** into the double bond of hydrindene **26** could be confidently predicted on the basis of approach of the complex to the less sterically hindered face of the double bond, the regioselectivity of the insertion would, at first glance, appear to be questionable at best. Fortuitously, the sole regioisomeric product of the reaction was, indeed, the desired one, and in a case of a rationalization after the event, it was proposed that the selectivity was due to stereoelectronic effects in the transition state for 1,2-insertion. Finally, palladacycle **29** was found to be uniquely effective in catalyzing the intramolecular Heck reaction, with more-conventional catalyst systems proving to be much less efficient. Even more impressively, it was subsequently found that the direct conversion of **25** and **26** into tetracyclic

compound **30**, in a domino reaction without the need for isolation of intermediate **28**, could be effected by treatment of a mixture of the two starting materials with catalyst **29**, although the overall yield (35%) was slightly lower than that of the two-step process.

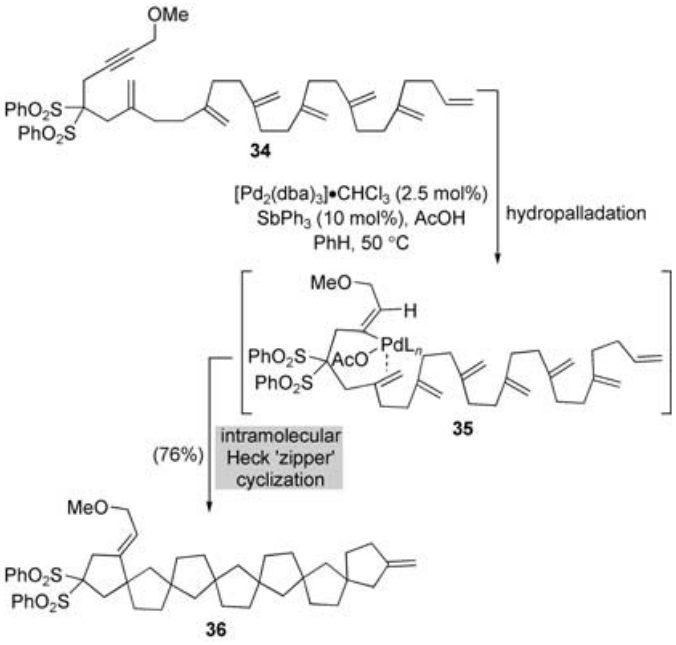
A famous and equally stunning application of the domino intramolecular Heck reaction can be found in the formation of the steroidal ring framework in compound **33** in a single operation from the polyunsaturated acyclic precursor molecule **32** (Scheme 7).[53] It was Negishi and co-workers who



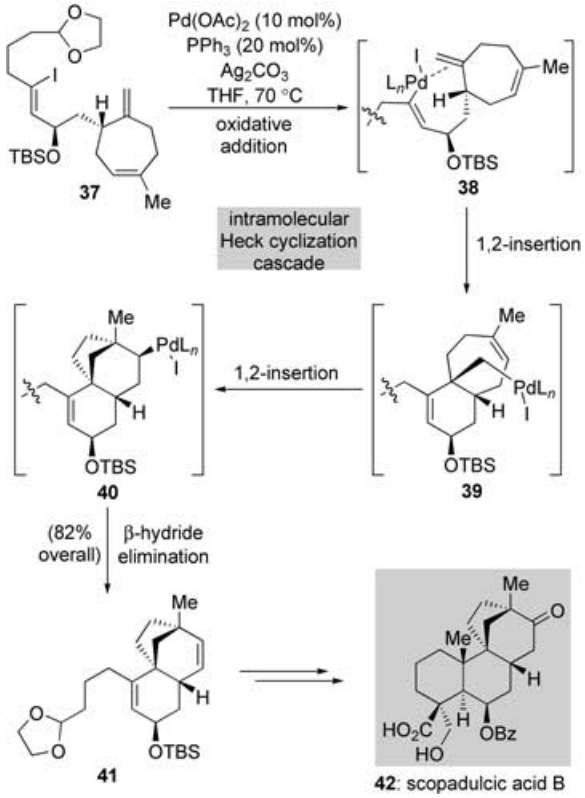
Scheme 7. A palladium-catalyzed "zipper" tetracyclization approach to steroidal skeletons (Negishi et al., 1990).[53]

demonstrated this transformation by treatment of iodide **32** with $[Pd(PPh_3)_4]$ catalyst (3 mol%) in the presence of triethylamine in refluxing acetonitrile. This reaction involves a series of consecutive carbopalladations that lead to the regiocontrolled formation of four new carbon–carbon bonds and four carbocyclic rings, ultimately generating polycycle **33** in an impressive 76% overall yield. Not to be outdone, the Trost group subsequently reported even more spectacular examples of intramolecular Heck-type polycyclization processes. These studies are exemplified by the hydridopalladium acetate catalyzed formation of the intriguing heptacyclic structure **36** in a single operation from the open-chain precursor **34** (Scheme 8).[54] Such cascade cyclization processes, colorfully termed "zipper reactions", provide efficient and economical means of generating polycyclic molecular complexity from simple acyclic materials in a manner that would have been impossible before the advent of palladium-catalyzed carbon–carbon bond-forming reactions, and are illustrative of the enabling power of this methodology.[55,56]

An application of a palladium-catalyzed polyene cyclization reaction in the context of total synthesis can be found in the pioneering approach of the Overman group towards the synthesis of the scopadulcic acid family of diterpenes.[57] In this highly inventive strategy, it was reasoned by the group that the three of the four rings of the formidable tetracyclic structure of the target products, including the sterically congested bridged bicyclic system and two of the three quaternary stereocenters, could be fashioned from a simple monocyclic precursor and in a single step through a palladium-catalyzed intramolecular Heck cyclization cascade process. The realization of this hypothesis in practice is illustrated by the total synthesis of scopadulcic acid B (**42**), as shown in Scheme 9, in which the substituted cycloheptene **37** was converted into tricyclic compound **41** in one step. This cascade was triggered by the addition of $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), and Ag_2CO_3 to a refluxing solution of iodide **37** in THF. The initial oxidative addition into the carbon-iodine bond generated intermediate **38** with retention of configuration. This was followed by the first intramolecular cyclization to generate alkylpalladium(II) intermediate **39**, which was unable to exit the catalytic cycle



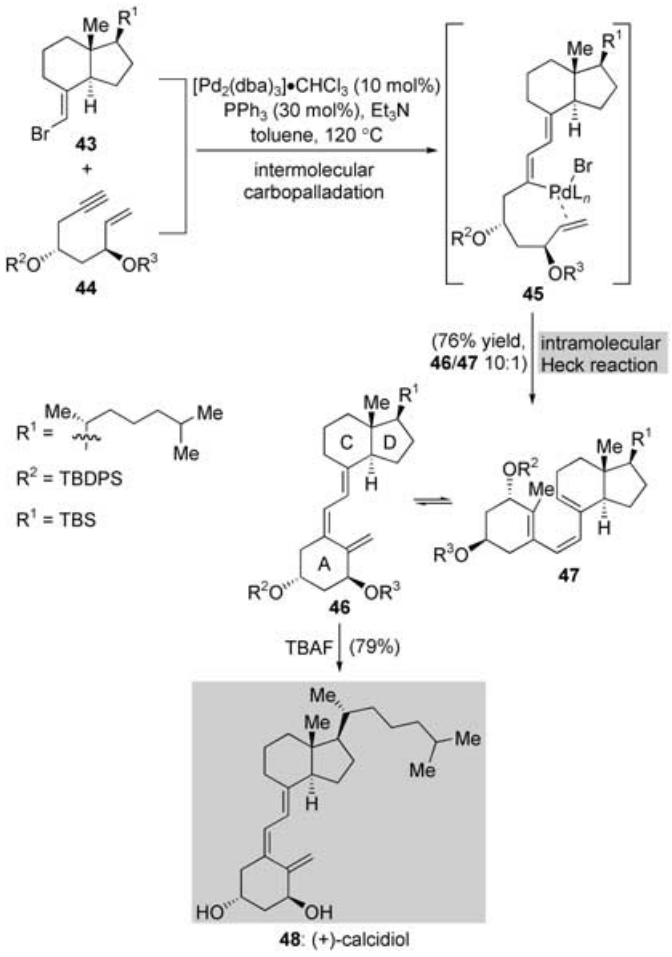
Scheme 8. A hydridopalladium acetate-catalyzed "zipper" polycyclization (Trost and Shi, 1991).[54]



Scheme 9. A sequential intramolecular Heck cyclization approach to the total synthesis of scopadulcic acid B (**42**) (Overman et al., 1993).[57]

by β-hydride elimination owing to the absence of any suitably disposed hydrogen atoms and thus underwent the second 1,2-insertion reaction into the trisubstituted alkene conveniently located within bonding distance. The resulting species **40**, having exhausted its possibilities for intramolecular carbon–carbon bond formation, finally succumbed to β-hydride elimination to afford the isolated product **41**. Each of these steps proceeded with remarkable efficiency and selectivity: tricyclic compound **41** was isolated in 82% yield as a single stereoisomer! This intermediate could then be elaborated in a number of steps, which included the fusion of the final carbocyclic ring onto the tricyclic system, to complete the total synthesis of scopadulcic acid B (**42**). This synthesis provides further evidence for the utility of the Heck reaction in the construction of sterically crowded systems and quaternary stereocenters through cascade processes.

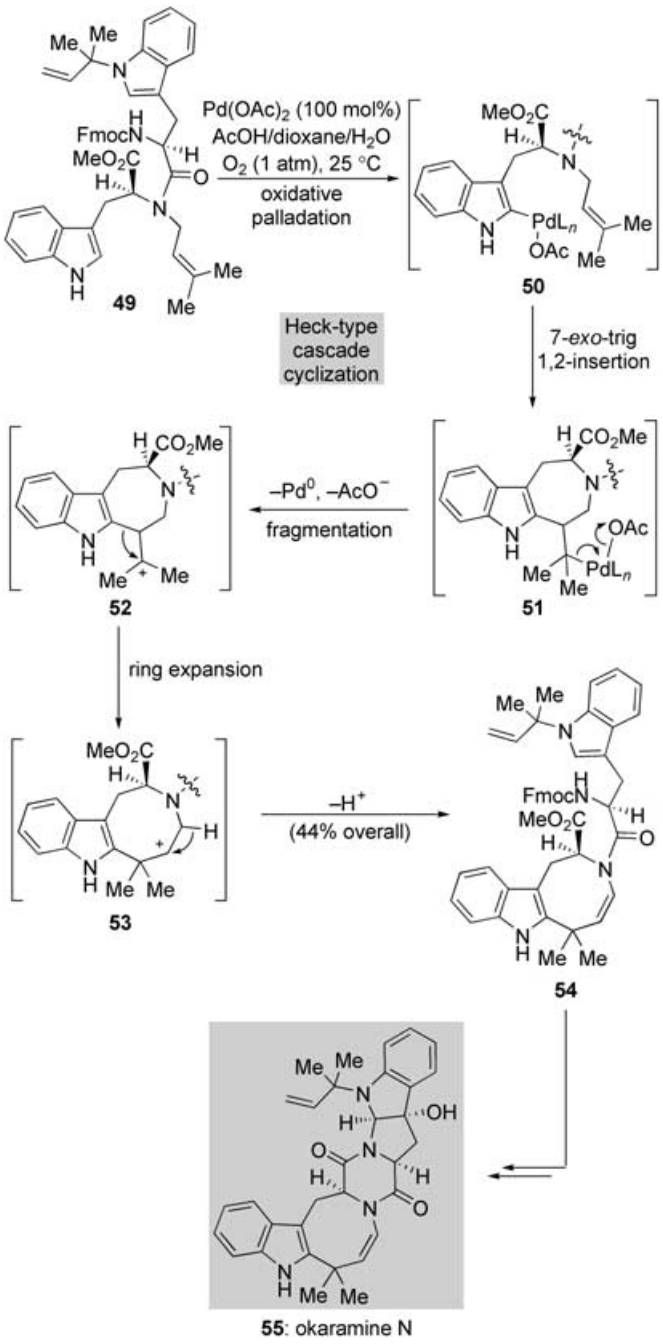
The Trost group has reported an interesting addition to the menagerie of methods documented for the preparation of the clinically important 1α-hydroxyvitamin D (calcidiol) and its analogues,[58] in a convergent strategy based on a palladium-catalyzed cascade reaction (Scheme 10).[59,60] Thus, the addition of a mixture of bromide **43** and enyne **44** to a heated solution of $[Pd_2(dba)_3]\cdot CHCl_3$ (10 mol%) and PPh_3 (30 mol%) in toluene/Et_3N (1:1 v/v) initiated a sequence involving the oxidative addition of the carbon–bromine bond of vinyl halide **43** to Pd^0 followed by chemoselective intermolecular carbopalladation of the alkyne moiety of compound **44** to yield intermediate **45**. The latter was suitably arranged to undergo a subsequent regioselective intramolecular Heck reaction to form the final carbon–carbon bond of the product. The net result of this reaction sequence was the attachment of the CD-ring fragment, formation of ring A, and creation of the requisite triene system in a single operation! The desired product **46** was in fact isolated as a 10:1 mixture with the isomeric triene **47**. It was shown that this triene mixture derives from a thermal equilibration, by means of a 1,7-sigmatropic hydrogen shift, of the initially formed product **46** under the reaction conditions. Separation of the minor product component **47** and subsequent thermal reequilibration increased the overall yield of the desired triene **46** to 76%. Removal of the two silyl protecting groups then completed the total synthesis of (+)-calcidiol (**48**).[61]



Scheme 10. A tandem intermolecular carbopalladation/intramolecular Heck cyclization approach to the synthesis of (+)-calcidiol (**48**) (Trost et al., 1992).[59]

The versatility of the Heck reaction is such that it is continually finding applications in novel carbon–carbon bond-forming processes, seemingly limited only by the ingenuity of the practitioner. As one recent example, we highlight the masterful synthesis of okaramine N (**55**, Scheme 11) by the Corey group.[62] In this instance, one of the key issues facing the researchers was the formation of the eight-membered medium ring, a motif often notoriously difficult to construct by traditional cyclization methods owing to a combination of enthalpic and entropic factors.[63,64] Nevertheless, the team surmised that it would, in fact, be possible to generate this ring system in a single step from an appropriately substituted acyclic precursor by employing palladium chemistry. Indeed, as shown in Scheme 11, it was found that treatment of indole **49** with $Pd(OAc)_2$ (100 mol%) in an AcOH/dioxane/H_2O solvent system under O_2 (1 atm) at ambient temperature led to the direct formation of pentacyclic compound **54** in reasonable yield (44%).

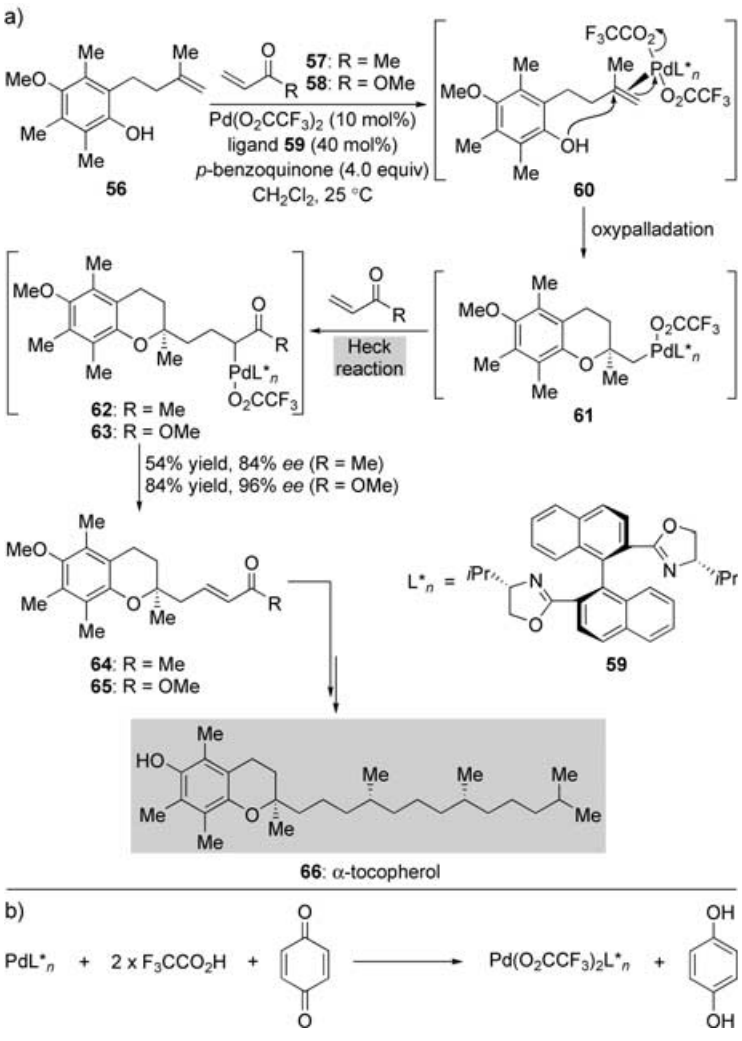
The visual relationship between the starting material **49** and the product **54** obscures the fact that the proposed mechanism of the reaction linking the two is, in reality, comprised of five distinct transformations, none of which is the apparent 8-*endo* mode of ring closure. Indeed, it may not be readily apparent how the reaction is initiated since, unlike all the other examples discussed so far, there is no carbon–halogen (or triflate) bond within the starting material **49** into which a Pd^0 species can insert. In fact, the first step in the mechanism proposed for this remarkable transformation is the selective and direct palladation of the unprotected indole unit, in the presence of the other *N*-prenylated indole motif, at C2 to generate indolyl–palladium(II) intermediate **50**.[65] Once formed, this palladated species can then undergo the expected 7-*exo*-trig 1,2-insertion to generate the next intermediate in the sequence, namely η^1-alkyl–palladium(II) species **51**. At this point the course of the reaction diverges from that which would, at first inspection, appear to be the most likely outcome. Despite the presence of no fewer than seven appropriately located hydrogen atoms, compound **51** does not undergo β-hydride elimination, but instead suffers a heterolytic fragmentation to generate tertiary carbocation **52**.



Scheme 11. Use of a novel Heck-type cascade cyclization to furnish an 8-membered ring in the synthesis of okaramine N (**55**) (Corey et al., 2003).[62]

Selective migration of the most-electron-rich group (i.e. the β-(2-indolyl) group) then results in ring expansion to furnish the eight-membered ring system **53**, rapidly followed by loss of a proton to yield the observed product **54**. The researchers' faith in the viability of this whole process was won by earlier model studies that demonstrated its aptitude for the formation of similar systems;[66] nonetheless, its application in the complex setting described here was certainly not without risk, a risk which ultimately paid off handsomely. Critical to the success of this venture was the employment of an $AcOH/H_2O$ solvent system; in the absence of acetic acid, no cyclization occurred, whilst omission of water resulted in the near exclusive formation of seven-membered-ring cyclization products. The direct, selective C–H bond functionalization of the indole nucleus represents a particularly exciting aspect of this methodology.[67] However, such procedures have generally required stoichiometric amounts of palladium(II) salts, which from a practical and economic standpoint, limits their use somewhat, particularly on a large scale. Recently though, the Stoltz group reported protocols for the aerobic oxidative annulation of indoles through C–H bond functionalization that are truly catalytic in palladium and which would thus appear to hold great potential for future development.[68]

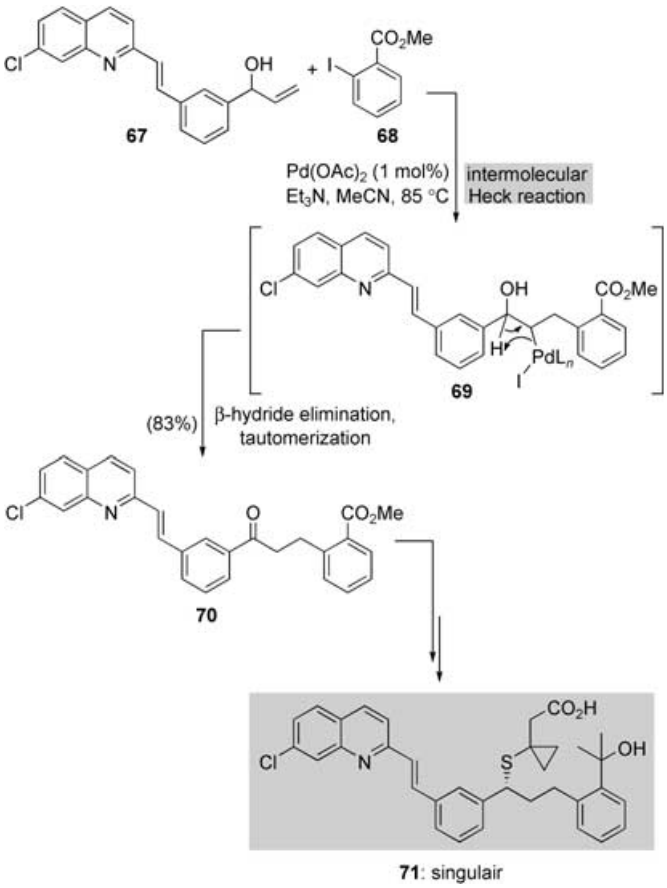
The Tietze group recently reported a novel palladium-catalyzed domino reaction for the synthesis of the vitamin E family of tocopherols and tocotrienols (Scheme 12a). This process combines sequential intramolecular enantioselective oxypalladation and intermolecular Heck reactions to rapidly assemble the chiral chroman framework of these biologically and commercially important antioxidant molecules.[69] Treat-



Scheme 12. a) A palladium-catalyzed enantioselective domino reaction in the synthesis of α-tocopherol (**66**); b) regeneration of the catalytically active Pd^{II} species from a Pd^0 complex (Tietze et al., 2005).[69]

ment of readily available alkene **56** with $Pd(O_2CCF_3)_2$ (10 mol%), ligand **59** (40 mol%), *p*-benzoquinone (4.0 equiv), and either methyl vinyl ketone (**57**) or methyl acrylate (**58**), in CH_2Cl_2 at ambient temperature triggers a series of events that lead to the corresponding products **64** (R = Me) or **65** (R = OMe) in good to excellent yield and with excellent enantioselectivity. The sequence presumably begins with the enantiofacial coordination of the chiral ligated Pd^{II} complex, generated from $Pd(O_2CCF_3)_2$ and the enantiomerically pure ligand **59**, to the 1,1-disubstituted alkene, yielding intermediate **60**. This coordination of Pd^{II} to the π system renders the alkene moiety susceptible to nucleophilic attack, thus enabling the intramolecular cyclization of the free phenolic hydroxy group to generate σ-alkyl–palladium(II) species **61**. Unable to undergo the customary β-hydride elimination, intermediate **61** is sufficiently long-lived to be intercepted by either **57** or **58** in an intermolecular Heck reaction process to afford the observed products **64** or **65**, respectively. Notably, the final β-hydride elimination from intermediates **62** and **63** concomitantly generates a Pd^0 species, whereas it is a Pd^{II} complex that is required, in this case, to initiate the domino reaction. Thus, to avoid the use of stoichiometric amounts of $Pd(O_2CCF_3)_2$, a method needed to be found for the reoxidation of Pd^0 to Pd^{II} in situ, and indeed this was the role played by *p*-benzoquinone (Scheme 12b). The functionalized side chains introduced in the intermolecular Heck reaction provided a sufficient handle for the elaboration of either **64** or **65** into α-tocopherol (**66**), the member of the vitamin E family with the most pronounced biological activity.

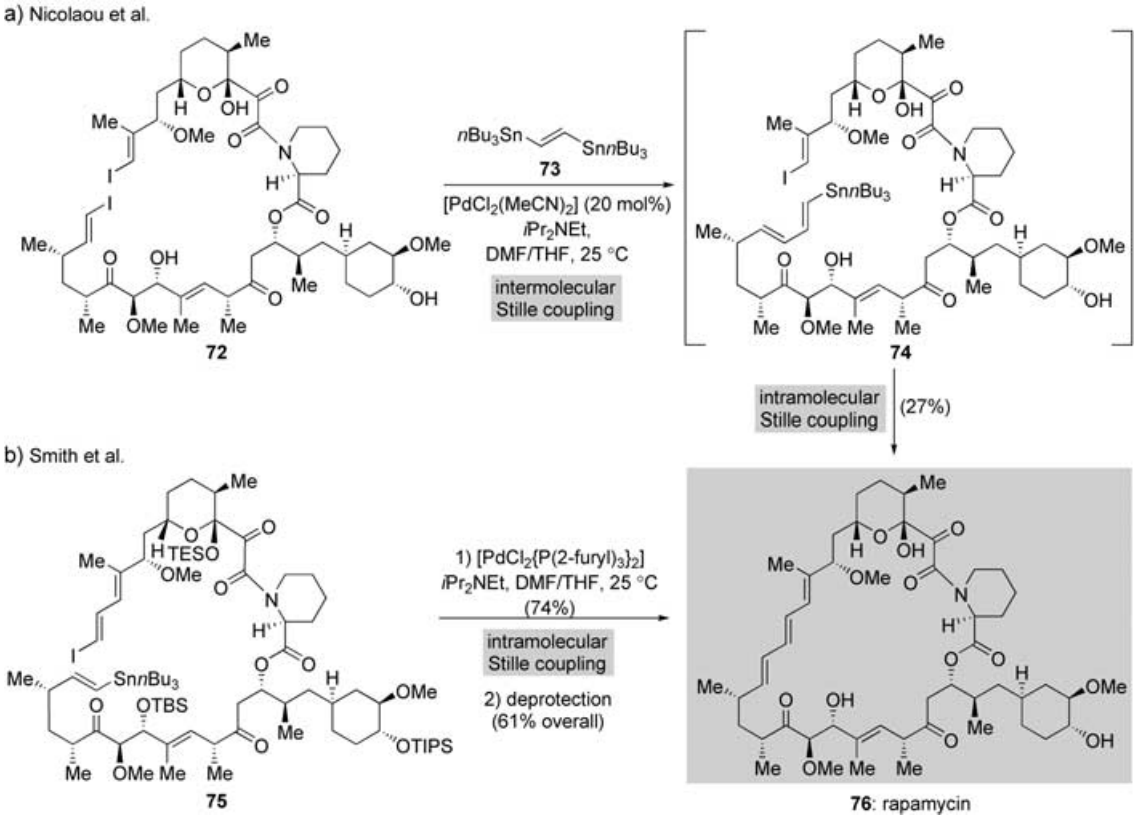
The impact of palladium-catalyzed coupling reactions has been felt in a number of fields outside academic research laboratories, particularly in the pharmaceutical industry. Palladium-catalyzed carbon–carbon bond-forming reactions have provided chemists with new avenues for the design, synthesis, optimization, and manufacture of therapeutic agents, and, as such, have dramatically benefited humanity.[70,71] One such example is found in the synthesis of singulair (**71**, Scheme 13), a selective leukotriene receptor antagonist marketed by Merck for the prophylaxis and chronic treatment of asthma. An intermolecular Heck reaction was utilized to couple the two key fragments;[72] treatment of a mixture of allylic alcohol **67** and aromatic iodide **68** with triethylamine and a low catalyst loading (1 mol% of $Pd(OAc)_2$) in refluxing acetonitrile, notably in the absence of any additional ligands for palladium, led to the formation of ketone **70** in 83% yield.[72] Isolation of ketone **70** on a large scale by direct crystallization of the product from the reaction mixture proved to be remarkably facile. The selective formation of ketone **70** in this reaction is the result of β-hydride elimination from the initially formed alkyl–palladium(II) intermediate **69** occurring regioselectively towards the hydroxy substituent as shown, to give an enol species that subsequently tautomerizes to the observed ketone **70**. The formation of carbonyl compounds in such a manner is the usual fate of allylic alcohols when subjected to the Heck reaction[73] and, therefore, this process constitutes a useful alternative to the traditional 1,4-conjugate addition reactions for the construction of such systems.



Scheme 13. The use of an intermolecular Heck reaction in the commercial synthesis of Singulair (**71**) (Merck, 1993).[72]

3. The Stille Reaction

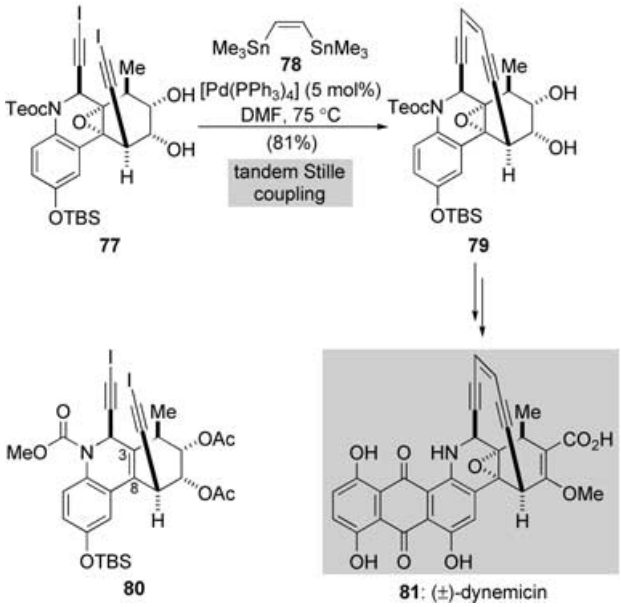
In addition to being a powerful intermolecular carbon–carbon bond-forming process, the Stille reaction has found widespread use in the generation of cyclic structures. The first examples of the intramolecular Stille reaction, reported by Piers and co-workers in 1985,[74] were concerned with the generation of five- and six-membered rings. However, it was not long before the utility of this process for the generation of a wider variety of ring sizes, macrocyclic systems in particular, was demonstrated.[75] Today, the Stille reaction constitutes a reliable and often-used method for the construction of carbocyclic and heterocyclic rings, be they common, medium or large.[76] A striking example of this type of reaction is the pioneering stitching-cyclization reaction applied by the Nicolaou group to construct rapamycin (**76**) from the bis(vinyl iodide) precursor **72** and *trans*-1,2-distannyl ethylene **73** (Scheme 14a).[77] The final step of the total synthesis of rapamycin involved a double Stille coupling process and proceeded from the naked (no protecting groups) precursor **72**, under the influence of $[PdCl_2(MeCN)_2]$ (20 mol%) and iPr_2NEt as a dilute solution in DMF/THF at ambient temperature, presumably through the intermediacy of iodostannane **74**. Thus, in one fell swoop, the 29-membered macrocyclic ring of rapamycin, with its *all-trans* triene system,



Scheme 14. Approaches to the total synthesis of rapamycin (**76**). a) A "stitching cyclization" to complete the total synthesis (Nicolaou and co-workers, 1993);[77] b) an intramolecular Stille macrocyclization approach (Smith et al., 1995).[78]

was installed from an acyclic precursor and without the need for any protection/deprotection operations. The success of this macrocyclization reaction undoubtedly relies, to no small measure, on the templating effect of the palladium center, which brings the two ends of the chain into the requisite close proximity for bond formation. A variation of this strategy was subsequently employed by Smith and co-workers in their elegant total synthesis of rapamycin,[78] in this case involving acyclic precursor **75** (Scheme 14b).[79,80]

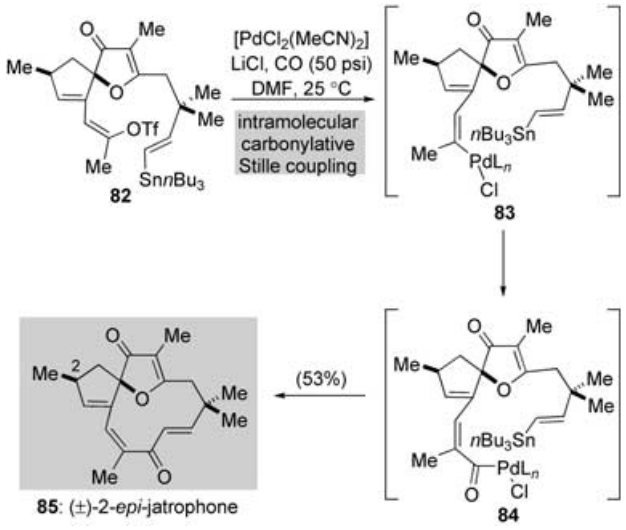
Another spectacular "stitching-cyclization" reaction involving a double Stille reaction was subsequently employed in the total synthesis of the enediyne anticancer antibiotic dynemicin (**81**) by Danishefsky and co-workers (Scheme 15).[81] The bis(iodoalkyne) substrate **77** reacted smoothly with *cis*-1,2-distannyl ethylene (**78**) in the presence of catalytic amounts of $[Pd(PPh_3)_4]$ in a dilute solution in DMF at 75 °C to afford the highly strained 10-membered-ring enediyne intermediate **79** in a remarkable 81% yield, with this pivotal intermediate thence being converted through a multistep sequence into the target molecule. Interestingly, when the structurally related olefin **80** (with a C3–C8 double bond instead of an epoxide moiety) was subjected to the same reaction conditions, none of the corresponding cyclized enediyne product was obtained. This observation highlights the importance of seemingly subtle conformational effects on the outcome of the process, with these factors often proving crucial to the success or failure of a given cross-coupling reaction.[82]



Scheme 15. A "stitching cyclization" route to the enediyne core in the total synthesis of dynemicin (**81**) (Danishefsky et al., 1996).[81]

In a beautiful example of the application of a carbonylative Stille coupling, the Stille–Hegedus group formed the 11-membered ring of 2-*epi*-jatrophone (**85**) by exposing vinyl triflate **82** to a catalytic amount of $[PdCl_2(MeCN)_2]$ and LiCl

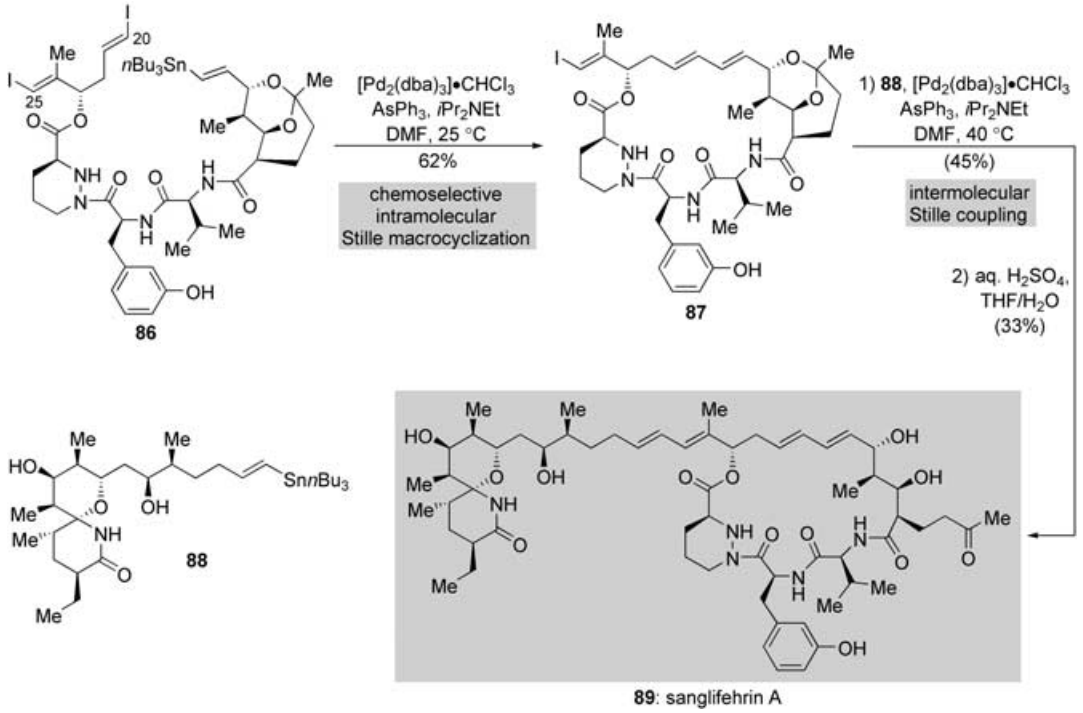
in DMF under a carbon monoxide atmosphere (50 psi) as shown in Scheme 16.[83,84] The mechanism of this impressive reaction, the final step in the total synthesis, presumably involves oxidative addition of a palladium(0) species into the



Scheme 16. The use of an intramolecular carbonylative Stille coupling to complete the synthesis of (±)-2-*epi*-jatrophone (**85**) (Stille et al., 1990).[83]

vinyl triflate C–O bond (**82**→**83**) followed by CO insertion to generate acylpalladium(II) intermediate **84**, and, finally, an intramolecular coupling to yield the observed product **85**. This transformation accomplishes the formation of two carbon–carbon bonds, the incorporation of the final carbon atom of the molecular framework, and the generation of the macrocyclic ring in a single operation—impressive indeed! It is worth recalling here that the carbonylative Stille coupling serves well as an alternative to Stille couplings of acid chlorides, especially when the latter intermediates are either not available or too labile to be used.

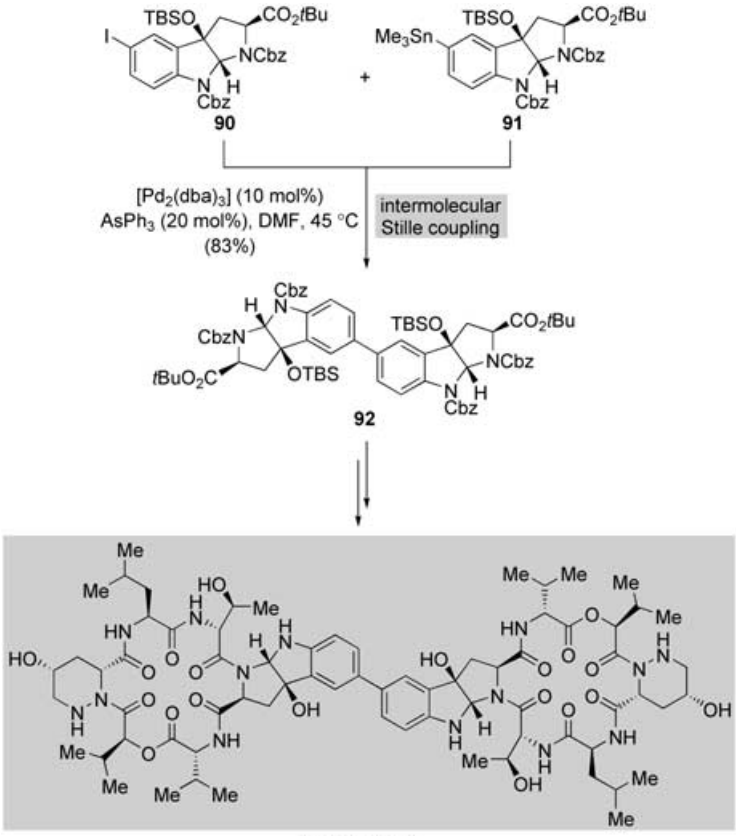
The remarkable level of control, in both a chemoselective and stereoselective sense, that is possible in executing Stille reactions is nicely illustrated by our total synthesis of the novel immunosuppressant agent sanglifehrin A (**89**, Scheme 17) by the Nicolaou group.[85] The cornerstone of the devised synthetic strategy was the proposed late-stage chemoselective Stille macrocyclization of bis(vinyl iodide) precursor **86** to generate the 22-membered ring intermediate **87** (Scheme 17), to which the complex spirolactam side chain would be appended through a second Stille coupling process. It was anticipated that participation of the less-hindered vinyl iodide group at C20 in the crucial macrocyclization reaction would be more favored over that involving the other vinyl iodide at C25, thus leading to the desired 22-membered ring, in preference to the alternative 21-membered macrocycle. In the event, this rather daring maneuver paid dividends, as it was found that treatment of a dilute solution of **86** in DMF with $[Pd_2(dba)_3]\cdot CHCl_3$ (15 mol%), $AsPh_3$ (60 mol%), and iPr_2NEt at ambient temperature led to the exclusive formation of the desired sanglifehrin cyclic intermediate **87** in 62% yield. A subsequent intermolecular Stille reaction between vinyl iodide **87** and alkenyl stannane **88** completed the carbon framework of the targeted natural product, which was finally unveiled by rupture of the acetal protecting group under aqueous acidic conditions. A second total synthesis of sanglifehrin A (**89**) was subsequently reported by the Paquette group, who also employed a Stille coupling reaction



Scheme 17. Chemoselective intra- and intermolecular Stille couplings in the total synthesis of sanglifehrin A (**89**) (Nicolaou et al., 1999).[85]

between the same two fully elaborated fragments **87** and **88** followed by cleavage of the acetal protecting group as the final synthetic steps.[86] In this case, however, the key macrocyclization step en route to vinyl iodide **87** involved the lactonization of an appropriately substituted seco-acid. Notably, once again the presence of unprotected functionalities such as amino, hydroxy, and secondary amide was tolerated under these palladium-catalyzed reaction conditions, thus underscoring the mildness of such protocols.

The use of transition metals in the formation of aryl–aryl bonds dates back to the beginning of the last century, with the discovery of the copper-promoted reductive coupling of aromatic halides (Ullmann reaction).[87] Whilst vast improvements in such copper-based protocols have been and continue to be made,[88] it was not until the advent of, at first, nickel-promoted and, subsequently, palladium-catalyzed carbon–carbon bond-formation methods that aryl–aryl coupling processes would assume the broad scope and generality that they enjoy today. The Stille reaction ranks among the most synthetically useful of the palladium-catalyzed processes for aryl–aryl bond formation, although arguably to a lesser extent than does the Suzuki reaction (see Section 4), and has found widespread use in this task.[89] An illustrative example of the utility of this transformation can be found in the total synthesis of himastatin (**93**, Scheme 18), a structurally intricate actinomycete metabolite with potent antibacterial and antitumor properties, by Danishefsky and Kamenecka.[90]

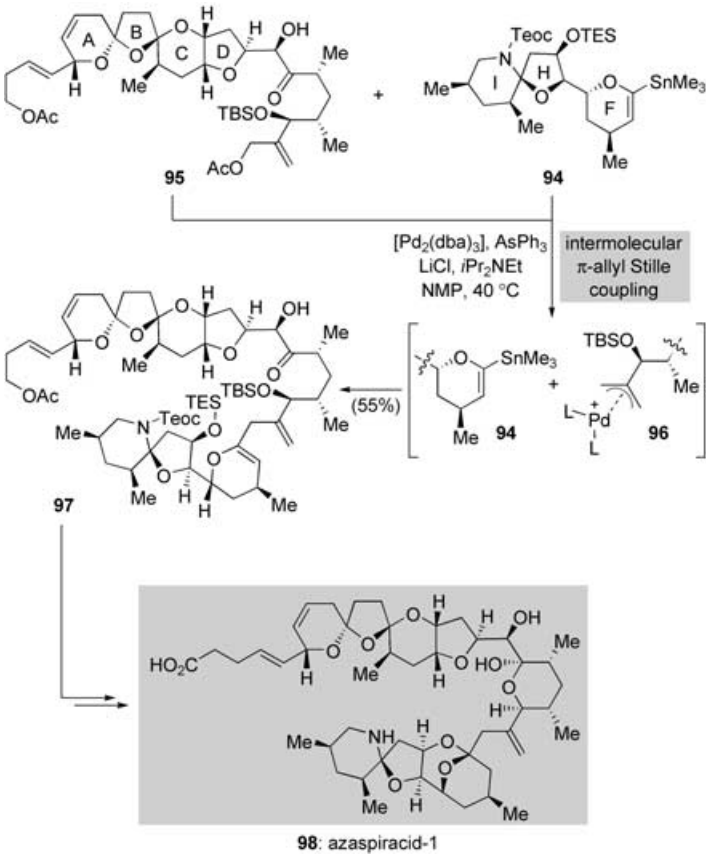


Scheme 18. Formation of an aryl-aryl linkage through a Stille coupling in the total synthesis of himastatin (**93**) (Danishefsky and Kamenecka, 1998).[90]

Smooth coupling between aryl iodide **90** and aryl stannane **91** was induced by treatment with catalytic amounts of $[Pd_2(dba)_3]$ (10 mol%) and $AsPh_3$ (20 mol%) in warm DMF to forge the key carbon–carbon bond between the two central indolyl moieties in an impressive 83% yield. Importantly, these reaction conditions were found to be compatible with the sensitive pyrroloindoline core present within both coupling partners **90** and **91**, which allowed the advancement of intermediate **92** through a number of steps to the targeted natural product. It is important to note that, although aryl iodides, bromides, and triflates are by far the most commonly used electrophilic coupling partners in this context with aryl stannanes, there have been extensive efforts at developing viable coupling conditions with the corresponding cheaper and often more readily available (but also far less reactive) aryl chlorides.[91,92]

The examples of Stille reactions discussed so far have focused on $C(sp^2)$–$C(sp^2)$ couplings, that is, between vinyl or aryl halides or triflates and vinyl or aryl organostannanes, which necessarily result in the formation of diene (or higher polyene) systems. However, the use of allylic halides allows formal $C(sp^2)$–$C(sp^3)$ couplings and broadens considerably both the scope of the Stille reaction and the structural diversity of the products that can be formed. This so-called π-allyl Stille coupling reaction provides a reliable and general method for the synthesis of "skipped" 1,4-diene systems. An important development in Stille reaction methodology was the discovery by the Stille–Hegedus group that the more readily available corresponding allylic acetates could be coaxed, under appropriate reaction conditions, into functioning as viable electrophiles for palladium-catalyzed coupling reactions with organostannanes.[93] An example of this type of reaction in the construction of complex natural products can be found in the recent total synthesis and structure elucidation of the marine toxin azaspiracid-1 by the Nicolaou group.[94] As shown in Scheme 19, addition of the vinyl stannane FHI-ring intermediate **94** to a mixture of the allylic acetate ABCD-ring intermediate **95**, LiCl, iPr_2NEt, and catalytic amounts of $[Pd_2(dba)_3]$ and $AsPh_3$ in NMP at 40 °C led to smooth coupling of the two fragments, presumably through the intermediacy of π-allyl–palladium complex **96**, to generate compound **97**. The latter advanced intermediate was elaborated into **98**, the spectroscopic data of which were shown to be identical to those of the natural product, thus solving the mystery and intrigue surrounding the structural identity of one of Nature's most remarkable natural products.

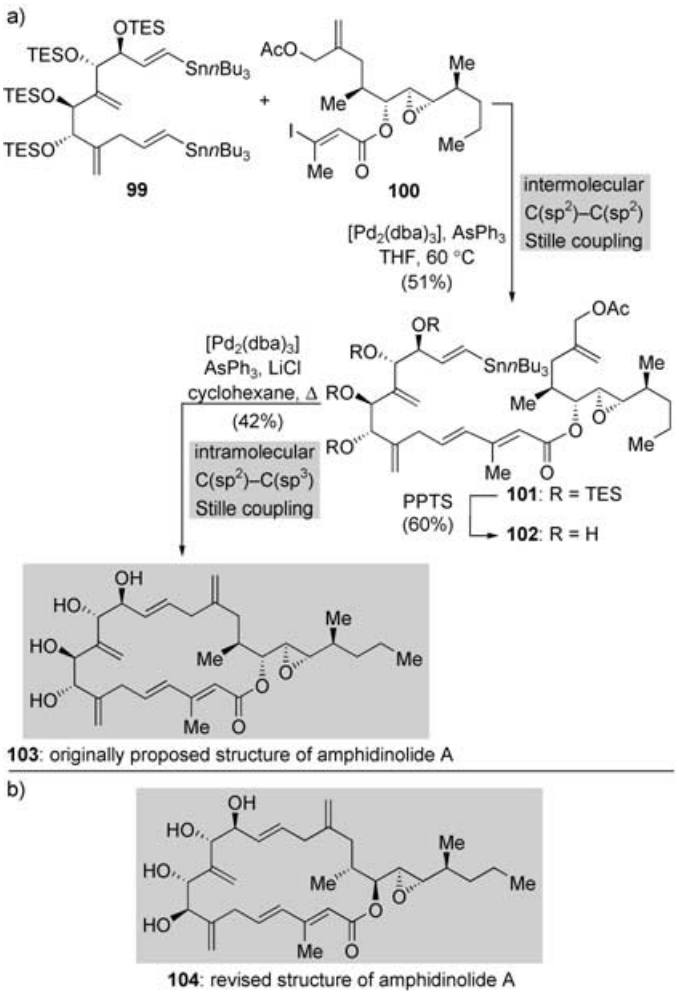
An intramolecular variant of the π-allyl Stille coupling was employed in the elegant total synthesis of the originally proposed structure of amphidinolide A by Pattenden and Lam (Scheme 20).[95,96] In this tour de force of Stille chemistry, an intermolecular coupling reaction between bis(stannane) **99** and vinyl iodide **100** was used to assemble the cyclization precursor **101**. Removal of the silyl protecting groups gave tetraol **102**, which was



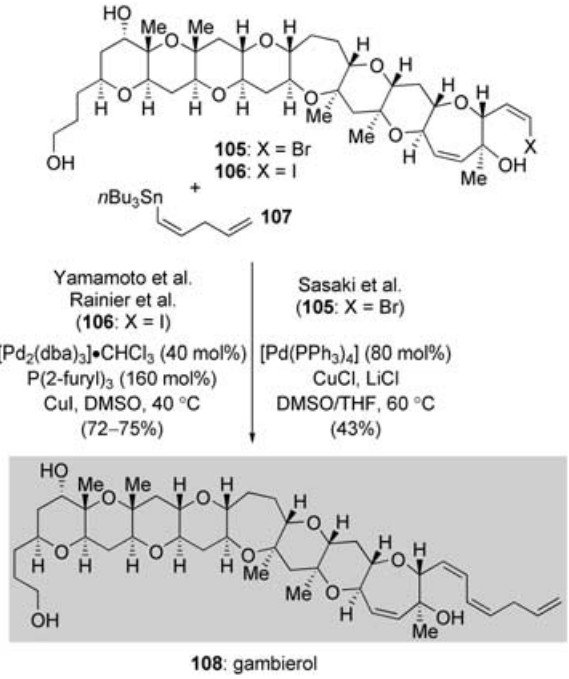
Scheme 19. The use of a fragment-coupling π-allyl Stille coupling in the synthesis of azaspiracid-1 (**98**) (Nicolaou et al., 2004).[94]

treated with catalytic amounts of $[Pd_2(dba)_3]$ and $AsPh_3$ to effect the desired π-allyl–palladium-mediated macrocyclization. The selectivity of the initial coupling between **99** and **100** is particularly noteworthy in view of the number of products that could potentially be formed in this step. Thus, the exclusive formation of the single desired product **101** is the result of discrimination not only between the two stannane units in **99**, but also between the vinyl iodide and allylic acetate moieties embedded within the coupling partner **100**. Thus, remarkably, under the particular conditions employed, coupling is only observed between the less-hindered stannane group in **99** and the more-reactive vinyl iodide group in **100**. Much to the researchers' chagrin, however, the spectroscopic data of the final compound **103** did not match those of the natural product, thus suggesting that the proposed configuration at one or more stereogenic centers was incorrect. Two more years would elapse before the ambiguity surrounding the structure of amphidinolide A was finally resolved, through further chemical synthesis studies by the Trost group (see structure **104**, Scheme 20).[97,98]

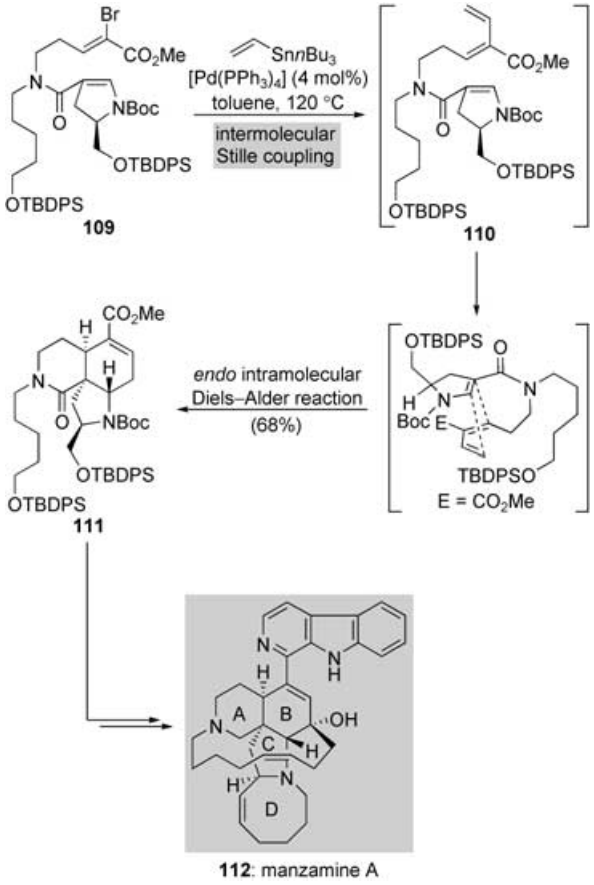
In addition to intramolecular cyclization reactions and fragment-coupling processes, the Stille reaction is also a powerful method for effecting appendage attachments. The utility of this protocol is dramatically manifested in the total syntheses of gambierol (**108**, Scheme 21) by the Sasaki[99] and Yamamoto groups.[100] Both groups employed a Stille reaction in the final step of their respective syntheses to append the delicate triene-containing side chain onto a fully elaborated, protecting-group-free polycyclic ether precursor. The Sasaki group coupled stannane **107** with vinyl bromide **105**, while Yamamoto and co-workers utilized the corresponding vinyl iodide **106**. Although there were significant differences in the reaction conditions employed by the two groups, in both cases the presence of cocatalytic Cu^I salts was necessary to facilitate the transmetalation event and, hence, allow the reactions to proceed at acceptable rates. In both cases, the coupling product was formed with the expected retention of the geometry of the alkene, and the overall efficiency of these processes is quite remarkable, given both the steric encumbrance around the coupling site and the sheer size and complexity of the vinyl halides **105** and **106**. Interestingly, this appendage attachment was postponed by both teams until the last step out of necessity rather than choice. While similar couplings could be effected by both groups without undue difficulty at earlier stages in their syntheses (on compounds related to **105** or **106**, but in which the hydroxy functional groups were protected), the sensitivity of the resulting triene systems thwarted all attempts at the successful liberation of



Scheme 20. a) Sequential $C(sp^2)$–$C(sp^2)$ and $C(sp^2)$–$C(sp^3)$ Stille couplings in the synthesis of the structure originally proposed for amphidinolide A (**103**) (Pattenden and Lam, 2002);[95] b) revised structure of amphidinolide A (**104**) (Trost and Harrington, 2004).[97]



Scheme 21. Appendage of the triene-containing side chain to complete the total synthesis of gambierol (**108**) (Sasaki et al., 2002; Yamamoto and et al.; 2003, Rainier et al., 2004).[99–101]

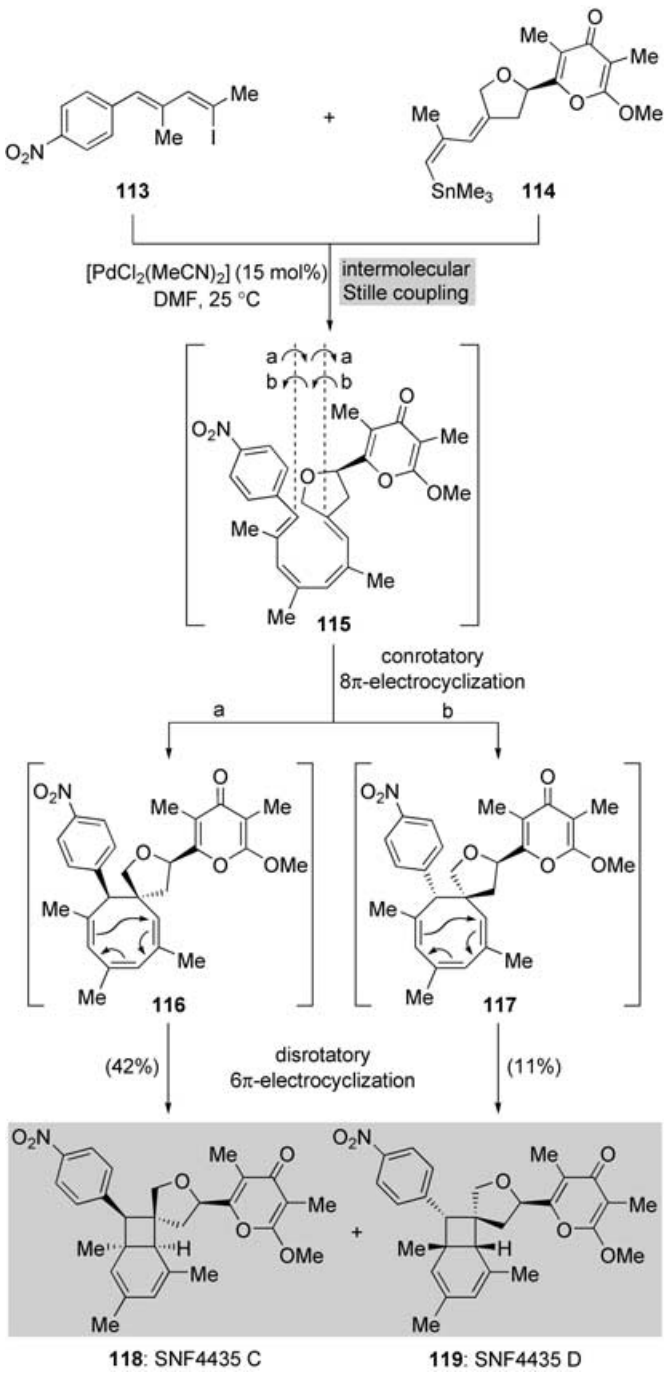


Scheme 22. A tandem intermolecular Stille coupling/intramolecular Diels–Alder approach to the tricyclic core structure of manzamine A (**112**) (Martin et al., 1999).[102]

the said functionality, which, incidentally, highlights once again the sometimes fickle nature of protecting groups in total synthesis. Most recently, Rainier and co-workers have also reported a novel total synthesis of gambierol (**108**).[101] These researchers made use of the conditions employed by the Yamamoto group to install the unsaturated side chain through a Stille reaction, a transformation that was again left until the very end of the synthetic sequence and which, in this case, proceeded in 75% yield.

An extremely useful application of the Stille reaction involves the generation of transient intermediates that can react further, typically in an intramolecular fashion, to produce often dramatic increases in structural complexity in a single operation. Owing to the usually mild conditions of the Stille reaction, intermediates that would otherwise be too fleeting or unstable to be isolated can be produced cleanly and rapidly for subsequent transformations, thus giving rise to powerful cascade sequences. An elegant example of this strategy can be found in the total synthesis of the marine-sponge-derived alkaloid manzamine A (**112**, Scheme 22), by Martin and co-workers, whereby a novel Stille coupling/intramolecular Diels–Alder cascade sequence was employed to furnish the tricyclic core structure of the target molecule.[102,103] Thus, as shown in Scheme 22, treatment of vinyl bromide **109** with vinyl(tri-*n*-butyltin) and a catalytic amount of $[Pd(PPh_3)_4]$ in refluxing toluene initially effected an intermolecular Stille reaction to afford diene **110**, which was suitably disposed to then undergo an *endo*-selective intramolecular Diels–Alder cycloaddition to afford tricyclic compound **111** in 68% yield as a single stereoisomer. In this remarkable transformation, the first notable example of the application of such a cascade process in total synthesis,[104] three new carbon–carbon bonds and three new stereocenters are formed in a single operation, with the relative and absolute stereochemistry of the product **111** being defined by the lone stereocenter in the vinyl bromide starting material **109**.

A number of alternative reaction pathways, besides [4+2] cycloadditions, can be envisaged for the polyene systems generated through Stille fragment-coupling reactions. One such approach that has received considerable attention recently is the development of Stille coupling/electrocyclization cascade processes that provide a rapid entry into polycyclic compounds with high stereospecificity from simple precursor coupling partners. As an astounding example of this principle, we highlight here the recent total syntheses by Parker and Lim[105] of SNF4435 C (**118**) and SNF4435 D (**119**, Scheme 23), two immunosuppressant agents isolated from a culture broth of *Streptomyces spectabilis*.[106] The bicyclo[4.2.0]octadiene core structure of these intriguing natural products bears a striking resemblance to that of the endiandric acids,[107] for which a biosynthetic pathway involving an electrocyclization reaction cascade had been proposed by Black and co-workers[108] and subsequently demonstrated experimentally by the Nicolaou group more than 20 years ago.[109] Therefore, by analogy, it was postulated that the SNF compounds arise through sequential conrotatory



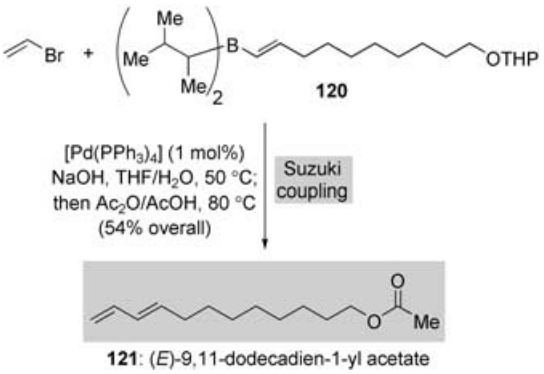
Scheme 23. A tandem Stille fragment coupling/electrocyclization cascade sequence in the total synthesis of SNF4435 C (**118**) and SNF4435 D (**119**) (Parker and Lim, 2004).[105]

8π- and disrotatory 6π-electrocyclizations of the fully elaborated *Z*,*Z*,*Z*,*E*-tetraene **115**, as shown in Scheme 23.[110] The total synthesis of the natural products by Parker and Lim, following this biomimetic strategy, involved as the pivotal step the union of vinyl iodide **113** and vinyl stannane **114** in DMF at room temperature, under the influence of catalytic amounts of $[PdCl_2(MeCN)_2]$, to generate stereoselectively the putative tetraene intermediate **115**. The latter intermediate spontaneously underwent the desired electrocyclization cascade to afford directly a mixture of the target molecules SNF4435 C (**118**) and SNF4435 D (**119**) in 42 and 11 % yields, respectively.[111,112] Interestingly, the ratio of synthetic **118**/**119** produced in this manner (4:1) is not too different from that of the natural products found in Nature (2.3:1). Coupled with the observation that the electrocyclization cascade occurs under ambient laboratory conditions, this result lends credence to the suggestion that this step in the biosynthesis of these compounds is not enzyme-catalyzed.

As we conclude this discussion of the Stille reaction in total synthesis, it is worth mentioning an interesting development in the evolution of metal-mediated cross-coupling reactions of organostannanes with organic electrophiles. Many researchers have reaped the rewards from the beneficial effect of cocatalytic Cu^I salts in accelerating the rate of stubborn Stille coupling reactions, a phenomenon first reported in 1990.[36b] More recently, however, the Liebeskind group pioneered a "palladium-free" Stille reaction protocol in which the coupling of the organostannane and organohalide components is mediated by stoichiometric amounts of Cu^I thiophene carboxylate (CuTC) and proceeds rapidly at or below room temperature.[113] This methodology offers the synthetic chemist a complementary and useful alternative to the traditional palladium-catalyzed Stille coupling processes.[114,115]

4. The Suzuki Reaction

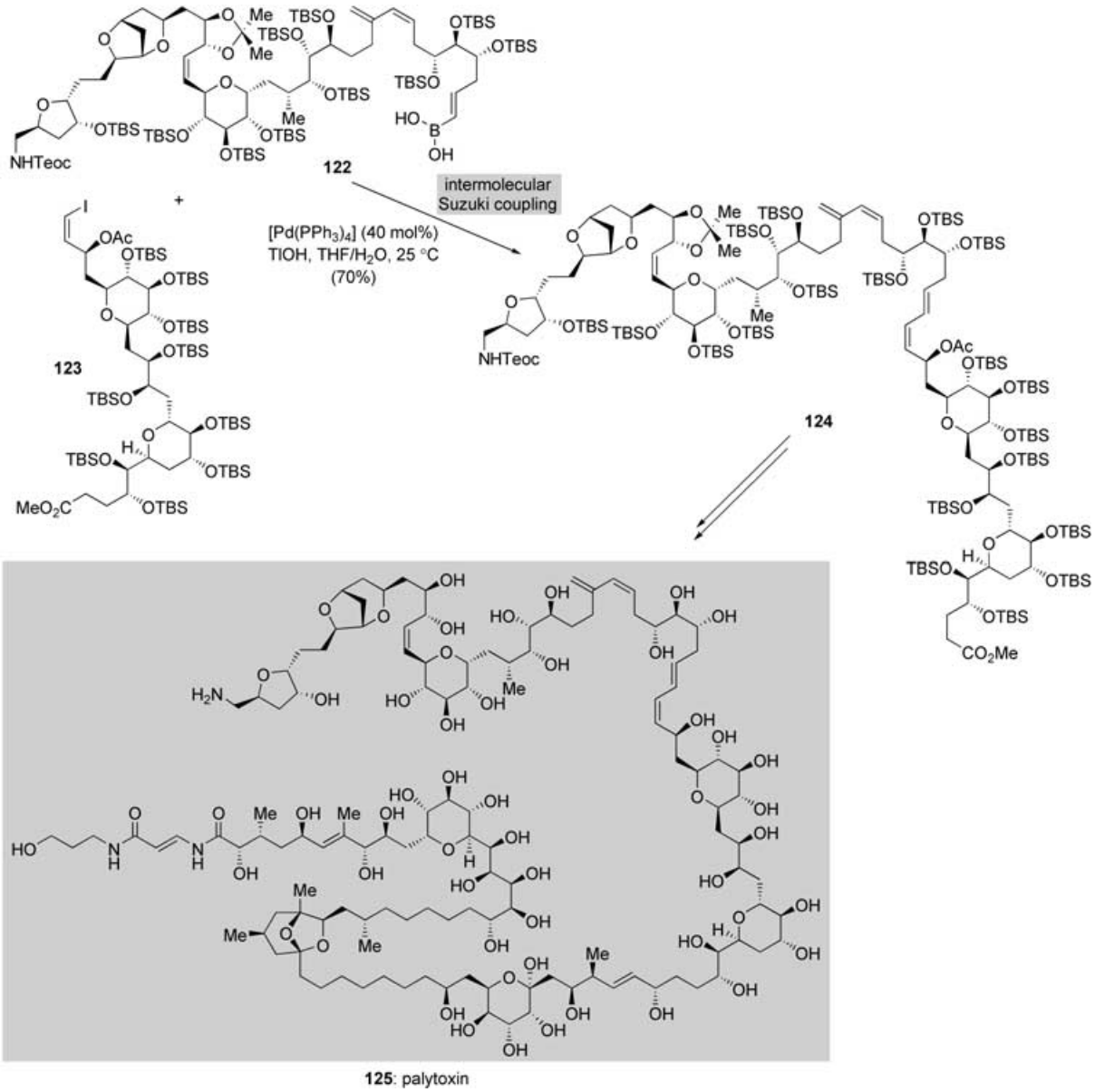
The first application of this cross-coupling reaction in natural products synthesis was reported by Rossi and coworkers in 1981, less than two years after the seminal publications by the Suzuki group,[12] detailing an expedient synthesis of (*E*)-9,11-dodecadien-1-yl acetate (**121**), an insect sex pheromone isolated from *Diparopsis castanea*.[116] Thus, as illustrated in Scheme 24, the targeted compound was prepared by means of the palladium-catalyzed coupling reaction between vinyl borane (*E*)-**120** and vinyl bromide, followed by treatment of the resulting crude product mixture with acetic anhydride in acetic acid to effect the direct conversion of the tetrahydropyranyl protecting group into the corresponding acetate. Although certainly modest by today's standards, this, and other similar early applications demonstrated, for the first



Scheme 24. The first application of a Suzuki reaction in a total synthesis, that of the insect pheromone **121** (Rossi et al., 1981).[116]

time, the potential of such palladium-catalyzed cross-coupling reactions for the synthesis of diene systems under mild conditions, in good yield, and with a high stereospecificity—often lacking in the traditional olefination methods available at the time. Indeed, it was ground-breaking work such as this that paved the way for the remarkable developments in the field that would be forthcoming over the next quarter of a century. It is certainly instructive to compare this early example with the more-recent applications of the Suzuki reaction highlighted in order to more fully appreciate the degree to which the field has flourished in the intervening years.

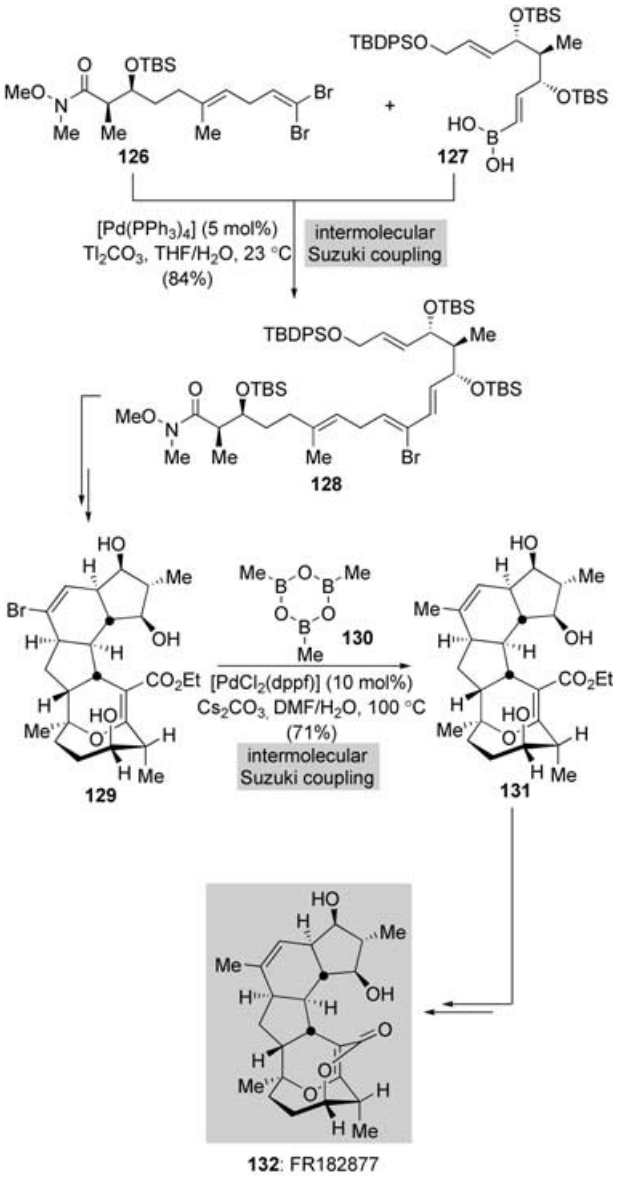
One of the most remarkable applications of the Suzuki reaction in natural products synthesis is found in the synthesis of palytoxin (**125**, Scheme 25) by Kishi and co-workers.[117] This Herculean feat holds a special place in the history of total synthesis in that palytoxin is the largest secondary metabolite synthesized to date, in terms of both molecular weight and number of stereocenters.[118] Of no less significance is the fact that, as is often the case with total synthesis, this mammoth endeavor led to the discovery and development of a number of synthetically useful reactions and protocols, among which was a refinement of the conditions of the Suzuki coupling. The researchers' initial efforts at effecting the union of advanced intermediates **122** and **123** (Scheme 25) under conventional Suzuki coupling conditions were met with frustrating failure; thus, forced by necessity, the team proceeded to investigate methods for increasing the rate of the reaction. Eventually, a synthetic roadblock was turned into an avenue of discovery, as it was found that the use of TlOH as the base had a pronounced effect,[119] to the extent that the desired coupling between **122** and **123** occurred rapidly at ambient temperature upon treatment with a substoichiometric amount of $[Pd(PPh_3)_4]$ (40 mol%) in



Scheme 25. Use of a thallium base in a fragment-coupling Suzuki reaction towards the total synthesis of palytoxin (**125**) (Kishi et al., 1994).[117]

aqueous THF. The product **124** was then elaborated in a series of operations to complete the total synthesis of palytoxin.

The use of thallium bases in Suzuki coupling reactions has since often proved to be superior to many other procedures, particularly with sensitive substrates that would otherwise be labile under prolonged exposure to basic conditions.[120] Evans and Starr made use of this protocol in their recent total synthesis of (−)-FR182877 (**132**, Scheme 26),[121] a structurally and biologically remarkable hexacyclic natural product isolated from a *Streptomyces* species.[122] It was anticipated that the advanced acyclic intermediate **128** could be assembled through the selective Suzuki coupling of boronic acid **127** with the *E* vinyl bromide moiety in 1,1-dibromoolefin **126**. In practice, this coupling was first attempted by following a TlOEt-mediated procedure described by Roush and co-workers.[120] Although the desired product **128** was indeed obtained in 40% yield under these conditions, the reaction



Scheme 26. Suzuki reactions in the total synthesis of FR182877 (**132**) (Evans and Starr, 2002).[121]

was complicated by the unexpected formation of significant amounts (≈20%) of a by-product arising from the reaction of boronic acid **127** with both bromine moieties in dibromide **126**. A number of other bases were then screened, but these reactions were plagued by the formation of a myriad of by-products from competitive decomposition of the starting materials **126** and **127**. To the researchers' delight, however, they ultimately found that the use of Tl_2CO_3 translated to an improved selectivity for the desired coupling product **128** whilst maintaining a reasonable rate of reaction at room temperature and under the optimum coupling conditions ($[Pd(PPh_3)_4]$ (5 mol%), Tl_2CO_3, THF/H_2O 3:1, 23 °C). Compound **128** could be reliably produced in an excellent yield of 84%.

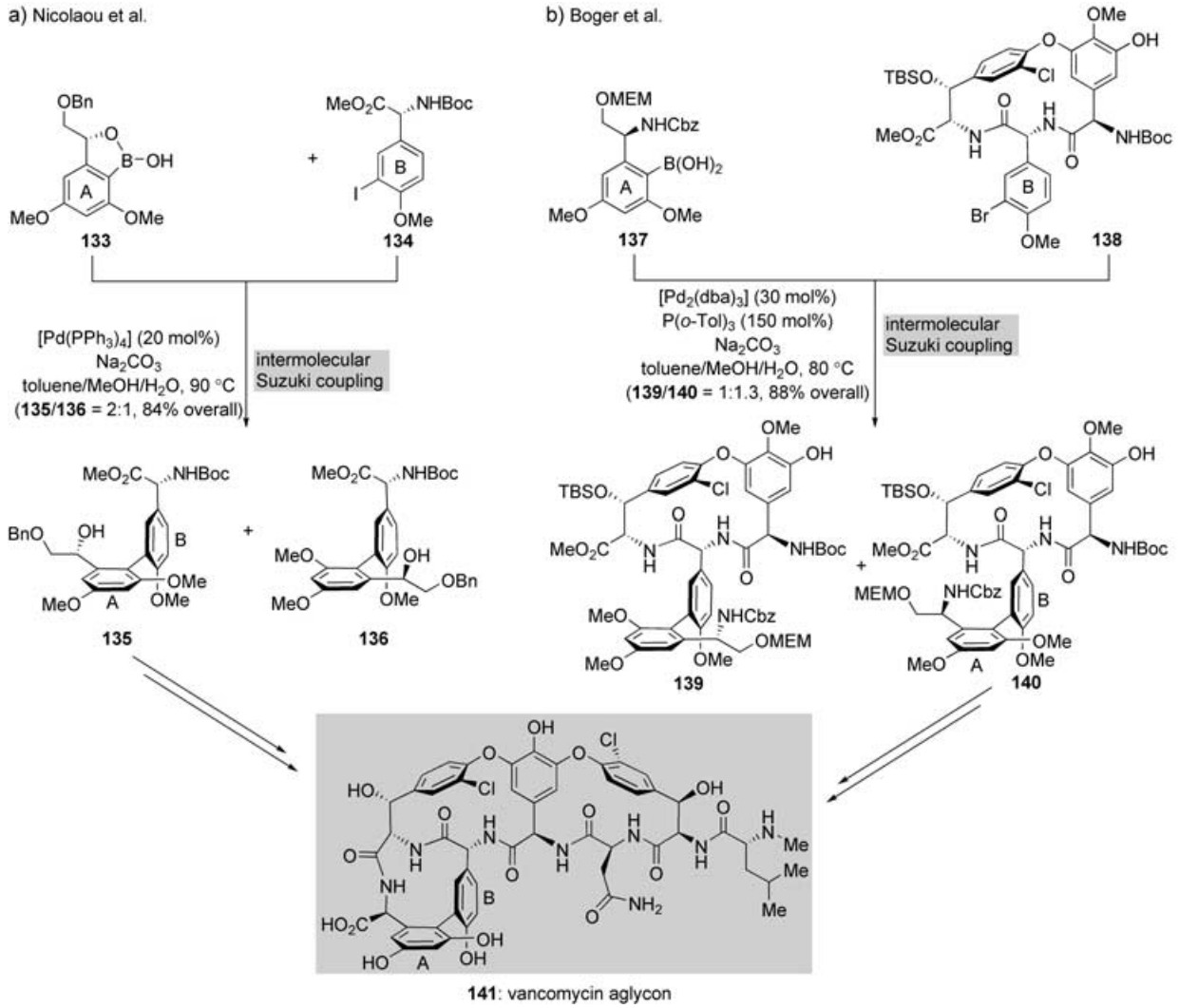
These tribulations serve as an important caveat not only for the Suzuki reaction but, indeed, for most transition-metal-catalyzed carbon–carbon bond-forming processes: a great deal of skill and persistence is often required to unearth the best experimental conditions for a given reaction and these conditions are often very substrate-dependent. Procedures for all types of bond-forming processes that are equally applicable and effective to all substrate types remain an elusive "Holy Grail" in transition-metal-based organic synthesis research. Notably, the selectivity of the formation of compound **128** in this case is due to the faster rate of oxidative addition of the *E* vinyl bromide moiety within the 1,1-dibromoolefin **126** to the Pd^0 species than that of the more sterically hindered *Z* vinyl bromide unit; this general phenomenon which has been employed extensively in natural product synthesis since the pioneering studies of Roush and Riva.[123] Having subsequently converted intermediate **128** into pentacyclic compound **129** through a beautifully orchestrated cascade sequence of transannular Diels–Alder reactions,[124,125] as first suggested by the insightful biosynthetic proposal of Sorensen and co-workers,[126] Evans and Starr were then faced with the task of replacing the remaining bromine atom in intermediate **129** with a methyl group. Again, it proved to be the Suzuki reaction that rose to the challenge. Thus, inspired by the earlier work of Gray and co-workers,[127] the required transformation was effected by treatment of bromide **129** with trimethylboroxine **130**, [$PdCl_2$-(dppf)] (10 mol%), and Cs_2CO_3 in aqueous DMF at 100 °C, yielding compound **131** in 71% yield. Crucially, not only was the presence of the vinylogous ester and the three unprotected hydroxy groups tolerated in this step, but also the delicate and highly strained "anti-Bredt" bridgehead olefin[128] emerged unscathed from the coupling reaction, underlining again the mildness of these protocols.

As touched upon in the previous section, the Suzuki reaction represents one of the, if not the most, widely used methods for aryl–aryl bond formation in modern organic synthesis. Given the ubiquitous occurrence of biaryl systems in a host of scientifically and economically important fields, from natural products to ligands for asymmetric catalysis, pharmaceutical compounds, and nanomaterials, extensive research efforts have recently been expended to develop further the utility and efficiency of the Suzuki reaction within this context. For the purposes of this Review, it is instructive to divide, somewhat arbitrarily, Suzuki aryl–aryl couplings

into two categories: 1) those resulting in biphenyl-type systems, including binaphthyls, and 2) those leading to heteroatom-containing biaryls. Below we highlight selected examples of both categories in total synthesis.

Our first examples of the former category are found in the approaches to the total synthesis of the vancomycin aglycon (**141**, Scheme 27) described first by the Nicolaou group,[129] and subsequently by Boger and his group.[130] The carbon–carbon bond linking the aryl rings A and B would appear to be a prime candidate for formation through Suzuki coupling, and indeed this was the method adopted by both groups.[131] However, an additional degree of complexity which needed to be taken into consideration in planning such a procedure arises from the atropisomerism of the AB ring-coupled product which is enforced by the restricted rotation around the biaryl axis.[132] For instance, the protocol adopted by the Nicolaou group, involving the coupling of boronic acid **133** with iodide **134**, could potentially produce either or both atropisomeric products **135** and **136** (Scheme 27a), and it is not easy to gauge through cursory inspection which of the two compounds would predominate in such a reaction. As events transpired, under the optimum coupling conditions (Na_2CO_3 and $[Pd(PPh_3)_4]$ (20 mol%) in toluene/MeOH/H_2O (20:2:1) at 90 °C) the two stereoisomers **135** and **136** were formed in a 2:1 ratio and in 84% total yield. Gratifyingly, the major reaction product **135** was shown to have the configuration corresponding to that in the target aglycon and, following chromatographic separation from the undesired minor isomer **136**, was subsequently elaborated to complete the total synthesis.

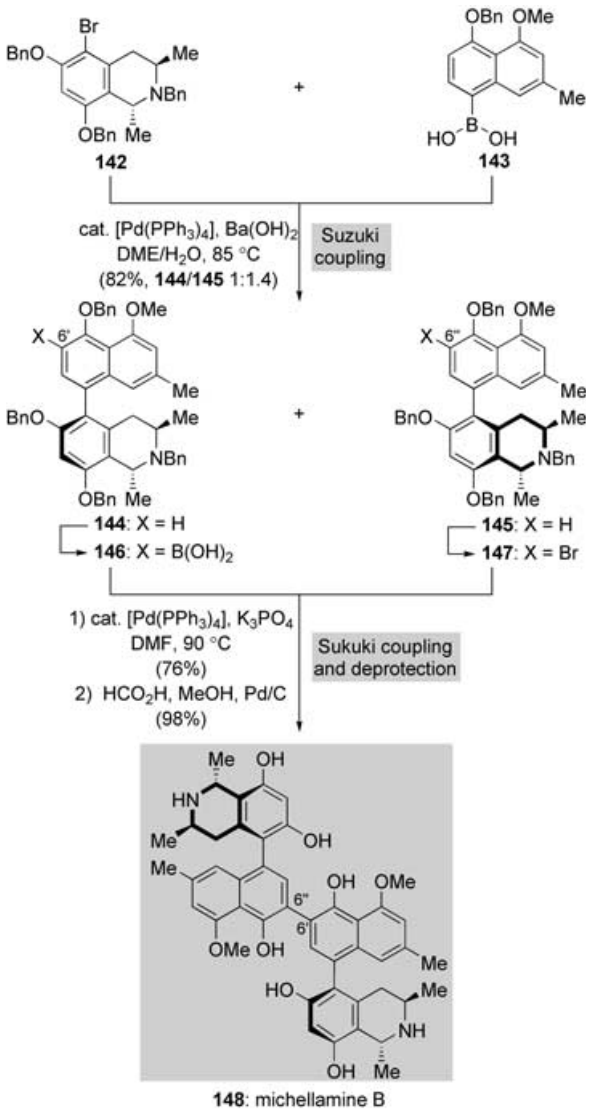
In the strategy adopted by the Boger team, a Suzuki coupling between an A-ring boronic acid unit and a B-ring aromatic halide was also used to forge the crucial biaryl linkage; however, their approach differed conceptually in two respects from that employed by the Nicolaou group. First, a more elaborate B-ring halide **138** (Scheme 27b) was utilized in which the CD-ring bisaryl ether containing macrocycle was already incorporated. Second, it was anticipated that although the inherent axial stereoselectivity of the Suzuki coupling would not initially be controllable, a subsequent thermal equilibration of the atropisomeric products would, perhaps, yield the desired atropisomer preferentially. Indeed, the



Scheme 27. Atropselective approaches to the AB-ring biaryl domain of vancomycin aglycon (**141**). a) Nicolaou et al. 1998;[129] b) Boger et al., 1999.[130]

coupling of boronic acid **137** with bromide **138** yielded a nearly stereorandom mixture of the desired product **140** and the unwanted atropisomer **139** (**139**/**140** ≈ 1:1.3), although the overall yield for the process was again excellent (88%). Given the steric congestion and electron-rich nature of the coupling partners **137** and **138**, the overall efficiency of this Suzuki reaction is all the more remarkable. Key to its success was the use of the catalyst system derived from $[Pd_2(dba)_3]$ (30 mol%) and P(*o*-tolyl)$_3$ (150 mol%). At elevated reaction temperatures P(*o*-tolyl)$_3$ has often been found to be a superior ligand to the more traditional PPh_3 in such couplings. This is true particularly with organic electrophiles that prove recalcitrant towards oxidative addition to Pd^0, since the more bulky phosphine minimizes undesired quaternization of the phosphorus atom by the halide and also results in the formation of the more thermally stable 14-electron [Pd{P(*o*-tolyl)$_3$}$_2$] complexes.[133] After separation of the two products, it was found that the undesired component **139** could be thermally equilibrated upon heating to 120°C in chlorobenzene to provide a mixture of the two atropisomers that was now significantly enriched in the desired stereoisomer **140** (**139**/**140** ≈ 1:3). In this way, the axial selectivity of the Suzuki coupling could be controlled indirectly, with the majority of the material being channeled down the desired pathway. Note that the preexisting C-O-D bisaryl stereogenic axis was not affected by the conditions employed for the thermal equilibration of the AB-ring system in compound **139** owing to the significantly higher activation energy barrier to isomerization of the former unit (30.4 versus 25.1 kcal mol^{-1}).

As another example of the use of the Suzuki coupling to fashion atropisomeric systems, we consider the total synthesis of michellamine B (**148**, Scheme 28), a representative member of a class of homo- and heterodimeric alkaloid natural products that exhibit potent anti-HIV activity,[134] by Dawson and co-workers.[135] The coupling of enantiomerically pure bromotetrahydroisoquinoline **142** with naphthyl boronic acid **143** under the influence of $Ba(OH)_2$ and a catalytic amount of $[Pd(PPh_3)_4]$ in aqueous DME at 85°C yielded a nearly equimolar mixture of the two atropisomeric products **144** and **145** in a combined yield of 82%. The team's choice of the Suzuki reaction to effect this coupling was influenced to no small degree by the previously reported model studies of Hoye and Chen, who had demonstrated the clear superiority of this process over both the Stille reaction and the palladium-catalyzed cross-coupling of zinc derivatives for the union of similarly hindered and electron-rich aryl derivatives.[136] Although this step lacked atropselectivity, the researchers were able to turn this to their advantage on the basis of the configuration of the two coupling products **144** and **145** which corresponds exactly to that found in the "bottom" and "top" halves, respectively, of the targeted natural product. Thus, if a method could be found for joining intermediates **144** and **145** through their respective C6′ and C6″ positions (michellamine B numbering), an expeditious and stereospecific route to the complete michellamine B framework could be at hand. To the researchers' delight, compounds **144** and **145** could indeed be regioselectively converted into the corresponding boronic acid and bromo derivatives **146** and **147**, respectively, and another Suzuki coupling was then employed to effect their

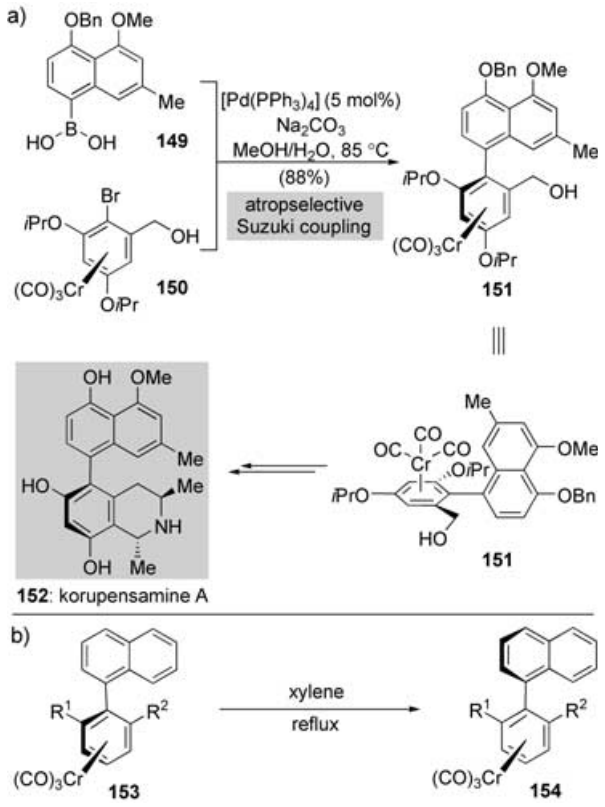


Scheme 28. Sequential Suzuki aryl-aryl couplings in the total synthesis of michellamine B (**148**) (Dawson et al., 1996).[135]

union. Removal of all eight benzyl protecting groups from the coupling product through standard procedures then yielded the targeted compound **148**.[137] The coupling of **146** and **147** was initially attempted under the conditions employed earlier in the synthesis, giving the product in 61% yield. However, it was subsequently discovered that the yield for this second merger could be increased to 76% under non-aqueous conditions (cat. $[Pd(PPh_3)_4]$, K_3PO_4, DMF, 90°C), which is somewhat surprising given not only the generally recognized tolerance of water, but also its often beneficial effect in the Suzuki reaction. Note that atropisomerism about the newly formed C6′–C6″ bond is not observed, as rotation about this bond is evidently not sufficiently hindered by the steric environment.

An interesting approach to this issue of atropisomerism in biaryl synthesis, championed in particular by the Uemura group, involves the use of planar chiral tricarbonyl-(arene)chromium complexes[138] in palladium-catalyzed cross-coupling reactions.[139] An illustrative example of this

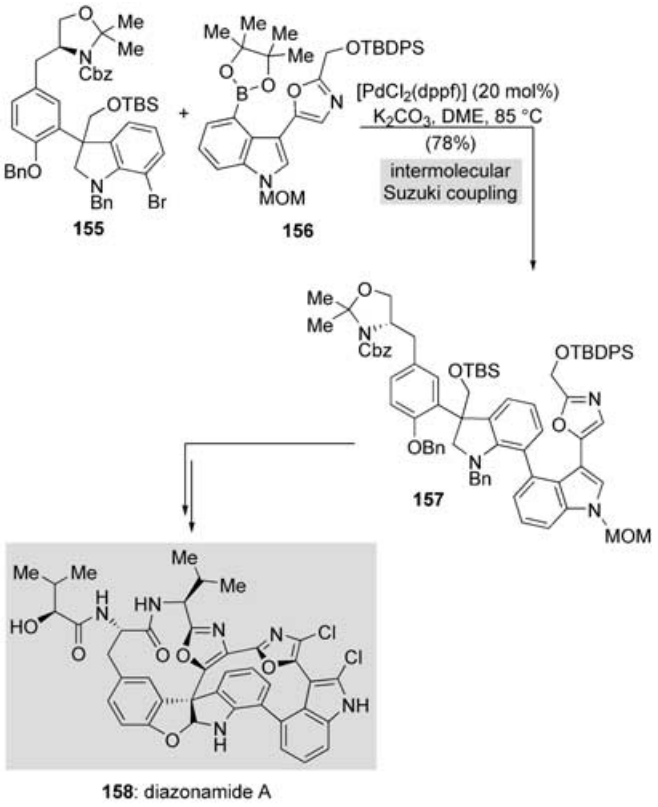
strategy is found in the synthesis of the alkaloid korupensamine A (**152**, Scheme 29),[140] a molecule that can be formally considered as the monomeric unit of the michellamine alkaloids alluded to above. Thus, as shown in Scheme 29a, the Suzuki coupling of naphthyl boronic acid **149** with enantiopure tricarbonylchromium-complexed aryl bromide **150** led to the smooth formation of biaryl system **151** in 88% yield and as a single stereoisomer. The sense of stereochemical induction in the formation of the atropisomeric biaryl axis in the product **151** is dictated by the preexisting chirality inherent in the starting tricarbonylchromium complex **150**, with the product shown in Scheme 29a having the same configuration as that found in korupensamine A (**152**). This result had, in fact, been anticipated by the research team on the basis of previous studies on similarly highly stereoselective cross-couplings, although the sense of stereochemical induction was found to be remarkably dependent on the nature of the *ortho*-substituent(s) on the tricarbonyl(arene)chromium complex.[141] Intermediate **151** was then elaborated to give the target molecule **152** in a series of steps that maintained the stereochemical integrity of the biaryl axis. Intriguingly, the coupling reaction (**149** + **150** → **151**) yields the less thermodynamically stable isomeric product, in which the axial configuration is such that the naphthyl ring is oriented in the same direction (*syn*) as the tricarbonylchromium unit, and hence suffers from severe steric interactions (as in **151**). To rationalize this counter-



Scheme 29. Atropselective Suzuki coupling of a planar chiral tricarbonyl(arene)chromium complex in the enantioselective synthesis of korupensamine A (**152**) (Uemura et al., 2000).[140]

intuitive phenomenon, it was proposed that isomer **151** represents the kinetic reaction product, which is not subsequently equilibrated to the thermodynamic isomer under the reaction conditions. It was also shown that a number of such kinetic coupling products could indeed be subsequently isomerized to generate the thermodynamically more stable *anti* atropisomers (i.e. **153** → **154**, Scheme 29b), thus enabling the selective formation of either biaryl atropisomer from a single chiral chromium complex. While these results are indeed impressive, the utility of this methodology is mitigated somewhat by the fact that the synthesis of the enantiopure (or enantioenriched) chiral chromium complexes is often far from trivial. Indeed, for all the enabling power of transition-metal-catalyzed reactions discussed herein, synthetic chemists are still singularly lacking truly general methods for the selective synthesis of biaryl atropisomers.

Nevertheless, despite these current limitations, the Suzuki reaction remains an extraordinarily effective and powerful method for aryl–aryl bond formation, particularly with sensitive, densely functionalized substrates and for the construction of sterically congested systems. A case in point is the second-generation synthesis of the revised structure[142] of diazonamide A, reported by the Nicolaou group in 2003.[143] As shown in Scheme 30, indoline bromide **155** and indole boronate ester **156** were successfully merged by employing a catalytic amount (20 mol%) of [$PdCl_2$(dppf)] in the presence of K_2CO_3 in anhydrous degassed DME at 85 °C. The advanced intermediate **157** contains all but one of the aromatic systems destined to be incorporated in the final target structure **158**,

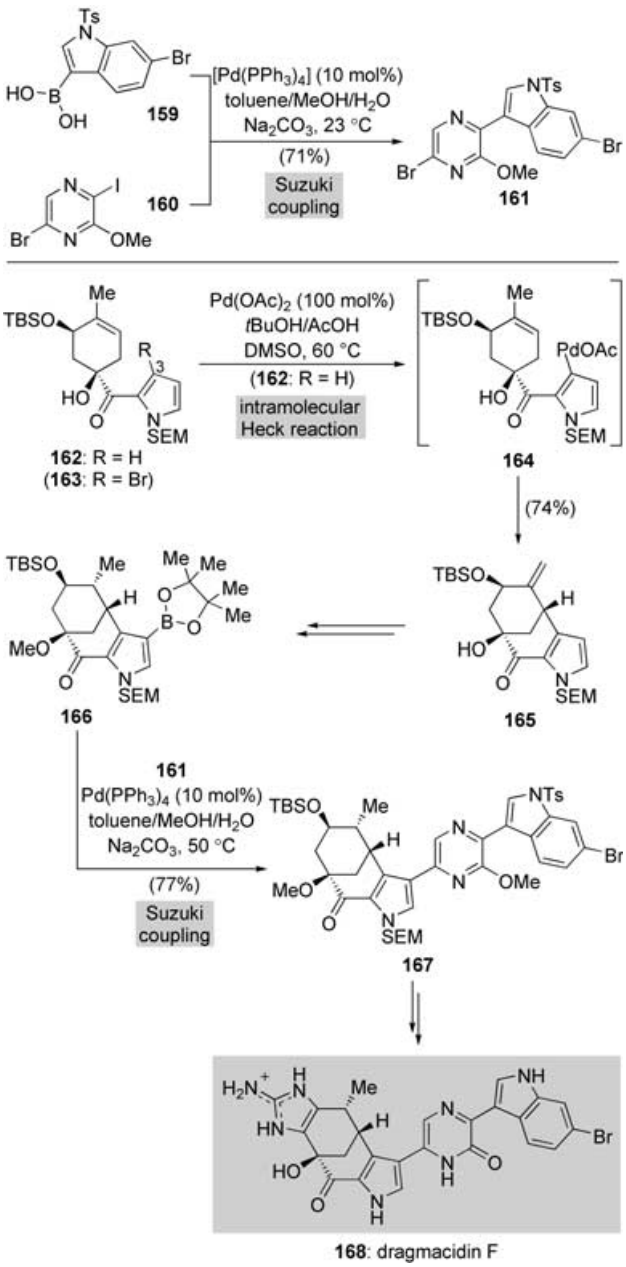


Scheme 30. Formation of a biaryl system through a Suzuki coupling in the total synthesis of diazonamide A (**158**) (Nicolaou et al., 2003).[143]

thus illustrating both the degree of synthetic convergence (and hence efficiency) and the rapid increase in molecular complexity that are possible through the application of the Suzuki reaction and related processes.[144,145]

Palladium-catalyzed reactions have also revolutionized the synthesis of heteroatom-containing biaryl systems, with the Suzuki reaction being at the forefront of this new technology.[146] Over the last 25 years there has been a fundamental shift away from the generation of such motifs through iterative (and often cumbersome) heterocyclic ring syntheses by classical cyclization and dehydration reactions, towards the direct palladium-catalyzed union of preformed, and often fully functionalized, heterocycles.[147] As an illustrative example, such coupling reactions were used not once, but twice in the recent elegant synthesis of dragmacidin F (**168**, Scheme 31) by the Stoltz group.[148] In an exquisitely marshaled sequence of Suzuki coupling events, pyrazine derivative **160** was first coupled with indolyl boronic acid **159** to afford dibromide **161**, which was subsequently coupled with the advanced pyrrole boronate ester fragment **166** to complete a rapid synthesis of the core heptacyclic framework of the targeted natural product. The selectivity of these transformations is outstanding, with the required indolyl bromide unit surviving both transformations intact. This selectivity is the combined result of 1) the faster rate of oxidative addition of pyrazine carbon–halogen bonds to Pd^0 species than that of the corresponding benzenoid carbon–halogen bonds, and 2) the greater susceptibility of carbon–iodine bonds over the corresponding carbon–bromine bonds to oxidative addition. An important finding on the part of the researchers was that precise control of the temperature at which these couplings were conducted was essential to maintain the desired selectivity. Interestingly, the reason for the adoption of this Suzuki coupling strategy was that the team had been thwarted in their earlier attempts to generate similar polycyclic structures through the construction of the central pyrazine ring by classic cyclocondensation chemistry of advanced intermediates, owing to the recalcitrance of the reacting partners to undergo the required cyclization processes.[149] Palladium-mediated chemistry was also instrumental in permitting the synthesis of the pyrrole coupling partner **166**, in which a key carbon–carbon bond-forming step was the oxidative Heck cyclization of monosubstituted pyrrole precursor **162** to produce the congested pyrrole-fused bicyclic structure **165** in good yield and as a single regio- and stereoisomer. Although this transformation, of which we saw a related example in the synthesis of okaramine N (**55**; see Section 2, Scheme 11) described earlier, could not be made catalytic in palladium, it is nevertheless particularly remarkable in that it effects the C–H functionalization of the deactivated C3 position of the acyl pyrrole unit. Furthermore, this direct cyclization of compound **162** (R = H) was found to be superior in terms of both regioselectivity and overall yield to the intramolecular Heck reaction of the corresponding bromide **163** (R = Br).

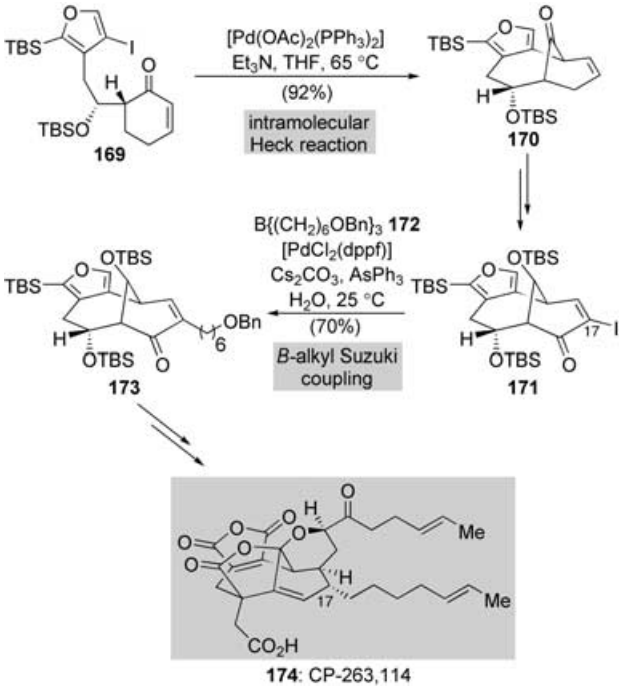
An important trend in the Suzuki reaction over the last 15 years has been the development and application of what have become known as *B*-alkyl Suzuki–Miyaura coupling reactions. In this process an alkyl group (i.e. sp^3-hybridized C atom), as opposed to the more traditionally used vinyl or aryl groups, is transferred from the organoborane component during the palladium-catalyzed coupling process with vinyl or aryl halides or triflates. Compared to the aforementioned $C(sp^3)$–$C(sp^2)$ Stille reactions,[150] *B*-alkyl Suzuki–Miyaura couplings have a much broader scope in that a potentially vast range of alkyl boranes (typically prepared through the regio- and chemoselective hydroboration of readily available alkene precursors and used in situ) can be employed in the reaction.[151] While the Suzuki coupling reactions illustrated so far in this section have been concerned with the assembly of diene systems and biaryl structural motifs, the *B*-alkyl Suzuki–Miyaura reaction is typically, though by no means always,



Scheme 31. Multiple use of palladium-catalyzed carbon–carbon bond-forming reactions in the total synthesis of dragmacidin F (**168**) (Stoltz et al., 2004).[148]

used for the stereoselective generation of isolated alkene units. The first examples of this process were reported by Miyaura and Suzuki in 1986;[152] since its pioneering application in the total synthesis of (+)-quadrilure in 1990 by the Mori group,[153] the *B*-alkyl Suzuki–Miyaura coupling has developed into a versatile and powerful tool in total synthesis.[154] In particular, and as we shall see below, this reaction has recently emerged as a viable alternative to the ring-closing-metathesis of olefins as a method for ring formation. In conjunction with this process, it is worth recalling here, that in an interesting reversal of reactivity, great progress has been made even more recently in the development of practical methods for the coupling of alkyl (i.e. sp^3) halides with vinyl and aryl (i.e. sp^2) organoboron species, which involve the reversal of reactivity of the two reactive ends of the coupling partners.[16]

During the course of their epic,[155] and ultimately successful[156] approach to the total synthesis of the architecturally unique nonadride natural products CP-225,917 and CP-263,114,[157] Danishefsky and co-workers employed a *B*-alkyl Suzuki–Miyaura coupling reaction to append a side chain at C17 of the functionalized tricyclic α-iodoenone **171** (Scheme 32). Thus, the treatment of **171** with trialkylborane **172** in the presence of Cs_2CO_3 and catalytic amounts of [$PdCl_2$(dppf)] and $AsPh_3$ in aqueous DMF led to smooth coupling, generating the alkylated product **173** in 70% yield. First introduced by Johnson and co-workers in 1993,[158] these particular coupling conditions have been found by many researchers to be quite mild and effective for the *B*-alkyl Suzuki–Miyaura reaction, and have subsequently found widespread use in its application. [$PdCl_2$(dppf)] is often shown to be the catalyst of choice for these couplings, as it has

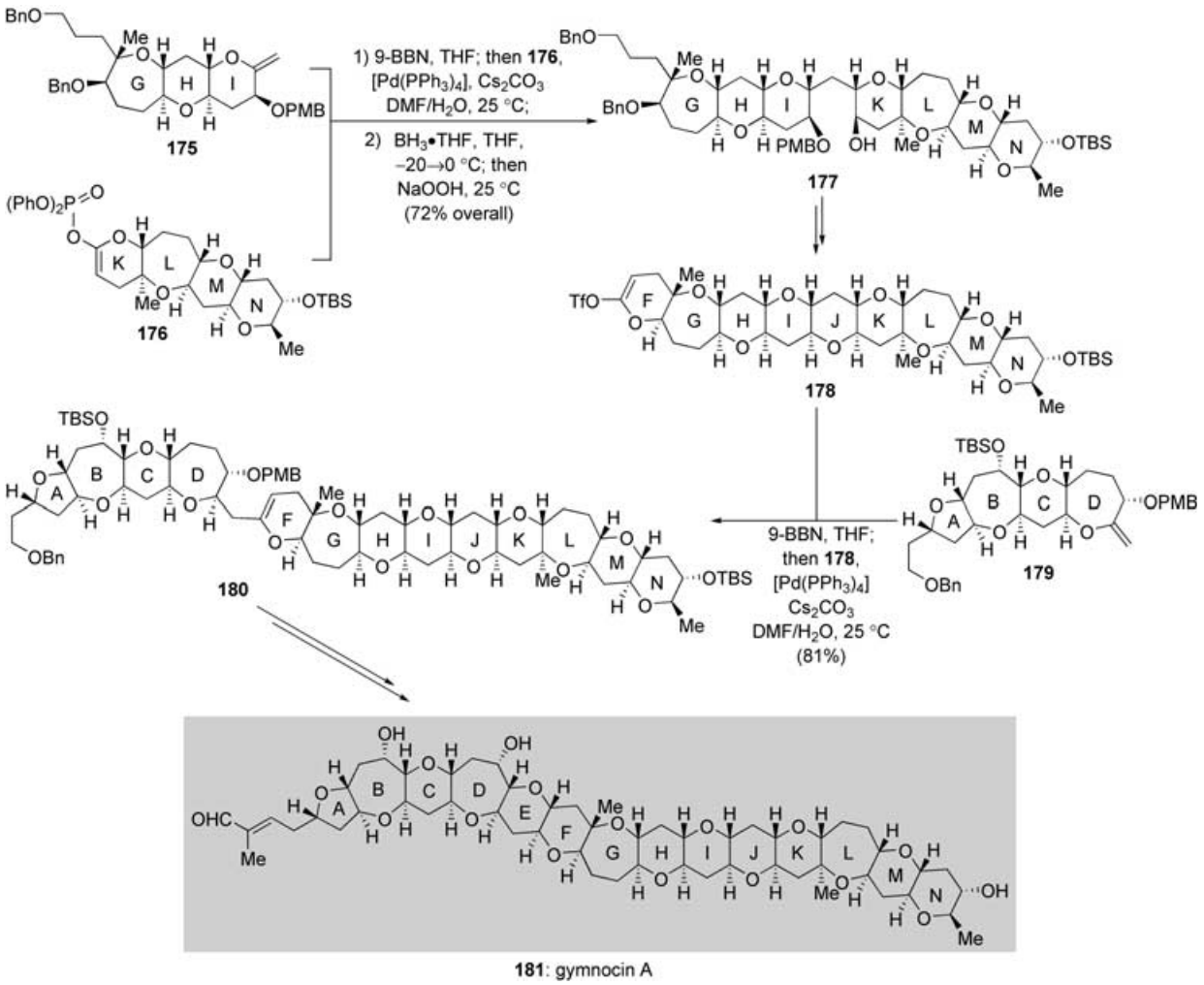


Scheme 32. Sequential intramolecular Heck and intermolecular *B*-alkyl Suzuki reactions in the total synthesis of CP-263,114 (**174**) (Danishefsky et al., 2000).[156]

been suggested that the rate of undesired β-hydride elimination from the transmetalated [Pd(dppf)(alkyl)(vinyl)] complex is slowed down by the presence of the large bidentate ligand,[159] whilst the rate of the product-forming reductive elimination is concurrently enhanced owing to the large bite angle of the ligand.[160] The α-iodo enone coupling partner **171** was prepared through a short sequence of reactions from tricyclic compound **170**, which was itself synthesized by another palladium-catalyzed bond-forming reaction, namely the intramolecular Heck cyclization of the *anti* aldol precursor **169** (Scheme 32). Exposure of compound **169** to a catalytic amount of [$Pd(OAc)_2(PPh_3)_2$] in THF in the presence of Et_3N at 65 °C led to clean, if somewhat slow (4 days were required for the completion of the reaction), cyclization to generate the desired tricyclic compound **170** in 92% yield. The remarkable regioselectivity of this reaction is noteworthy in view of the fact that coupling was observed exclusively between the furan ring and the α-carbon atom of the α,β-unsaturated system, with no trace of the alternative ring closure mode, that is, between the furan ring and the β-carbon atom. This selectivity is presumably a consequence of subtle, yet pivotal, differences between the molecular arrangements (and hence relative energies) required for the two different modes of 1,2-insertion, with the former (α-carbon attack) proving much more facile.

The power and utility of the *B*-alkyl Suzuki–Miyaura reaction in fragment-coupling processes is dramatically manifested in the recent total synthesis of gymnocin A,[161] a member of the polycyclic ether class of marine natural products associated with the notorious "red-tide" phenomena,[162,163] by Sasaki and Tsukano.[164,165] The salient features of the highly convergent synthetic strategy adopted by the Sasaki team are highlighted in Scheme 33. Thus, exocyclic enol ether **175** was subjected to a regio- and diastereoselective hydroboration with 9-BBN and, without purification, the resulting alkyl borane adduct was treated with cyclic ketene acetal phosphate **176** under Johnson conditions to afford, following the regio- and steroselective hydroboration/oxidation of the resulting trisubstituted enol ether, coupled product **177** in good overall yield (72%). Elaboration of the coupling product **177** then gave cyclic ketene acetal triflate **178**, which entered into the second key *B*-alkyl Suzuki–Miyaura fragment coupling reaction, this time with the alkyl borane species derived from hydroboration of the ABCD-ring exocyclic enol ether unit **179**, to give compound **180** in 81% yield. Intermediate **180** was then advanced further to complete the total synthesis of gymnocin A (**181**) in short order. Given the structural complexity and sheer size of the individual fragments, the remarkable efficiency of this second cross-coupling bears testament to the power and reliability of this process in total synthesis. The Sasaki group has developed this efficient approach to polyether construction, and through its application have accomplished the total synthesis of a number of other members of this class of marine natural products.[166]

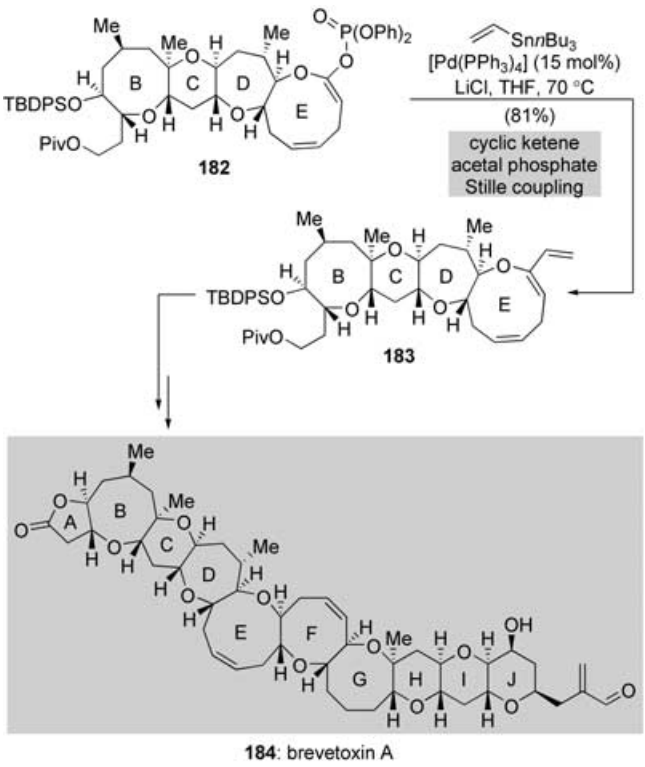
The use of cyclic ketene acetal phosphates in palladium-catalyzed cross-coupling reactions was pioneered by the Nicolaou group,[167] who was subsequently the first to apply this methodology in the total synthesis of the polyether



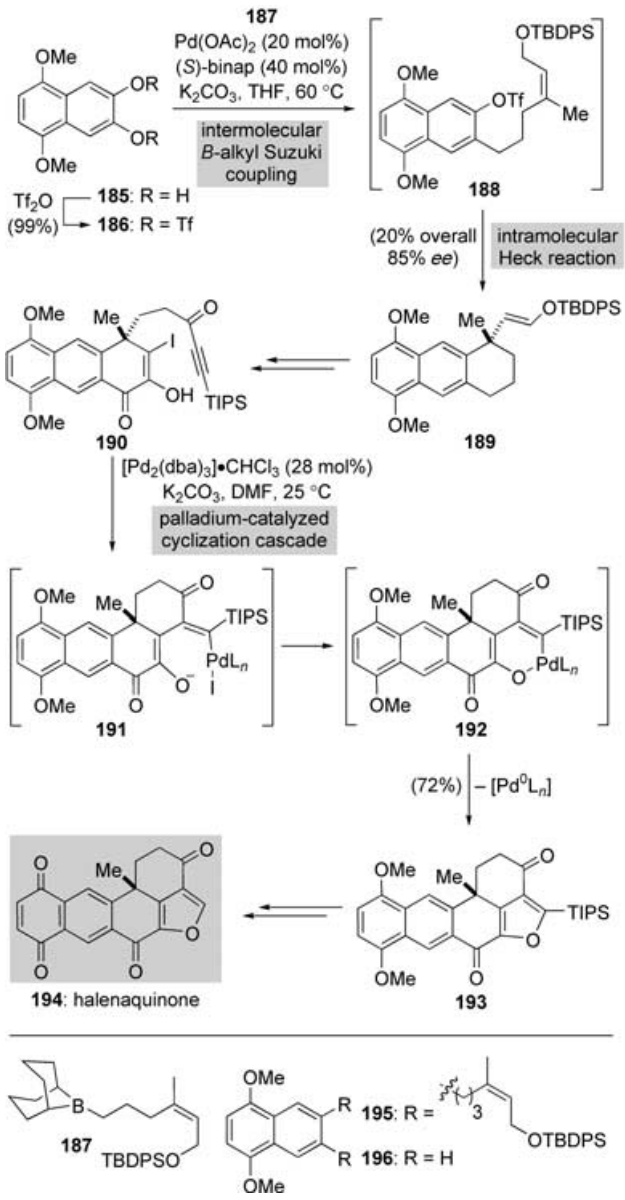
Scheme 33. Intermolecular *B*-alkyl Suzuki–Miyarua couplings in the total synthesis of gymnocin A (**181**) (Sasaki et al., 2003).[161]

marine neurotoxin brevetoxin A (**184**, Scheme 34).[168] They later expanded the scope of this technology to encompass the corresponding cyclic aminal phosphates.[169] Cyclic ketene acetal (or aminal) phosphates, readily prepared from the corresponding lactones (or lactams) by treatment with a strong, non-nucleophilic base followed by quenching with diphenylphosphoryl chloride, smoothly enter into a variety of palladium-catalyzed carbon–carbon bond-forming reactions, including the Stille, Suzuki, and Sonogashira reactions, as well as into carbonylative processes. Furthermore, cyclic ketene acetal phosphates often prove to be superior substrates for these palladium-catalyzed reactions than the corresponding cyclic ketene acetal triflates, owing to the lower cost of the reagents involved in their preparation and their higher stability.[168,169]

Shibasaki and co-workers made use of a number of novel palladium-catalyzed transformations in their elegant synthetic approach to halenaquinone (**194**, Scheme 35) and related pentacyclic marine natural products.[170] The team had previously secured a somewhat arduous synthetic route from the symmetrical catechol derivative **185** to the advanced tricyclic compound **189** in which an intermolecular *B*-alkyl Suzuki–Miyaura coupling reaction and an intramolecular Heck cyclization were used as the carbon–carbon bond-forming steps between a number of protection/deprotection operations. They subsequently realized a significant upgrade in elegance and efficiency in their route to tricyclic system **189** through the application of an unprecedented intermolecular *B*-alkyl Suzuki–Miyaura coupling/intramolecular asymmetric Heck cyclization cascade sequence to fuse the six-membered ring to a symmetrical bis(triflate) precursor **186**, whilst concomitantly installing the benzylic quaternary stereocenter. The desired product **189** could indeed be formed in a single operation from bis(triflate) **186** by treatment with borane **187**,[171] K_2CO_3, and catalytic amounts of $Pd(OAc)_2$ (20 mol%) and (*S*)-binap (40 mol%) in THF at 60 °C. Tricyclic compound **189** was formed with good enantioselectivity (85% *ee*); however, the overall yield for this process was rather low (20%) and, despite the researchers' best efforts, could not be increased further. Major by-products in this reaction were identified as the reduced compound **196** and the double Suzuki coupling product **195**, with the propensity for formation of the latter likely being due to the generally lower rates of Heck reactions than those of Suzuki couplings. Intriguingly, it was found that the use of achiral ligands resulted in much better conversion into (racemic)



Scheme 34. Pioneering use of cyclic ketene acetal phosphates as organic electrophiles in a palladium-catalyzed cross-coupling reaction, in the total synthesis of brevetoxin A (**184**) (Nicolaou et al., 1998).[168]

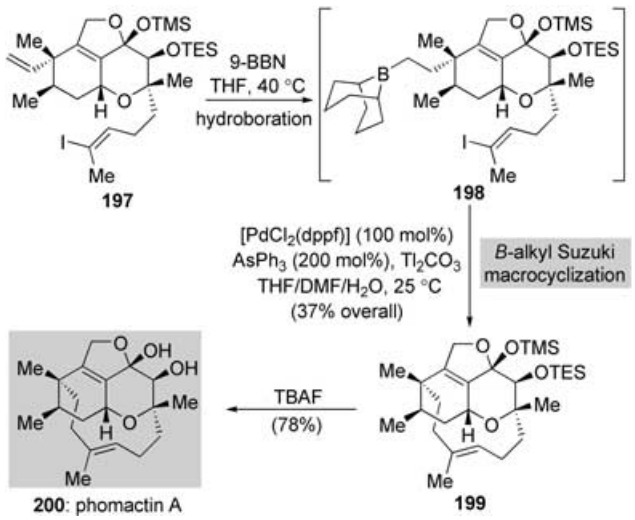


Scheme 35. Novel palladium-catalyzed cascade processes in the total synthesis of halenaquinone (**194**) (Shibasaki et al., 1996).[170]

tricyclic compound **189**. Thus, replacing the (*S*)-binap with $AsPh_3$ more than doubled the yield of this cascade process from 20 to 46%. After the elaboration of cyclization product **189** to give acetylenic ketone **190**, another novel palladium-catalyzed cyclization cascade reaction was employed to append the final two rings of the pentacyclic structure, including the highly substituted furan ring, in a single step to give diketone **193**.[172] A few more steps then completed the total synthesis of halenaquinone (**194**). Hence, two palladium-catalyzed reactions resulted in the creation of four new bonds ($3 \times$ C–C), three new rings, and, enantioselectively, a quaternary stereocenter.[173]

The intramolecular variant of the *B*-alkyl Suzuki–Miyaura reaction also proves to be a valuable, if still relatively uncharted and underutilized, addition to the repertoire of methods available to the synthetic chemist for ring construction. In particular, this intramolecular cross-coupling protocol allows for the highly regio- and stereocontrolled formation of endo- and exocyclic alkene systems of defined double-bond geometry, especially in the fusion of new rings to preexisting cyclic systems. Although the first such applications reported in 1989 were directed toward the construction of five- and six-membered ring systems,[174] more recently the potential of this reaction in the formation of a wider range of ring sizes, in synthetically useful yields, has begun to be tapped.

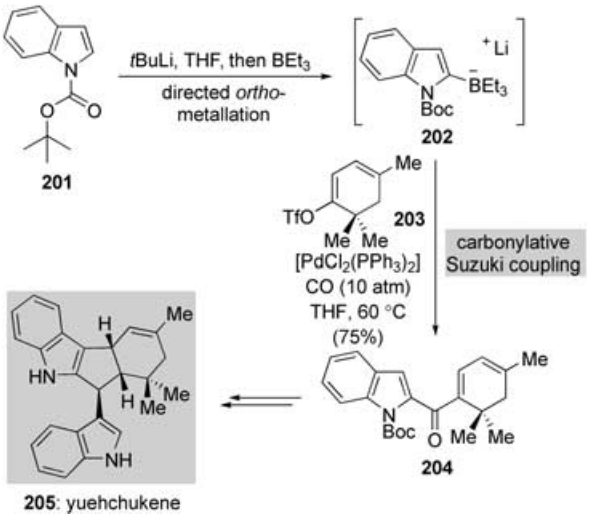
One of the most sophisticated applications in total synthesis of the intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction to date was reported by Halcomb and his group, who employed it to forge the 12-membered macrocyclic ring of the terpenoid natural product phomactin A (**200**, Scheme 36).[175] Once the fully elaborated tricyclic precursor **197** had been prepared, the major remaining synthetic hurdle facing the team was the construction of the macrocycle in the presence of the other sensitive functionalities within the molecule, particularly the protected dihydroxyfuran motif. To their delight, they were able to effect the selective regiocontrolled (anti-Markovnikov addition) hydroboration of the terminal alkene in the presence of both the tri- and tetrasubstituted alkene systems upon treatment of compound **197** with 9-BBN in THF at 40 °C to afford the primary trialkyl borane intermediate **198**. Without purification, this intermediate was then slowly added to a mixture of $[PdCl_2(dppf)]$ (100 mol%), $AsPh_3$ (200 mol%), and Tl_2CO_3 in a THF/DMF/H_2O solvent system to afford the desired transannular macrocyclization product **199** in 37% yield. The



Scheme 36. Use of the *B*-alkyl Suzuki–Miyarua coupling to effect a macrocyclization in the synthesis of phomactin A (**200**) (Halcomb and Mohr, 2003).[175]

subsequent unmasking of the two protected hydroxy groups then completed the total synthesis. Although the yield of this key cyclization is moderate at best, and a high "catalyst" loading is required, it nevertheless sets a new standard for such processes. Note that only the (desired) primary alkyl group is transferred from the boron atom (as its corresponding "ate" complex) during the transmetalation event in the catalytic cycle, owing to the much faster rate of transmetalation relative to that with the secondary alkyl groups on boron. Indeed, reports of synthetically useful *B*-alkyl Suzuki–Miyaura coupling reactions involving secondary alkyl borane species are scarce.[176] The researchers found that the choice of base was crucial to the efficiency of the reaction, and that the use of Tl_2CO_3 (rather than Cs_2CO_3 as in the original Johnson conditions) gave the best results. Presumably, the use of the thallium base increases the rate of the desired macrocyclization to a greater degree than it does the rates of competitive, undesired, intermolecular oligomerization pathways, a factor also influenced by the use of high dilution conditions.[177] The macrocyclization event was postponed until a late stage in the synthesis because of the anticipation that the rigid structure of the tricyclic core would bias the system towards the desired intramolecular process. As expected, the cyclized product **199** was formed exclusively as a single stereoisomer and with retention of configuration of the trisubstituted alkene moiety. This potential for control over olefin geometry in macrocyclization reactions compares favorably with that encountered in the corresponding ring-closing olefin-metathesis processes in which mixtures of isomers are often obtained and the stereochemical course of ring closure is generally not predictable. Thus, the intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction offers a complementary approach to metathesis-based protocols.

In a similar manner to the carbonylative Stille reactions described earlier, the palladium-catalyzed, three-component cross-coupling of organic electrophiles, carbon monoxide, and organoborane compounds also provides an efficient means for the synthesis of unsymmetrical ketones from simpler precursor building blocks.[178] This procedure was applied as one of the key steps in an expedient synthesis of the bisindole alkaloid yuehchukene (**205**) by Ishikura and co-workers,[179] in which a carbonylative Suzuki reaction was used to assemble the 2-indolyl ketone intermediate **204** rapidly (Scheme 37).



Scheme 37. Three-component, carbonylative Suzuki coupling in the total synthesis of yuehchukene (**205**) (Ishikura et al., 1996).[179]

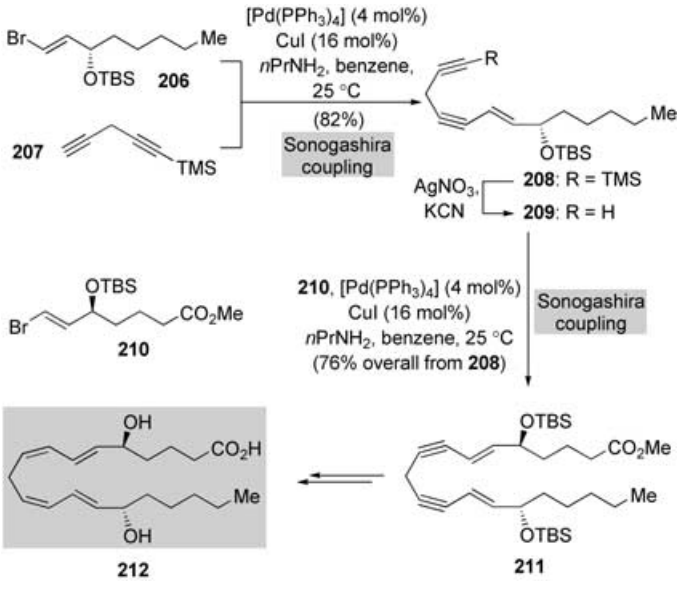
Directed *ortho*-metalation[180] of *N*-Boc-indole (**201**) followed by treatment with triethylborane led to the formation of lithiated "ate" complex **202**, which was not isolated but, instead, added directly to a solution of vinyl triflate **203** and a catalytic amount of $[PdCl_2(PPh_3)_2]$ in THF at 60 °C under a pressurized (10 atm) carbon monoxide atmosphere to effect the desired coupling in good overall yield. It will be noticed that, unlike the other examples of the Suzuki reaction highlighted so far, no additional base is required in the cross-coupling step, since the negatively charged, four-coordinate boron "ate" complex that is required to undergo the transmetalation step in the catalytic cycle is already present. The use of carbon monoxide under high (or at least greater than atmospheric) pressure has often been found to be a convenient method for suppressing a major side reaction sometimes encountered in carbonylative palladium-catalyzed reactions, namely the direct coupling of an organic electrophile and an organometallic component without carbon monoxide insertion.[181] A number of vinyl and aryl halides and triflates were shown to be viable coupling partners in this carbonylation process, enabling the synthesis of a variety of 2-indolyl ketone derivatives.[182] This method for the regioselective acylation at C2 of indoles is complementary to more traditional Friedel–Crafts-type acylations, which result in the preferential functionalization at C3.[183]

5. The Sonogashira Reaction

The Sonogashira reaction has emerged in recent years as one of the most general, reliable, and effective methods for

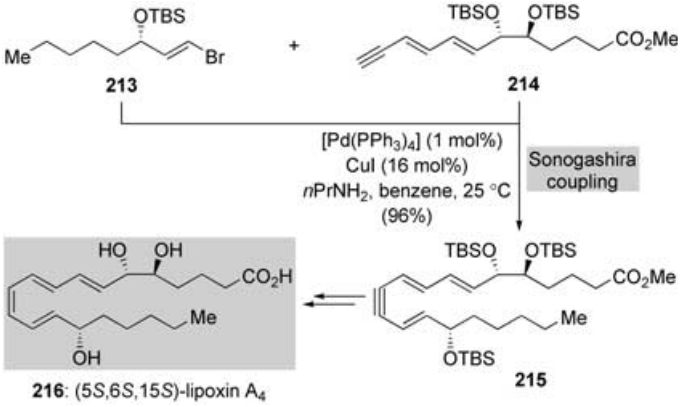
the synthesis of substituted alkynes.[184] The palladium-catalyzed coupling of a number of preformed metal acetylides (e.g. Zn,[185] Mg,[186] B,[187] Al,[188] and Sn[189] derivatives) with organic electrophiles also provides a useful access to substituted alkynes. Nevertheless, the Sonogashira protocol (employing cocatalytic Cu^I salts) is the most widely used of the palladium-catalyzed alkynylation methods, particularly in the context of total synthesis, largely owing to its broad applicability and convenience.

An early application of the Sonogashira reaction in total synthesis can be found in the generalized synthetic route to the biologically significant lipoxins and related eicosanoids pioneered by the Nicolaou group in the early 1980s. As an illustrative example, we highlight the stereospecific synthesis of (5*S*,15*S*)-dihydroxy-6,13-*trans*-8,11-*cis*-eicosatetraenoic acid (**212**),[190] an important metabolite of arachidonic acid. Besides securing the stereochemistry of the remote hydroxy-bearing stereogenic centers, the central problem in the synthesis of this and similar polyunsaturated compounds resides in the construction of an aliphatic chain that have double bonds of defined geometry in specified positions within the molecule. The solution devised by the Nicolaou group involved the stereospecific formation of the conjugated unsaturated systems through Sonogashira coupling reactions in which the acetylene components function as masked *Z*-alkene motifs. Thus, as illustrated in Scheme 38, the coupling of vinyl bromide (*E*)-**206** with the terminal alkyne **207** upon exposure to $[Pd(PPh_3)_4]$ (4 mol%), CuI (16 mol%), and nPrNH$_2$ (1.2 equiv) in benzene proceeded smoothly at room temperature to afford enediyne **208** in good yield. As expected, compound **208** was formed as a single geometric isomer, with the anticipated retention of configuration about the *E* double bond. After the liberation of the terminal acetylene to give compound **209**, a second Sonogashira reaction, this time with vinyl bromide **210** under the same coupling conditions gave bis(enyne) **211** as a single isomer and again in good yield. With the entire molecular framework of the target natural product thus rapidly assembled through this convergent and flexible approach, the few remaining synthetic steps required only selective hydrogenation of the two alkyne units, under Lindlar conditions, and removal of protecting groups.



Scheme 38. Sequential Sonogashira couplings in the total synthesis of **212** (Nicolaou and Webber, 1984).[190]

Variations on this general Sonogashira coupling theme allowed the synthesis of a number of other structurally and biosynthetically related eicosanoid natural products, including the lipoxin family of secondary metabolites. For example, (5*S*,6*S*,15*S*)-lipoxin A$_4$ (**216**) was readily obtained through the smooth union of the enantiomerically pure building blocks **213** and **214**, followed by standard Lindlar reduction and protecting-group cleavage procedures (Scheme 39).[191] A



Scheme 39. Application of a fragment-coupling Sonogashira reaction in the total synthesis of (5*S*,6*S*,15*S*)-lipoxin A$_4$ (**216**) (Nicolaou et al., 1985).[191]

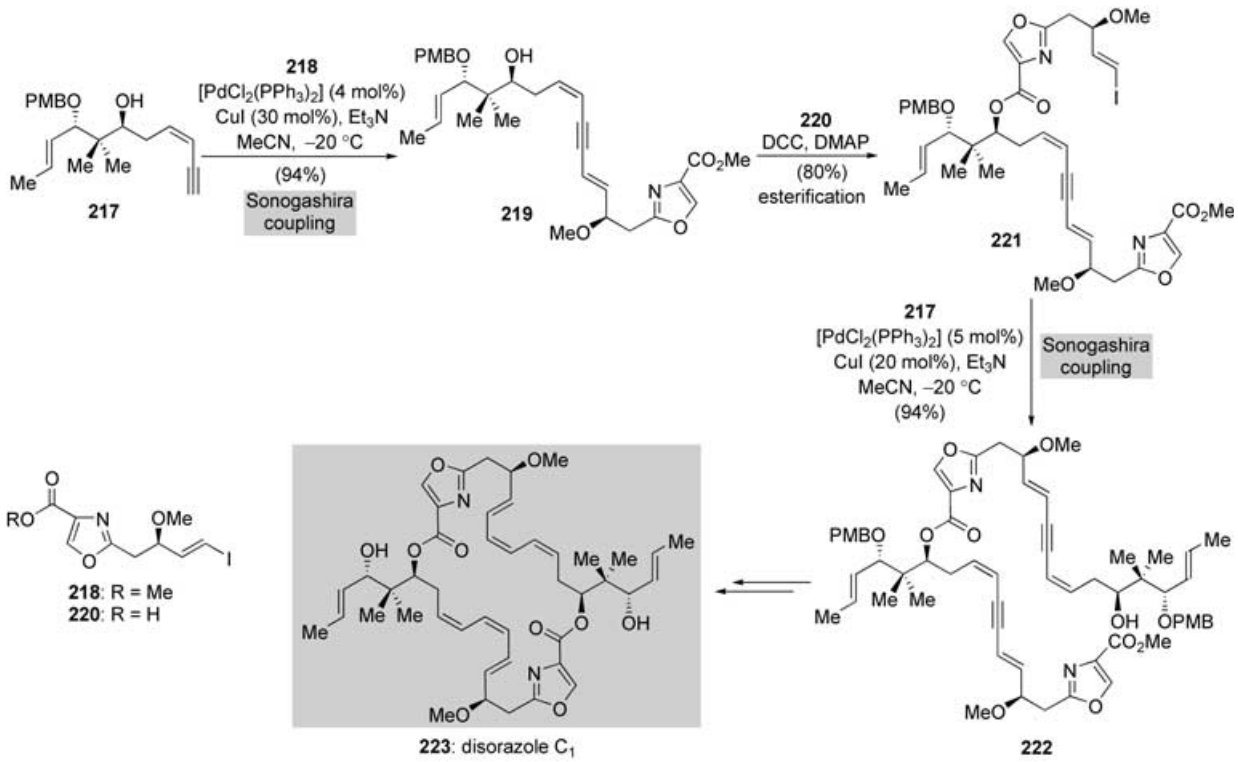
large number of isomeric lipoxin A[192] and lipoxin B[193] derivatives were produced by analogous routes, which enabled not only the identification and structure elucidation of a number of naturally occurring isomers of this series, but also provided meaningful quantities of materials for further biological investigations.[194]

These instructive examples serve to highlight the fact that the Sonogashira reaction provides an important alternative to the Stille and Suzuki reactions for the stereoselective synthesis of polyene systems, by means of this two-step protocol of alkyne–alkene coupling followed by selective reduction of the triple bond. Such methodology proves to be of particular use when the organostannane or organoboron components, required for the Stille or Suzuki coupling reactions, respectively, are either unavailable or too unstable to be synthetically useful. It is important to note that both the corresponding *E*- and *Z*-alkene isomers can be readily prepared in a stereoselective fashion from the parent alkyne. Thus, whereas the *Z* alkenes are typically prepared by catalytic hydrogenation procedures, a number of routes are available for the synthesis of the corresponding *E* isomers;[195] the hydrosilylation protocols recently developed by the Fürstner[196] and Trost groups[197] are potentially convenient and chemoselective methods.

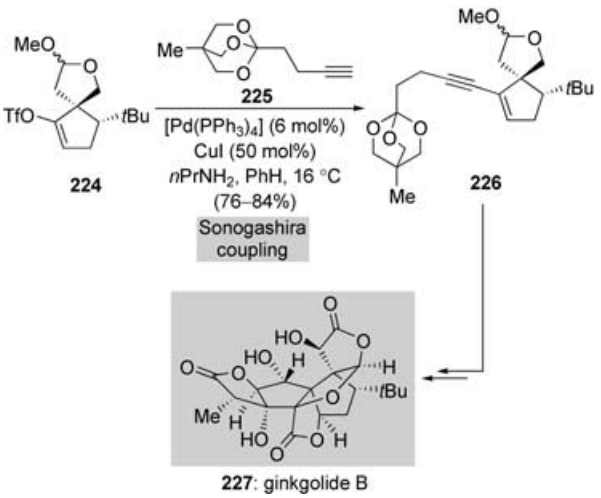
The power of the Sonogashira reaction in fragment-coupling processes is nicely illustrated in the synthesis of disorazole C_1 (**223**) by Wipf and Graham (Scheme 40).[198] Noting the symmetry elements inherent within the natural product, the team reasoned that the formidable molecular framework of their target could be broken down into just three relatively simple fragments that could be appropriately unified through the judicious employment of esterification, Sonogashira, and macrolactonization reactions. As shown in Scheme 40, the coupling of alkyne **217**, containing an unprotected secondary hydroxy group, with vinyl iodide **218** occurred rapidly in the presence of $[PdCl_2(PPh_3)_2]$ (4 mol%), CuI (30 mol%), and Et_3N in MeCN to yield the desired coupling product **219** in nearly quantitative yield. The secondary hydroxy group in compound **219** was then esterified with carboxylic acid **220** to give vinyl iodide **221**, onto which was appended another molecule of alkyne **217** through another high-yielding Sonogashira coupling. Hence, in only three operations, the entire carbon framework of the final target structure had been assembled under mild conditions and in a stereospecific manner from the simple starting materials **217**, **218**, and **220**, with no protecting-group manipulation required. A few more steps then completed the total synthesis, with the two sensitive *E*,*Z*,*Z*-triene systems being unveiled in the last step through the selective hydrogenation of the alkyne moieties facilitated by the Lindlar catalyst. Thus, as was the case in the synthesis of **212**, the alkyne unit serves a dual function in the synthesis: as a coupling handle for carbon–carbon bond formation and as a surrogate for a *Z* alkene, enabling the postponement of the unveiling of the latter, rather delicate structural motif until a late stage in the synthesis.

In a similar vein to the other palladium-catalyzed processes discussed so far, the finding that vinyl triflates (also known as enol triflates) are effective electrophiles in cross-couplings with terminal alkynes has significantly expanded the scope and utility of the Sonogashira reaction.[199] One of the first such applications in total synthesis, which indeed remains a prime example of this methodology in natural products synthesis, can be found in the masterful synthesis of ginkgolide B (**227**) by E. J. Corey and co-workers, reported in 1988.[200] In this true classic in total synthesis,[118] one of the key early steps was the formation of enyne **226** through the coupling of enol triflate **224** (derived from the corresponding ketone) with the orthoester-substituted terminal alkyne **225** (Scheme 41). The required transformation was induced by treatment of a mixture of the coupling partners **224** and **225** with a catalytic amount of $[Pd(PPh_3)_4]$ (6 mol%), a substoichiometric amount of CuI (50 mol%), and nPrNH$_2$ (excess) in toluene, providing the desired product **226** in yields between 76 and 84%.

One of the most common applications of the Sonogashira reaction in total synthesis is the incorporation of two-carbon alkyne motifs into synthetic intermediates, either as ring appendages or as a means of acyclic-chain elongation. (Trimethylsilyl)acetylene serves as a conveniently handled acetylene equivalent, with the added benefit that, because one terminus of the alkyne unit is blocked as the corresponding trimethylsilane, monocoupling products are observed exclusively. Such a reaction was applied by Isobe and co-workers at an early juncture in the course of their asymmetric total synthesis of tetrodotoxin,[201] the notorious puffer fish poison that has been called "one of Nature's great marvels".[202] Thus, (trimethylsilyl)acetylene was smoothly cou-

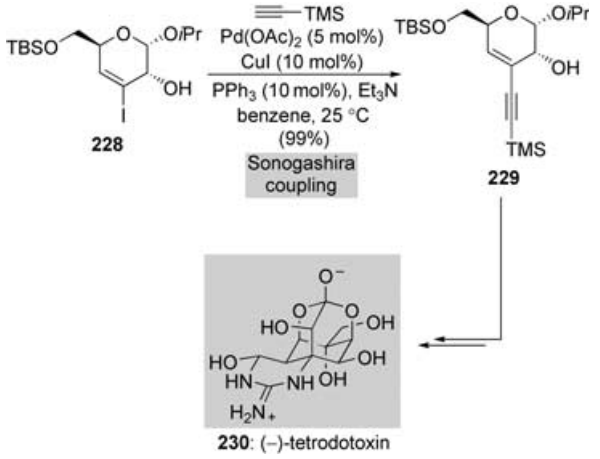


Scheme 40. Sequential use of fragment-coupling Sonogashira reactions in the total synthesis of disorazole C_1 (**223**) (Wipf and Graham, 2004).[198]



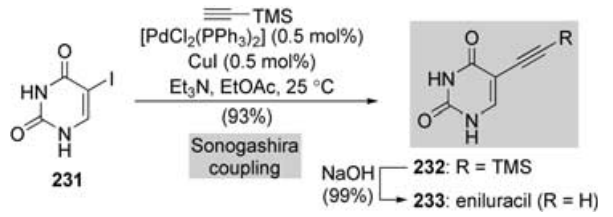
Scheme 41. Application of an enol triflate in a Sonogashira coupling in the total synthesis of ginkgolide B (**227**) (Corey et al., 1988).[200]

pled with vinyl iodide **228** upon exposure to catalytic amounts of $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), and CuI (10 mol%) in the presence of Et_3N in benzene at ambient temperature to afford enyne **229** in near-quantitative yield (Scheme 42). This product was then advanced through a number of steps to complete the total synthesis.



Scheme 42. Use of the Sonogashira reaction to introduce an ethynyl group in the enantioselective synthesis of (–)-tetrodotoxin (**230**) (Isobe et al., 2003).[201]

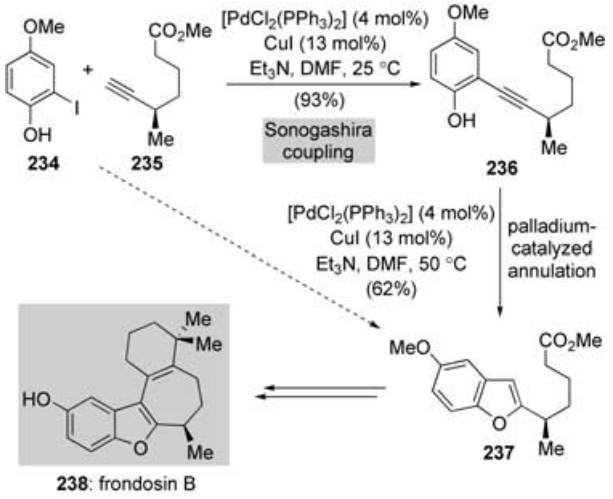
This protocol has also found industrial application, for example, in the concise synthesis of eniluracil (**233**, Scheme 43), a chemotoxic agent enhancer developed by GlaxoSmithKline and used for the treatment of breast and colorectal cancers.[203] In this synthesis, the coupling of 5-iodouracil (**231**) with (trimethylsilyl)acetylene proceeded in excellent yield and, on a large scale, in the presence of catalytic amounts of $[PdCl_2(PPh_3)_2]$ and CuI in EtOAc at ambient temperature. It was found that the catalyst loading of both the palladium complex and the copper salt could be lowered to a mere 0.5 mol% each while maintaining an acceptable reaction rate, with the resultant benefits of lower



Scheme 43. Use of the Sonogashira reaction to introduce an ethynyl group in the synthesis of eniluracil (**233**) (Glaxo SmithKline, 2001).[203]

reagent costs and minimal heavy-metal contamination in the process. The subsequent basic hydrolytic cleavage of the silyl protecting group to afford the target compound also proceeded smoothly and in nearly quantitative yield. Thus, this protocol provides a mild, safe, and high-yielding method for the introduction of an unsubstituted ethynyl fragment, thus offering a versatile alternative to the synthesis of such motifs through the standard homologation of aldehyde precursors.[204]

An interesting approach to the total synthesis of the interleukin-8 receptor antagonist frondosin B by employing palladium-catalyzed chemistry was reported by Danishefsky and co-workers.[205] The researchers proposed that a concise and convergent synthetic route to the pivotal benzofuran intermediate **237** could be secured through a heteroannulation reaction between *ortho*-iodophenol derivative **234** and terminal alkyne **235** (Scheme 44). This cascade process would involve the initial Sonogashira coupling between **234** and **235** to generate intermediate **236**, which would then undergo the required intramolecular cyclization in a process that was already known to be catalyzed by palladium salts.[206,207] While it was, indeed, found that this one-pot process could be effected to yield benzopyran **237** directly from **234** and **235**, such procedures were invariably plagued by numerous competing side reactions and decomposition pathways, to the detriment of the formation of the desired product **237**, which, even under optimum conditions, could be isolated only

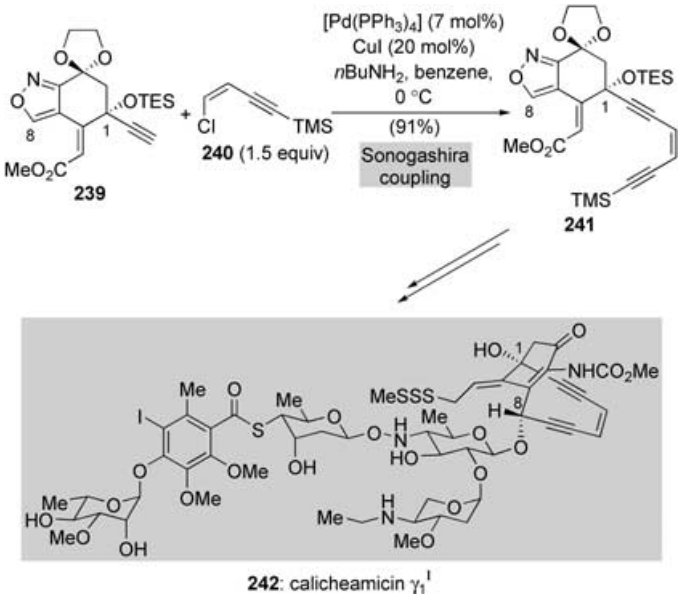


Scheme 44. Use of the Sonogashira reaction in a heteroannulation protocol in the total synthesis of frondosin B (**238**) (Danishefsky et al., 2001).[205]

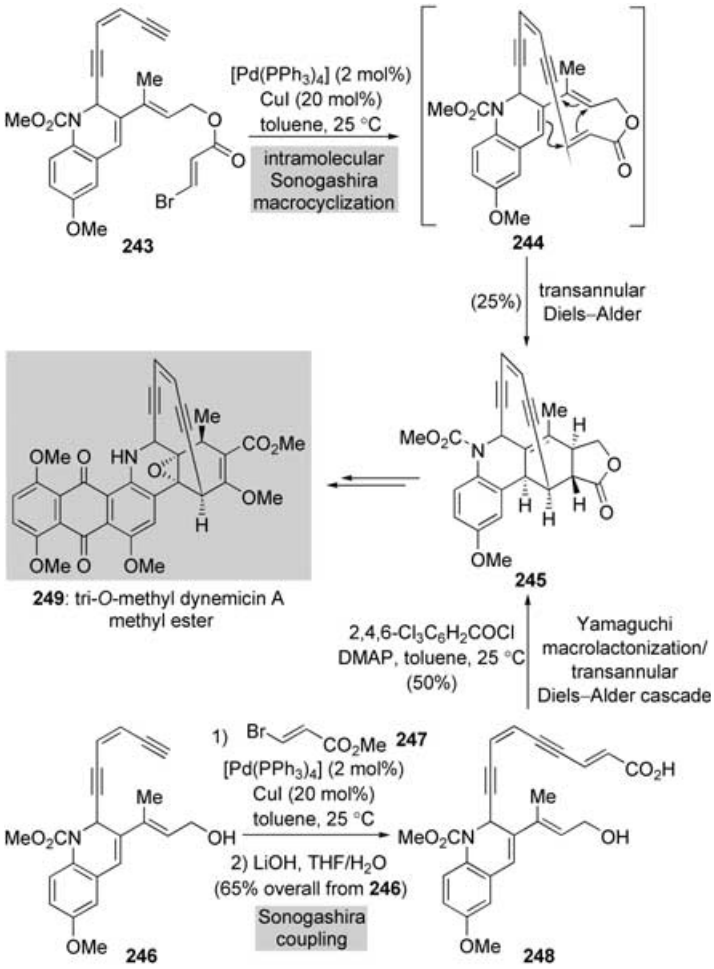
in modest yields (20–40%). To circumvent this dilemma, the researchers investigated the possibility of carrying out the Sonogashira coupling and heteroannulation reactions as separate, subsequent steps. Much to their delight, the coupling of **234** and **235** to give alkyne **236** proceeded in an excellent yield of 93% at room temperature under the influence of $[PdCl_2(PPh_3)_2]$ (4 mol%), CuI (13 mol%), and Et_3N (2.0 equiv) in DMF. The choice of base was found to influence the efficacy of this step dramatically; for example, replacement of Et_3N with piperidine lowered the yield of alkyne **236** to 74%. The isolated, purified alkyne **236** was resubjected to the same reaction conditions, except for the elevated temperature of 50 °C, to effect the smooth cyclization to give the sought-after benzofuran **237** in 62% yield. Both the initial coupling and the subsequent cyclization were found to occur without any erosion of stereochemical integrity of the resulting benzylic tertiary stereocenter.

Some of the most spectacular applications of the Sonogashira reaction can be found in synthetic approaches to various members of the enediyne class of antibiotics, as reported by numerous different groups.[208] The characteristic (*Z*)-1,5-diyne-3-ene motif contained within this family of natural products would appear to lend itself readily to assembly through palladium-catalyzed carbon–carbon bond-forming processes, and indeed has proven to be a significant testing ground for the Sonogashira coupling in total synthesis. We highlight but two of the many such elegant applications. The first of these is in the pioneering total synthesis of calicheamicin γ_1^I (**242**) by the Nicolaou group in 1992.[209] As illustrated in Scheme 45, the coupling of the densely functionalized cyclohexyl-substituted alkyne **239** with vinyl chloride **240** (itself prepared through the Sonogashira reaction of *cis*-1,2-dichloroethylene with trimethylsilyl acetylene) proceeded smoothly to afford the corresponding product **241** in 91% yield. Crucially, and as anticipated, this union occurred with retention of the *Z* geometry of the alkene coupling partner.

In contrast, Schreiber and co-workers made use of both inter- and intramolecular Sonogashira reactions in their captivating and highly inventive approach to the core molecular framework of dynemicin A.[210] The cornerstone of their synthetic strategy was the anticipation that macrocyclic lactone **244** (Scheme 46) could be coaxed into undergoing a transannular Diels–Alder reaction as shown to furnish the advanced pentacyclic intermediate **245**. Such an approach would differ fundamentally from previous approaches to the dynemicin skeleton in which the enediyne motif was appended onto a previously established tricyclic system (for an example see the approach by Danishefsky and co-workers, Section 3, Scheme 15).[211] The Schreiber group investigated the potential viability of two different strategies to the putative macrocyclic transannular Diels–Alder precursor **244**.



Scheme 45. Application of a Sonogashira coupling to generate the enediyne system in the total synthesis of calicheamicin γ_1^I (**242**) (Nicolaou et al., 1992).[209]



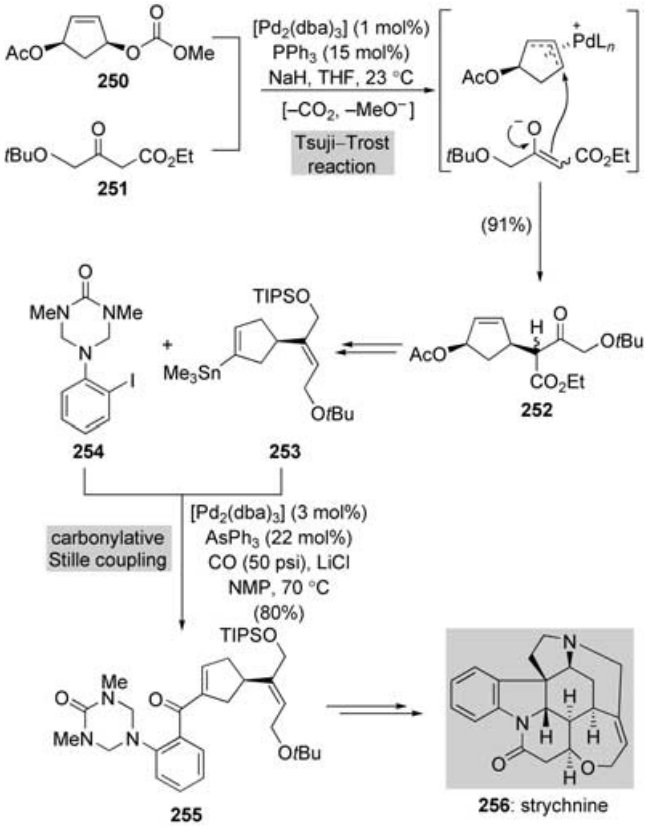
Scheme 46. Different uses of the Sonogashira coupling in cascade reactions en route to tri-*O*-methyl dynemicin A methyl ester (**249**) (Schreiber et al., 1993).[210]

In the first of these, it was proposed that the macrocyclic ring could be generated by the coupling of the terminal alkyne and the bromide-bearing vinyl carbon atom in ester **243** through a Sonogashira coupling reaction. However, to both their surprise and delight, when ester **243** was treated with [Pd(PPh_3)$_4$] (2 mol%) and CuI (20 mol%) in toluene, the sole isolable product was in fact found to be the Diels–Alder cycloadduct **245**, which had been formed as a single stereoisomer in 25% yield. In this amazing and unprecedented tandem Sonogashira/Diels–Alder reaction, three rings and four contiguous stereocenters were formed in a single operation and within 2 h at room temperature, presumably through the transient intermediacy of the expected macrocycle **244**. The second approach made use of an intermolecular Sonogashira coupling between enediyne **246** and bromoacrylate **247**, followed by basic hydrolysis of the resulting ester group, to generate the corresponding polyunsaturated carboxylic acid with complete retention of alkene geometry. When acid **248** was subjected to the Yamaguchi macrocyclization protocol,[212] cyclization to give lactone **244** was again spontaneously followed by the transannular Diels–Alder reaction at room temperature to generate the same pentacyclic intermediate **245**. Such cascade processes serve to highlight the utility and potential of the Sonogashira reaction in generating molecular complexity from much simpler precursor molecules.

6. The Tsuji–Trost Reaction

The alkylation of allylic substrates by stabilized nucleophiles is one of the most synthetically useful reactions catalyzed by palladium(0) complexes. From an historical perspective, this reaction reflects the first demonstration of a metalated species acting as an electrophile, providing a counterpoint to decades of research that had indicated that such entities only behaved as nucleophiles. On a more practical level, the Tsuji–Trost reaction, as this general process is known, typically proceeds under mild conditions, with (generally) high and predictable levels of chemo-, regio-, and stereoselectivity. The stoichiometric allylation of enolates with π-allyl–palladium complexes was first reported by the Tsuji group 40 years ago,[213] and subsequently developed into a catalytic reaction by Trost and co-workers.[25a] A wide range of allylic substrates undergo this reaction with a correspondingly wide range of carbanions, making this a versatile and important process for the formation of carbon–carbon bonds. Whilst the most commonly employed substrates for palladium-catalyzed allylic alkylation are allylic acetates, a variety of leaving groups also function effectively—these include halides, sulfonates, carbonates, carbamates, epoxides, and phosphates. As such, the Tsuji–Trost reaction has been widely embraced by synthetic chemists, and we can highlight but a few of the many elegant applications of this process here. It is important to recall that a wide variety of heteroatom nucleophiles (e.g. N, O, and S nucleophiles) also make excellent coupling partners in the Tsuji–Trost reaction; however, the utility of these processes are beyond the scope of this Review.

A classic and instructive example of the intermolecular Tsuji–Trost reaction can be found in the total synthesis of the naturally occurring enantiomer of strychnine (**256**, Scheme 47) by Overman and co-workers in 1993.[214] Com-

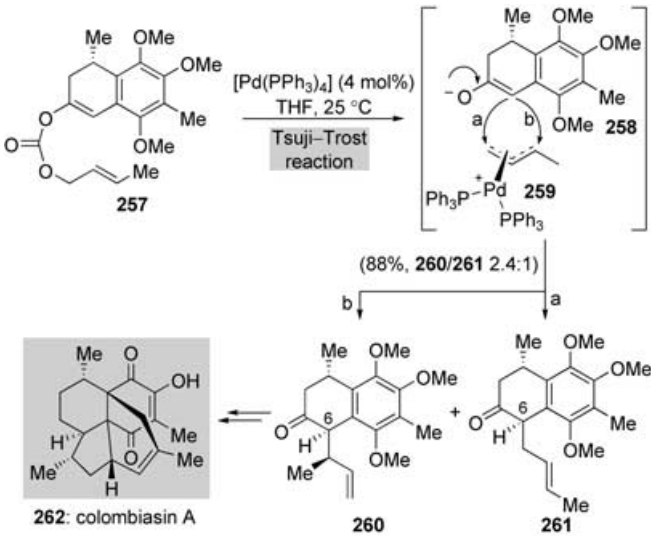


Scheme 47. Tsuji–Trost and carbonylative Stille coupling reactions in the total synthesis of strychnine (**256**) (Overman et al., 1993).[214]

prising only 24 skeletal atoms woven into a bewitching polycyclic structure, strychnine holds a special place in the annals of structure determination and natural product synthesis. However, following the landmark total synthesis of racemic strychnine by Woodward and co-workers in 1954,[215] enantioselective syntheses of this remarkable alkaloid would not be forthcoming for nearly 50 years, with the success of the Overman approach being, in a large part, due to the application of palladium-catalyzed reactions.[216] The first key step in the synthesis involved the allylation of acetoacetate derivative **251** (Scheme 47) with enantiopure allylic carbonate **250**, under the influence of [Pd_2(dba)$_3$] (1 mol%), PPh_3 (15 mol%), and NaH in THF at ambient temperature to furnish the *cis*-alkylated adduct **252** in 91% yield. Several features of this reaction merit further comment. First, the net stereochemical outcome of this reaction is the overall retention of the configuration at the leaving-group-bearing carbon atom, thus complementing normal S_N2 reactions, which proceed with inversion of configuration. As illustrated in Scheme 47, this is the consequence of two successive inversions at this center, and is a general feature of the Tsuji–Trost reactions of soft nucleophiles. Second, the regiochem-

istry of the alkylation is such that compound **252** is formed exclusively. In general, the regiochemical course of the alkylation of unsymmetrical allylic substrates is such that attack is favored at the less-substituted terminus; however, and as we shall see, this is somewhat dependent on the specific nature of the nucleophile, the electrophile, and the catalyst system. Although cyclopentene derivative **250** contains two potential leaving groups, namely the acetate and the carbonate units, the exclusive displacement of the latter was observed. This outcome had been anticipated on the basis of relevant precedent, which had demonstrated the higher reactivity of allylic carbonates in these processes than that of the corresponding acetates.[217] Finally, compound **252** was formed as a 1:1 mixture of epimers at the stereocenter adjacent to the ketone group, but this proved to be inconsequential as this mixture could be advanced to give stannane **253** as a single stereoisomer. A carbonylative Stille reaction was then employed to effect the linking of stannane **253** with aryl iodide **254** through a carbonyl bridge, affording tricyclic compound **255** in 80% yield. This intermediate was subsequently elaborated to complete the asymmetric total synthesis of (−)-strychnine.

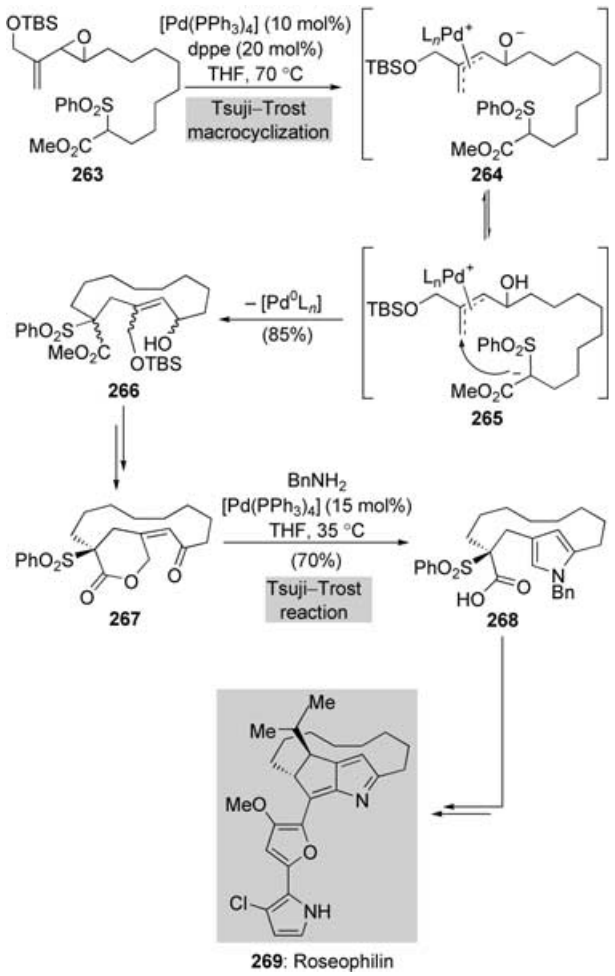
The pioneering total synthesis of the marine diterpenoid colombiasin A (**262**, Scheme 48) by the Nicolaou group in



Scheme 48. Regioselective Tsuji–Trost reaction of a crotyl enol carbonate precursor in the total synthesis of colombiasin A (**262**) (Nicolaou et al., 2001).[218]

2001[218] was the end result of the development of a number of synthetically useful techniques, foremost amongst them being the extension of the Tsuji–Trost allylation reaction to a new class of substrates as well as interesting observations regarding the regioselectivity of the addition of enolate nucleophiles to η^3-crotyl–palladium electrophilic complexes. The adopted synthetic plan called for the installation of the C6 side chain through a Tsuji–Trost reaction of an appropriately substituted crotyl enol carbonate precursor (i.e. **257**→**260**).[219] However, it was appreciated from the outset that there were a number of potential pitfalls associated with this novel transformation, not the least of which was the issue of the regioselectivity of the addition of enolate intermediate **258** to palladium complex **259**. Indeed, a substantial body of literature precedent suggested that addition would occur predominantly at the less-hindered terminus of the complex (path a) to generate the undesired regioisomeric product **261**. However, it was proposed that if the reaction conditions could be tailored such that electronic factors, rather than the customary steric effects, became the dominant factor in determining the regioselectivity of addition, then the reaction could indeed be coaxed into following the desired pathway (i.e. path b), as the site of greatest partial positive charge in the allylic domain of complex **259** resides at the secondary carbon atom terminus. Gratifyingly, it was found that exposure of enol carbonate **257** to $[Pd(PPh_3)_4]$ (4 mol%) in THF at ambient temperature led to the rapid formation of a mixture of the two regioisomeric products **260** and **261**, in a combined yield of 88%, in which the desired isomer predominated (**260**/**261** 2.4:1). The employment of PPh_3 as a ligand for palladium proved to be crucial in dictating this regiochemical outcome, as it presumably enabled the sufficient accumulation of partial positive charge character on the crotyl ligand in complex **259** to favor attack at the more-substituted carbon terminus. Indeed, it was observed that better σ-donor ligands (e.g. dppe or $P(OiPr)_3$), which would be expected to lower the cationic character of complex **259**, restored the "normal" regioselectivity, with the undesired product **261** predominating in these reactions. These groundbreaking results showed, for the first time in the context of complex molecule construction, that the regioselectivity of nucleophilic addition in the Tsuji–Trost reaction can, under appropriate conditions, be manipulated beyond mere steric control. Certainly, in this instance, it went against established doctrine. The regiochemistry issues notwithstanding, this allylation reaction was, in fact, extremely stereoselective, with both the undesired product **261** and, even more remarkably, the desired compound **260** being formed as single stereoisomers. This outcome presumably reflects the inherent influence of the remote methyl-group-bearing stereocenter in the starting material **257** on the allylation step.[220]

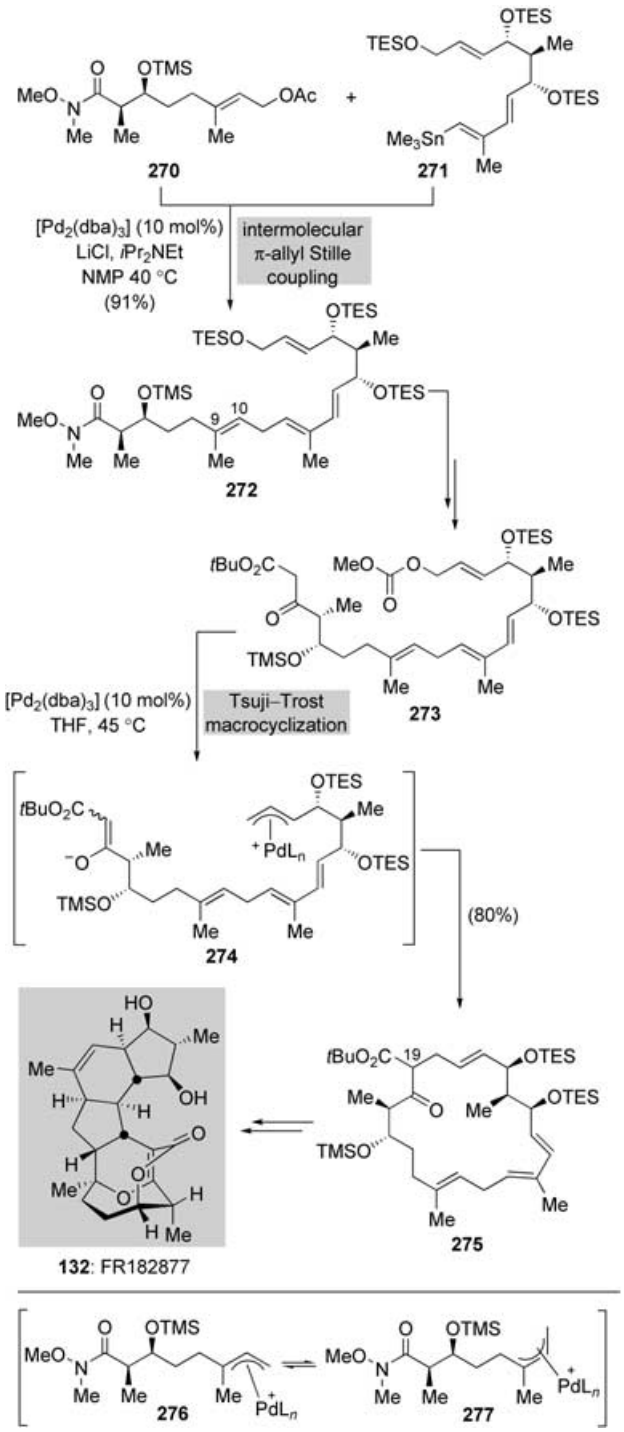
The intramolecular Tsuji–Trost reaction represents a powerful method for the formation of a broad spectrum of ring systems, be they carbocyclic or heterocyclic, small or large. An elegant example of the scope of this process is the total synthesis of the architecturally unique alkaloid roseophilin (**269**, Scheme 49) by Fürstner and Weintritt.[221,222] The central synthetic challenges confronting these researchers were the formation of both the azafulvene-type chromophore and the rather strained *ansa* 12-membered carbocyclic ring; the Tsuji–Trost reaction proved to be instrumental in addressing both these issues. Thus the initial formation of the macrocyclic ring was effected by the addition of a dilute solution of allylic epoxide **263** to catalytic amounts of $[Pd(PPh_3)_4]$ and dppe in refluxing THF to generate compound **266** in an impressive 85% yield (Scheme 49). As with the strychnine example described above, the reaction sequence was initiated by the selective oxidative addition of the more reactive unit of a bifunctional substrate to a palladium(0) species through the judicious modulation of leaving-group



Scheme 49. Sequential use of Tsuji–Trost reactions in the total synthesis of roseophilin (**269**) (Fürstner and Weintritt, 1998).[221]

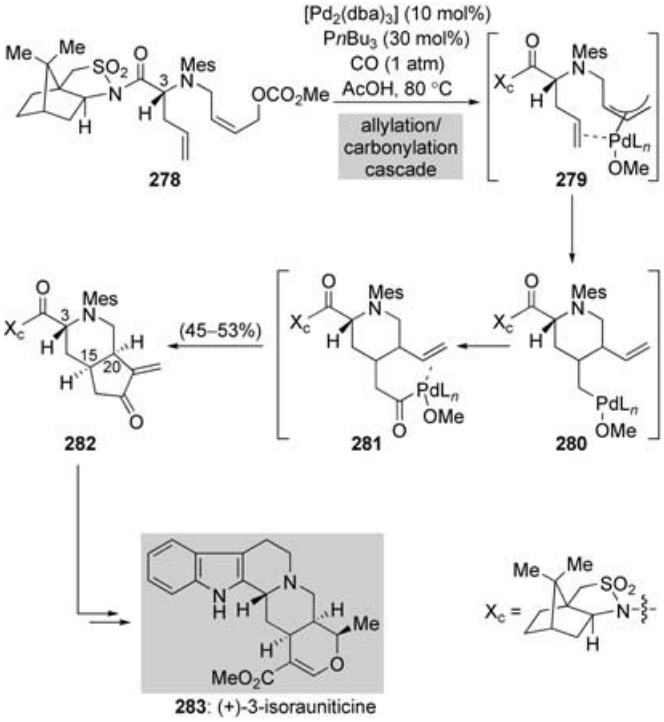
reactivity. Thus, in this case, the allylic epoxide moiety in compound **263** was opened selectively in the presence of the allylic silyl ether group, driven by the attendant release of ring strain, to generate the presumed alkoxide intermediate **264**. Following equilibration to generate the stabilized carbanion species **265**, macrocyclization can then occur at the less-hindered terminus of the π-allyl system to generate the observed product **266**. There was no inherent diastereoselectivity in this reaction, with the product **266** being formed as a mixture of all possible stereoisomers. This did not prove to be a hindrance as no tedious separation of the individual components was required, and all the isomers eventually converged into the one final target product. Note that the reaction proceeded under neutral conditions, with no external base needed in the reaction cocktail, which, in this case, is due to the generated alkoxide intermediate **264** being of sufficient basicity to deprotonate the β-sulfone ester group. High-dilution conditions were employed for this transformation to favor the desired macrocyclization over competing detrimental oligomerization processes. Following the elaboration of compound **266** to give lactone **267**, another Tsuji–Trost reaction was employed to generate the corresponding *meta*-pyrrolocyclophane **268**. This interesting palladium-catalyzed transformation, which again proceeds under mild neutral conditions, would appear to offer an appealing alternative to traditional acid-catalyzed condensation protocols for the formation of pyrrole ring systems from acyclic 1,4-diketones or their synthetic equivalents.[223]

Brilliant use of π-allyl–palladium(II)-mediated bond-forming reactions was made by Sorensen and co-workers in their enantioselective total synthesis of the naturally occurring enantiomer of FR182877 (**132**).[224] The first of these couplings was the π-allyl Stille reaction between allylic acetate **270** and dienylstannane **271** to afford intermediate **272** as a single stereoisomer in 91% yield (Scheme 50). That this reaction proceeded as superbly as it did was only the result of extensive prior investigative work on the part of the researchers to optimize the coupling conditions. In particular, it was found that the dienylstannane component **271** was exquisitely sensitive to traces of acid,[225] with the consequent protodestannylation of this partner competing with its coupling to allylic acetate **270**. Fortunately, the simple addition of a mild amine base (iPr$_2$NEt) to the reaction medium was found to be sufficient to suppress the undesired protodestannylative destruction of **271** almost completely. Of equal benefit was the discovery that only at reaction temperatures at or below 40 °C could coupling product **272** be obtained as the desired stereoisomer. At higher temperatures, significant amounts of the corresponding C9–C10 *Z* isomer of coupling product **272** were obtained. The formation of the latter was likely due to the erosion of stereochemical integrity of the presumed initially formed reactive π-allyl–palladium intermediate **276**, through competing thermal equilibration, to give a mixture of isomeric complexes **276** and **277** prior to coupling with stannane **271**. Nevertheless, with a practical and highly convergent route to coupled intermediate **272** thus secured, this compound was rapidly advanced to generate allylic carbonate **273**, the precursor for the second pivotal palladium-catalyzed reaction in the sequence, namely a Tsuji–Trost macrocyclization. To the researchers' delight, cyclization of precursor **273** to give the sought-after macrocycle **275** proved to be both remarkably facile and efficient and could be effected by simply treating a moderately dilute solution (0.05 M) of the starting material (**273**) in THF with [Pd$_2$(dba)$_3$] (10 mol%) at 45 °C. In this manner, the cyclized product **275** could be cleanly obtained in 60–85% yield and, interestingly, as a single diastereoisomer (i.e. only one stereoisomer at the newly formed C19 stereogenic center was produced in the cyclization event). The success of this reaction is undoubtedly due to the shrewd employment of a methyl carbonate as the allylic activating group. Carbonate groups enable irreversible palladium oxidative addition under mild conditions, promoted by the expulsion of a molecule of CO_2 and an alkoxide anion (in this case methoxide). This alkoxide anion serves a dual purpose in that, as with the analogous case in the synthesis of roseophilin discussed above, it also functions to deprotonate the activated β-ketoester methylene moiety, thus enabling the required ring closure. These spectacular examples clearly illustrate the practical utility of palladium-catalyzed carbon–carbon bond-formation processes via electrophilic π-allyl intermediates in the construction of complex molecules.



Scheme 50. Application of π-allyl Stille fragment-coupling and Tsuji–Trost macrocyclization reactions in the enantioselective synthesis of FR182877 (**132**) (Sorensen et al., 2003).[224]

The insertion of alkenes into π-allyl–palladium species is a key step in the carbocyclization of allylic electrophiles with alkenes, a process that represents a powerful method for the formation of five- and six-membered carbocyclic and heterocyclic ring systems.[226,227] The combination of palladium-catalyzed allylation and carbonylation reactions is especially attractive as it permits the (potentially stereoselective) formation of three carbon–carbon bonds plus the insertion of a ketone carbonyl group in a single step. The Oppolzer group has been one of the key pioneers and exponents of this methodology, the utility of which is magnificently demonstrated in their synthesis of the heteroyohimbine alkaloid 3-isorauniticine (**283**, Scheme 51).[228,229] Thus, the treatment of



Scheme 51. Application of an allylation/carbonylation cascade reaction in the enantioselective synthesis of 3-isorauniticine (**283**) (Oppolzer et al., 1991).[228]

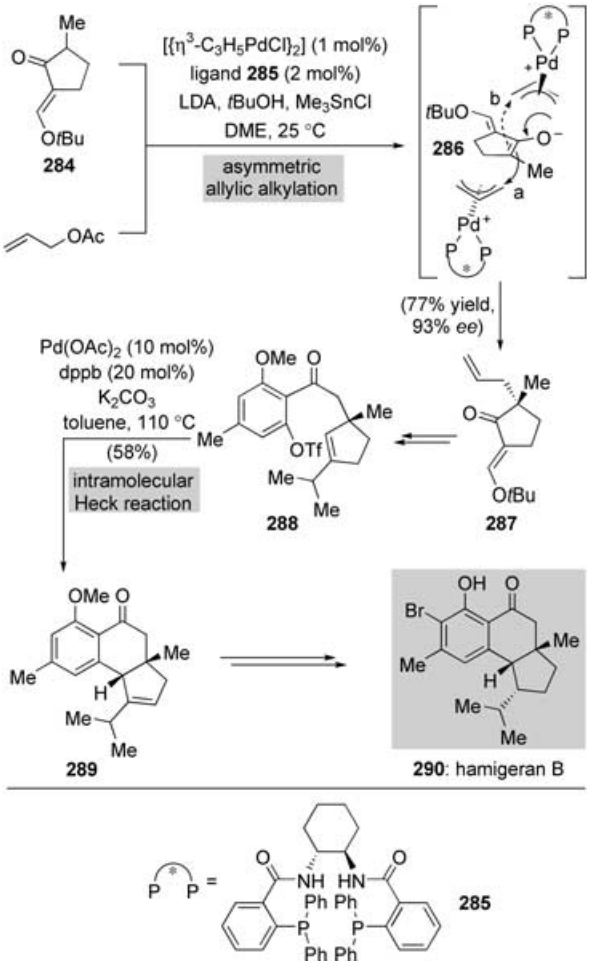
a solution of allylic carbonate **278** in AcOH with catalytic amounts of $[Pd_2(dba)_3]$ (10 mol %) and $P(nBu)_3$ (30 mol %) at 80 °C under carbon monoxide (1 atm) initiated a highly orchestrated sequence of carbon–carbon bond-forming steps, which culminated in the diastereoselective construction of bicyclic enone **282** in reproducible yields of roughly 50 %. The first step in this sequence is the selective ionization of the allylic moiety within the starting material **278** by a Pd^0 complex, to generate π-allyl–palladium intermediate **279**. This species then undergoes a regioselective insertion into the pendant terminal alkene system (which in effect acts as the nucleophile to capture the electrophilic π-allyl–palladium complex) to form η^1-alkyl–palladium(II) intermediate **280**. This process can be formally considered as a suprafacial palladium-ene cyclization. The insertion of carbon monoxide into η^1-alkyl–palladium(II) intermediate **280** to generate the next intermediate **281** is evidently much faster than the undesired β-hydride elimination. Finally, acyl palladium(II) intermediate **281** undergoes a regioselective intramolecular Heck reaction to afford the observed product **282**. The overall yield for this process was, in fact, more impressive than the illustrated yield of 45–53 % would appear to indicate, as two minor stereoisomeric products, diastereoisomeric with

respect to **282** at the newly formed ring junction, were also formed in a combined yield of 25%. Thus, the preexisting C3 stereogenic center exerted a moderate influence on the diastereoselectivity of the cyclization cascade in generating the C15 and C20 stereocenters.

The development of procedures to induce asymmetry during palladium-catalyzed allylic alkylation reactions has dramatically enhanced the synthetic utility of this process.[230] Any discussion of the asymmetric allylic alkylation reaction is complicated somewhat by the fact that there are a number of different possible mechanisms of enantiodiscrimination, depending on the nature of the nucleophile and/or electrophile and at which point in the catalytic cycle the chiral elements are set. We can but highlight a few of the more commonly applied types of processes here. Nevertheless, the ability to generate stereochemical complexity from simpler (often achiral) starting materials by using only catalytic quantities of chiral ligands, and equally significantly, in a reliable, predictable, and selective fashion, has propelled the asymmetric allylic alkylation reaction to the forefront of modern synthetic methodology.[231]

While stabilized carbanions (e.g. those derived from β-ketoesters or malonate-type compounds) have traditionally been, and indeed continue to be, the most widely used carbon nucleophiles in the asymmetric allylic alkylation reaction,[232] there has been considerable interest in expanding the scope of this process to include a broader range of nucleophiles. The Trost group has been instrumental in pioneering the recent development of viable protocols for the asymmetric alkylation of ketone enolates,[233] arguably the most synthetically useful class of potential nucleophiles, and has applied this to an elegant synthesis of hamigeran B (**290**),[234] an antiviral metabolite isolated from the marine sponge *Hamigera tarangaensis*.[235] As shown in Scheme 52, the synthetic route adopted called for the early installation of the methyl-group-bearing quaternary stereocenter, and this was fashioned by the asymmetric alkylation of cyclic ketone **284**. Under the optimum conditions shown, the desired alkylated product was readily obtained in excellent yield (77%) and with remarkable enantiopurity (93% *ee*) at ambient temperature. The basis of the enantioselectivity of this alkylation resides in the differentiation between the prochiral faces of the nucleophile by the π-allyl complex. Evidently, the chiral environment created around the π-allyl–palladium complex by the bidentate ligand **285** is sufficient to direct the alkylation almost exclusively towards the "bottom" face of enolate intermediate **286**,[236] that is, path a is significantly favored over path b.

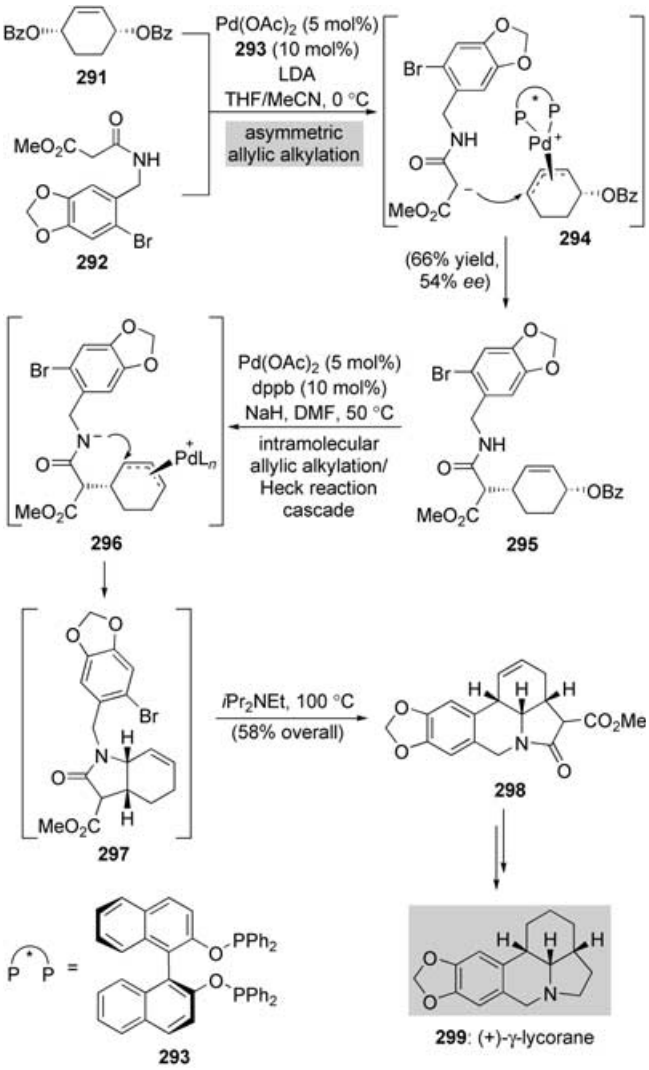
Following the elaboration of ketone **287** to give triflate **288**, it was envisaged that the final carbon–carbon bond could be forged by means of an intramolecular Heck reaction. Indeed, it was found that treatment of triflate **288** with $Pd(OAc)_2$ (10 mol%), dppb (20 mol%), and K_2CO_3 in refluxing toluene led to cyclization furnishing, stereoselectively, the desired *cis*-fused tricyclic compound **289** in 58% yield. Critical to the success of this venture was the employment of carbonate rather than tertiary amine bases, since the use of the latter led to simple hydrogenolysis of the triflate moiety without cyclization occurring. A few more steps then completed the total synthesis.[237] In the sense that the



Scheme 52. Use of asymmetric allylic alkylation and intramolecular Heck reactions in the total synthesis of hamigeran B (**290**) (Trost et al., 2004).[234]

stereoselectivity of formation of the remaining two stereogenic centers in the final target molecule **290** was directed by the initially installed quaternary center, all the chiral elements in the final product were thus installed through the asymmetric allylic alkylation reaction.[238] Very recently, the Stoltz[239] and Trost groups[240] independently reported the extension of the palladium-catalyzed enantioselective allylation reaction to produce a broader range of ketone derivatives bearing quaternary stereocenters, through the asymmetric decarboxylative alkylation of the corresponding allyl enol carbonate precursors.

One of the most useful and widely applied classes of asymmetric π-allyl–palladium reactions is the catalytic desymmetrization of *meso* substrates. Readily available *meso*-2-alkene-1,4-diol derivatives, typically contained within cyclic structures, are the most commonly employed electrophilic substrates. As an example of such an application in total synthesis, we highlight the concise enantioselective construction of the alkaloid γ-lycorane (**299**) by Mori and coworkers in 1995 (Scheme 53).[241] The key fragment-coupling step in this synthesis was the desymmetrization of *meso* dibenzoate **291** with the carbanion derived from amide **292** (generated with LDA), induced by catalytic amounts of



Scheme 53. Use of an asymmetric allylic alkylation reaction in the enantioselective total synthesis of (+)-γ-lycorane (**299**) (Mori et al., 1995).[241]

$Pd(OAc)_2$ (5 mol%) and chiral bis(phosphine) **293** (10 mol%). In this event, selective ionization of one of the two enantiotopic benzoate leaving groups, to generate π-allyl intermediate **294** preferentially, is induced by the chirality of the palladium–ligand complex and forms the basis of the asymmetric induction. Intermediate **294** is superficially similar to the π-allyl–palladium species we saw earlier in the course of the synthesis of strychnine (Scheme 47), and indeed the relative stereochemical outcome of both reactions is the same (i.e. net retention of configuration as the result of two subsequent inversions, nucleophilic attack at the less-hindered terminus of the π-allyl system). However, the two reactions differ fundamentally in how the absolute stereochemistry of the respective products **252** and **295** is introduced. In the present case, an achiral starting material **291** is converted into an enantioenriched product **295** through the action of a chiral, enantiomerically pure catalyst system, whilst in the synthesis of strychnine a chiral starting material **250** is converted into a chiral product **252** under the influence of an achiral catalyst system. It should be mentioned that the enantioselectivity of the alkylation to generate γ-lycorane intermediate **295** is, by modern standards, only moderate (54% *ee*). Indeed, asymmetric alkylations of similar substrates with newer generations of chiral ligands (e.g. **285**, Scheme 52) routinely proceed with greater than 95% *ee*.[242]

With the alkylated product **295** in hand, the remaining major obstacle separating the researchers' position from the final product was the task of fusing the remaining two rings of the natural product to the cyclohexene scaffold. In a masterful piece of synthetic planning, based on the recognition that intermediate **295** still retains an allylic ester moiety itself capable of undergoing a palladium-catalyzed nucleophilic displacement, the researchers reasoned that this task could be accomplished in a single operation directly from **295**, through the application of an unprecedented, intramolecular allylic alkylation/Heck reaction cascade sequence. Thus, treatment of amide **295** with $Pd(OAc)_2$ (5 mol%), dppb (10 mol%), and NaH in DMF at 50 °C triggered the initial intramolecular allylic alkylation to generate the presumed intermediate **297**, which upon the addition of iPr_2NEt followed by further heating to 100 °C, obligingly underwent the anticipated intramolecular Heck cyclization to afford pentacyclic compound **298** in 58% yield as a single diastereoisomer. Note that the regio- and stereochemical outcome of both the Heck and the (formal) S_N2' displacement steps were dictated solely by steric effects and constraints of the starting material **295**, hence the need for chiral ligands in this transformation was obviated. From this and the other examples discussed above, it is clear that the Tsuji–Trost reaction represents an extraordinarily useful method for carbon–carbon bond formation, yet it can be argued that the true potential of this process, in particular its asymmetric version, has only begun to be tapped.

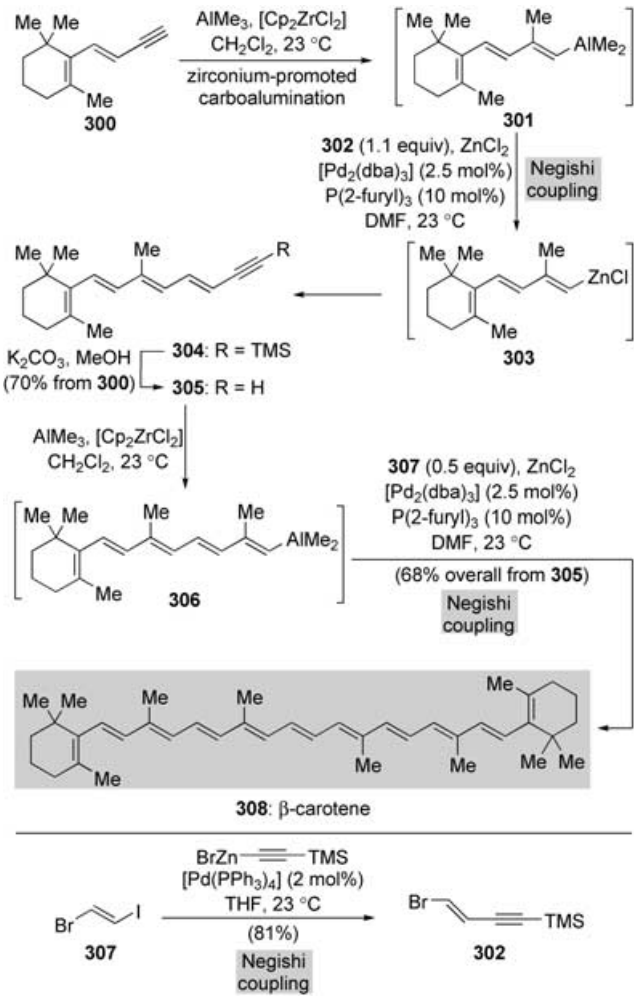
7. The Negishi Reaction

In the context of total synthesis, the Negishi coupling would appear to have been relatively underutilized, in particular having been overshadowed to a large extent by the developments in the Stille and Suzuki reactions. Nevertheless, recent years have seen renewed interest in the Negishi coupling which, in appropriate cases, is often the cross-coupling method of choice for a given synthetic task. The two classes of organozinc reagents that find most use in Negishi couplings are diorganozinc species (R_2Zn) and organozinc halides (RZnX). The latter, typically prepared either by the direct insertion of zinc (zinc dust) into organic halides or by transmetalation from other organometallic species, are particularly useful when functionalized zinc reagents are required.[243] Despite their only moderate reactivity towards many organic electrophiles, organozinc reagents are among the most reactive of nucleophilic species in palladium-catalyzed cross-coupling reactions, owing to their ability to undergo rapid transmetalation with transition-metal salts, most notably those of palladium. The Negishi reaction is particularly powerful when applied in an intermolecular context in fragment-coupling processes, often succeeding in

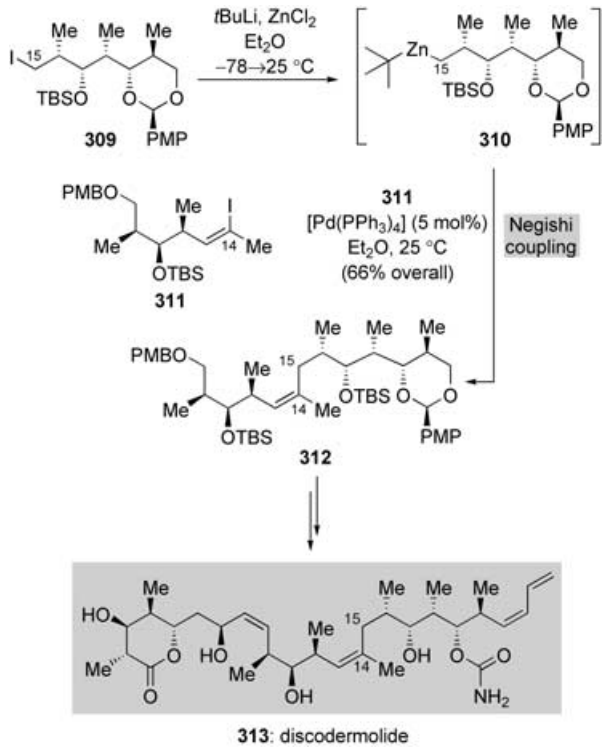
cases in which the corresponding Stille or Suzuki reactions founder. Alkyl–zinc reagents readily enter into the cross-coupling process, expanding the scope of the Negishi reaction beyond standard $C(sp^2)$–$C(sp^2)$ couplings. The major drawback of the Negishi coupling, at least by comparison with the Stille and Suzuki reactions, is the incompatibility of organozinc reagents with many common functional groups, together with their relative sensitivity towards oxygen and water.[244]

An elegant and instructive example of the utility of this coupling reaction to assemble conjugated polyene systems rapidly in high yield and with excellent stereoselectivity is the novel, general synthetic route to the carotenoids reported by the Negishi group.[245] As shown in Scheme 54 for the synthesis of β-carotene (**308**), the key feature of the researchers' approach was the regio- and stereoselective zirconium-catalyzed methylalumination of terminal alkyne precursors, followed by cross-coupling of the resulting vinyl alane intermediates with the appropriate vinyl halide electrophiles. These remarkable carbon–carbon bond-forming processes, each involving four different organometallic intermediates and three transmetalation processes (Zr→Al→Zn→Pd) proceed with remarkable overall efficiency and stereoselectivity, allowing the synthesis of the target molecule **308** in greater than 99% stereoisomeric purity and in only three operations from the starting alkyne **300**! This synthetic route would appear to compare favorably to traditional syntheses of carotenoids proceeding through the venerable Wittig or Horner–Wadsworth–Emmons reaction protocols, which are often plagued by low yields and the formation of stereoisomeric mixtures. Carbometalation (and, by extension, hydrometalation)/cross-coupling tandem processes of the type illustrated here are only made viable by the fast rate of the key transmetalation events to and from the zinc salt, as in its absence such coupling processes are often agonizingly lethargic. This principle of "double metal catalysis",[246] first introduced more than 25 years ago, offers considerable potential for the streamlining of synthetic processes.[247]

As a prime exemplar of both the utility of the Negishi reaction in fragment coupling reactions and the employment of alkyl zinc reagents in these processes to form $C(sp^2)$–$C(sp^3)$ bonds, we highlight here the gram-scale synthesis of the clinically relevant microtubule-stabilizing agent discodermolide (**313**, Scheme 55) by the Smith group.[248,249] In this approach, the two fragments **309** and **311** were coupled to forge the C14–C15 bond of the target product. Significantly, it was found that optimum results in this coupling reaction were obtained only when 3 equivalents of *t*BuLi were employed in the initial lithium–halogen exchange process; when the customary 2 equivalents were used, a 1:1 mixture of the iodide starting material **309** and the expected product **312** was obtained. This led to the proposal that, in this case, the mixed *tert*-butyl alkyl zinc intermediate **310** was in fact the reactive



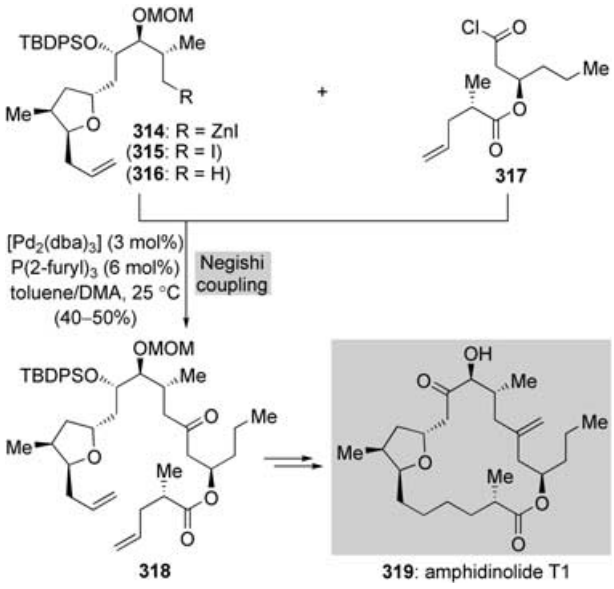
Scheme 54. Negishi coupling reactions in the total synthesis of β-carotene (**308**) (Negishi and Xeng, 2001).[245]



Scheme 55. Application of a Negishi fragment-coupling reaction in the enantioselective synthesis of discodermolide (**313**) (Smith et al., 2000).[248]

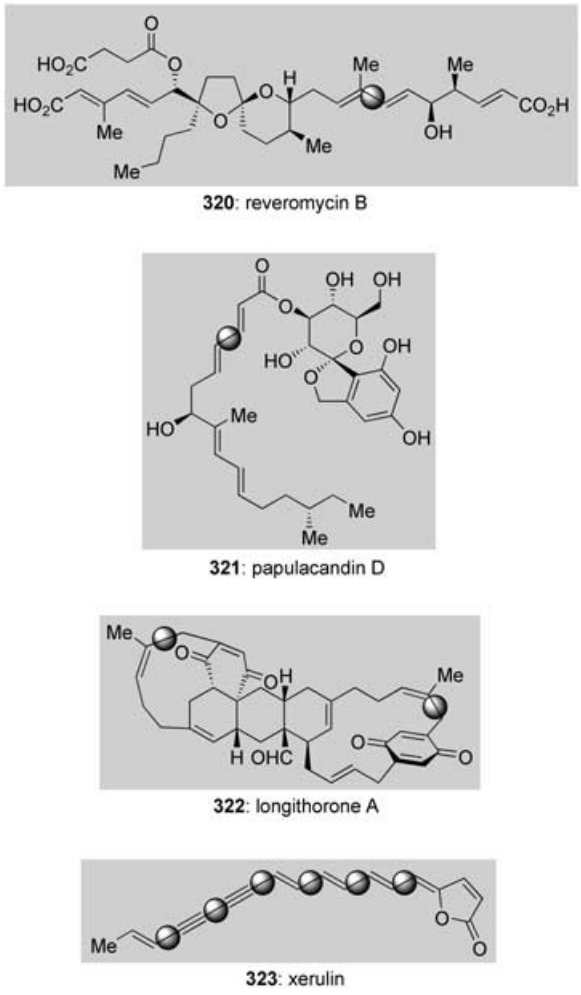
alkyl donor in the cross-coupling step (note then the selective transfer of the primary alkyl group from intermediate **310**), rather than the expected organozinc halide species (RZnI). The researchers also demonstrated the clear superiority of the Negishi protocol over both the palladium-catalyzed Grignard and *B*-alkyl Suzuki coupling, together with cuprate-based procedures, for the union of fragments **309** and **311**. Of no less significance, particularly from a material throughput point of view, was that the reaction proceeded efficiently when using a nearly equimolar ratio of the two coupling partners (**309**/**311** 1.1:1). In contrast, many cross-coupling reactions require a larger excess of one or the other coupling partner in order to proceed to completion, which can be particularly wasteful if it is a valuable, hard-won intermediate that has to be sacrificed in this manner.[250]

The palladium-catalyzed acylation of organozinc reagents with acid chlorides provides a convenient route to unsymmetrically substituted ketones.[251] Given the attenuated reactivity of organozinc compounds, overaddition of the reagent to the ketone product is not usually a troublesome issue in these reactions, which allows the production of a wide variety of alkyl, alkenyl, and aryl ketone systems in good yield and under mild conditions. One of the most elaborate examples of an acyl-Negishi coupling reported to date is that leading to the formation of ketone **318** (Scheme 56), an advanced intermediate in the synthesis of the marine-derived macrolide amphidinolide T1 (**319**) by Fürstner and co-workers.[252] Thus, after a considerable amount of experimentation, it was found that exposure of alkyl zinc iodide species **314** (R = ZnI), derived from the corresponding primary alkyl iodide (**315**, R = I) by treatment with a zinc/copper couple, to the enantiomerically pure acid chloride **317** in the presence of $[Pd_2(dba)_3]$ (3 mol%) and P(2-furyl)$_3$ (6 mol%) in a toluene/DMA mixed solvent system at ambient temperature led to coupling to give the desired ketone **318** in yields between 40 and 50%. Despite the researchers' best efforts, a significant amount (typically 20–30%) of the reduced compound **316** (R = H) was always also formed in this reaction. Nevertheless, sufficient quantities of the pivotal intermediate **318** could be secured by this route to enable the execution of the remaining few steps required to complete the total synthesis.



Scheme 56. Use of an acid chloride as the electrophile in the Negishi coupling in the total synthesis of amphidinolide T1 (**319**) (Fürstner et al., 2003).[252]

A selection of other architecturally intriguing natural products that have been the target of total syntheses involving Negishi couplings as key carbon–carbon bond-forming steps are highlighted in Scheme 57: reveromycin B (**320**) (Theodorakis and Drouet, 1999),[253] papulacandin D (**321**) (Barrett and co-workers, 1996),[254] longithorone A (**322**) (Shair and co-workers, 2002),[255] and xerulin (**323**) (Negishi and co-workers, 2000).[256] The carbon–carbon bond(s) formed in each case is(are) shown, and while such a cursory overview of the state of the art can neither be comprehensive nor do full justice to the remarkable developments in the field and the efforts of the many researchers involved who could not be acknowledged, it can hopefully serve to emphasize how the Negishi



Scheme 57. Selected examples of natural products syntheses employing Negishi reactions (the C–C bonds formed by this cross-coupling process are highlighted with circles): reveromycin B (**320**) (Theodorakis and Drouet, 1999),[253] papulacandin D (**321**) (Barrett et al., 1996),[254] longithorone A (**322**) (Shair et al., 2002),[255] and xerulin (**323**) (Negishi et al., 2000).[256]

coupling reaction offers the synthetic chemist a plethora of opportunities for carbon–carbon bond-forming operations.

8. Summary and Outlook

As amply demonstrated above, total synthesis has benefited enormously from the palladium-catalyzed cross-coupling reactions that have emerged in the last few decades. These marvelous tools allow the artisans of this flagship discipline of chemical synthesis to flourish and produce some of the most stunning masterpieces in the history of total synthesis. To be sure, the ever-growing expansion of these carbon–carbon bond-forming reactions into new vistas will undoubtedly enable even more impressive accomplishments in the future.

Just as the Grignard, Diels–Alder, Wittig, and hydroboration reactions as well as asymmetric oxidation and hydrogenation of double bonds enabled quantum leaps in our ability to construct complex molecules in the laboratory, so do the carbon–carbon cross-coupling reactions. In particular, these processes do not require the preparation of reactive intermediates prior to the carbon–carbon bond-forming event. Rather, they proceed by activation of stable and readily available starting materials in situ and, therefore, are both more practical and often more efficient in terms of overall yield. And beyond these processes, and fortunately for synthetic chemists, who have been empowered so much by them, a new group of reactions catalyzed by transition metals have appeared on the horizon. These powerful processes are known collectively as metathesis reactions, and their impact in total synthesis is discussed in the following Review article.[257]

Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
binap	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
Cp	cyclopentadienyl
dba	dibenzylideneacetone
DCC	1,3-dicyclohexylcarbodiimide
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
Fmoc	9-fluorenylmethoxycarbonyl
LDA	lithium diisopropylamide
MOM	methoxymethyl
M.S.	molecular sieves
NMP	1-methyl-2-pyrrolidinone
Piv	pivaloyl
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl
SEM	2-(trimethylsilyl)ethoxymethyl
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Teoc	2-(trimethylsilyl)ethoxycarbonyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THP	2-tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	4-toluenesulfonyl

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efficiency in charge carrier production (Table III), showing that the structure of the electron relay (not just the electrochemical driving force) is important in determining the rate of colloid-catalyzed water splitting.[44]

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(44) Whitten has reported that $CMMP^+$ is less effective than MV^{2+} as a relay for photocurrent generation (at a Pt electrode) sensitized by benzophenone in isopropyl alcohol.[45] Launikonis et al. have shown the H_2 yields are a function of pH, $E_{1/2}$ (between −0.5 and −0.7 V), and the structure of diquaternary pyridiniums (hydrogenation susceptibility).[46]

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Inverse Electron Demand Diels–Alder Reactions of Heterocyclic Aza Dienes. Studies on the Total Synthesis of Lavendamycin: Investigative Studies on the Preparation of the CDE β-Carboline Ring System and AB Quinoline-5,8-quinone Ring System

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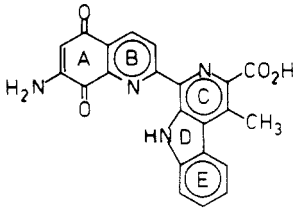
The investigation and utilization of the inverse electron demand [4 + 2] cycloaddition of 3,5,6-tris(ethoxycarbonyl)-1,2,4-triazine with electron-rich olefins and the subsequent implementation of a palladium(0)-mediated β-carboline synthesis for the preparation of the CDE ring system of lavendamycin are detailed. Studies on the introduction and preparation of the 7-aminoquinoline-5,8-quinone AB ring system of lavendamycin are described.

Lavendamycin (1)[2], an antitumor antibiotic[3] recently isolated from *Streptomyces lavendulae* and structurally related to streptonigrin, has been the focus of synthetic efforts[4] since its initial structural identification.[2] A recent,



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reported total synthesis of lavendamycin methyl ester, which proved identical with material derived from natural lavendamycin, has verified the proposed structure 1.[4a] Herein we describe full details[5] of initial efforts designed to construct the β-carboline CDE ring system and the 7-aminoquinoline-5,8-quinone AB ring system of lavendamycin which have been conducted in the development of a total synthesis of lavendamycin[6] and concurrent with our efforts to define the structural features responsible for or potentiating the antimicrobial and cytotoxic properties of quinoline-5,8-quinone antitumor antibiotics.

Studies on the Preparation of the CDE Ring System of Lavendamycin: Inverse Electron Demand Diels–Alder Reaction of 1,2,4-Triazines and Palladium(0)-Mediated β-Carboline Preparation. In recent reports we have detailed the utility of the inverse electron demand Diels–Alder reaction of electron-deficient, substituted 1,2,4-triazines with electron-rich olefins in the preparation of 4-arylpyridines and further demonstrated the potential of this process in a formal total synthesis of streptonigrin.[7,8] In a continued exploration of the factors governing the reactivity and regioselectivity of the [4 + 2] cycloaddition reactions of 1,2,4-triazines, we describe here full details of a short, effective approach to the preparation of the lavendamycin CDE ring system based on a regioselective inverse electron demand Diels–Alder reaction of 3,5,6-tris(ethoxycarbonyl)-1,2,4-triazine and the implementation of a newly developed palladium(0)-mediated β-carboline synthesis (eq 1).[5]

Thermal cycloaddition of the pyrrolidine enamine of *o*-bromopropiophenone (**5a**) with 3,5,6-tris(ethoxy-

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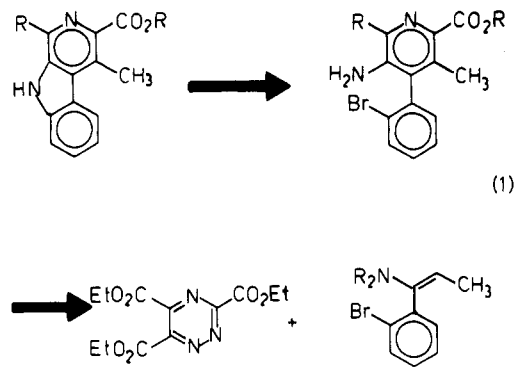
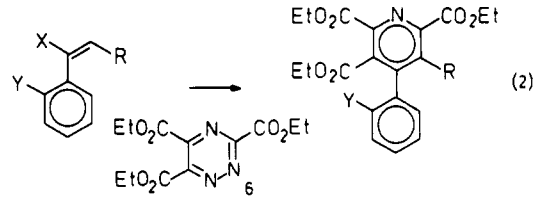


(1)

carbonyl)-1,2,4-triazine (**6**)[9] *proceeds at room temperature* to afford predominantly 4-(2-bromophenyl)-5-methyl-2,3,6-tris(ethoxycarbonyl)pyridine (**7a**) (Scheme I) accompanied by a small amount of the isomeric 3-arylpyridine. The desired adduct **7a** arises from cycloaddition across C-3/C-6 of the 1,2,4-triazine nucleus with the nucleophilic carbon of the electron-rich olefin attaching to C-3. The minor adduct, 5-(2-bromophenyl)-4-methyl-2,3,6-tris(ethoxycarbonyl)pyridine, similarly arises from addition across C-3/C-6 of **6** but with the nucleophilic carbon of the electron-rich olefin attaching to C-6 of the 1,2,4-triazine. This observed regioselectivity of the [4 + 2] cycloaddition is in full agreement with the observations detailed in prior investigations[7] with the exception that the [4 + 2] cycloaddition and subsequent aromatization proceed under milder conditions than anticipated or previously observed. This may be attributed to the enhanced reactivity of the pyrrolidine enamine of *o*-bromopropiophenone due to the presence of a large aryl ortho substituent and partial loss of the stabilizing aryl–olefin conjugation. Table I summarizes representative results of a study of this [4 + 2] cycloaddition reaction and illustrates three additional important observations. Modest increases in the reaction temperature decrease the regioselectivity of the [4 + 2] cycloaddition, and this observation is consistent with those detailed in prior investigations.[7] In addition, the morpholino enamine of 2-bromopropiophenone is less reactive than the corresponding pyrrolidine enamine and participates in a [4 + 2] cycloaddition with **6** with less (no) regioselectivity. While unanticipated, this observation is consistent with those described in a related recent investigation.[7] A third, important feature of the [4 + 2] cycloaddition reactions of substituted 1,2,4-triazines with α-styryl enamines that can be derived from these and related studies[7] is the decrease in rate and regioselectivity of the reaction that generally accompanies alkyl substitution of the β-styryl position of the α-styryl enamines (eq 2).

The introduction of the 3-pyridyl amine, which was anticipated to be derived from a modified Curtius rearrangement of a free C-3 carboxylate and necessarily preceded the β-carboline closure, required effective differentiation of the hindered C-3 ethoxycarbonyl group from the accessible C-2/C-6 ethoxycarbonyl groups. A related approach has been effectively employed in studies directed toward the total synthesis of streptonigrin,[7,10] and the results of our studies are detailed in Scheme I. Exhaustive ester hydrolysis of **7a** followed by selective Fischer esterification of the accessible C-2/C-6 carboxylates afforded 4-(2-bromophenyl)-2,6-bis(methoxycarbonyl)-5-methyl-



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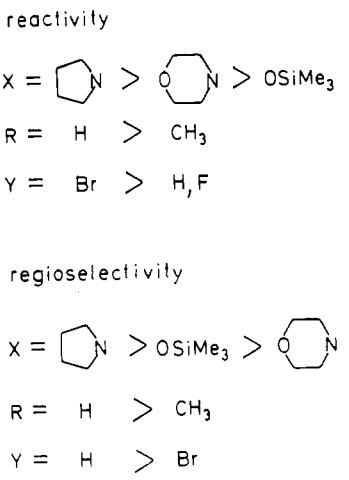
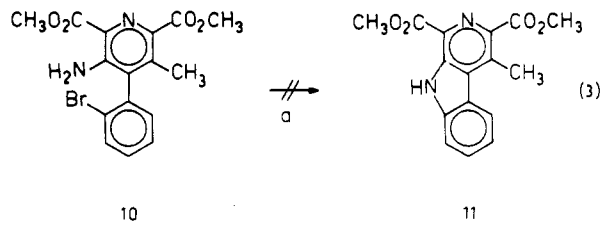


pyridine-3-carboxylic acid (**9**). Conversion of the free C-3 carboxylate to an amine utilizing a modified Curtius rearrangement and the Yamada–Shioiri reagent, diphenyl phosphoroazidate,[11] afforded **10**.

It was anticipated that conventional methods[12] for the formation of an aryl–nitrogen bond would provide the final stage for the CDE ring construction of the β-carboline. Initial, unsuccessful attempts to promote this closure are summarized in eq 3. The inability of these approaches



(3)

10 11

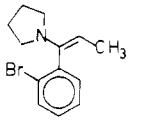
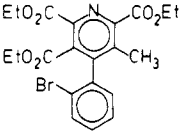
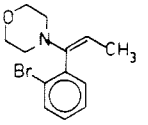
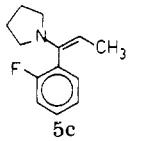
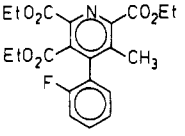
(a) NaH, CuBr;[12a] K_2CO_3, CuI;[12b] K_2CO_3, Cu(Zn);[12c] *t*-BuOK, Me_2SO.[12e]

to provide the desired β-carboline may be due to the noncoplanarity of the biaryl ring system, the result of two ortho substituents forcing the 4-aryl ring into a perpendicular arrangement relative to the pyridyl ring, and the inability of the nitrogen to readily reach the 2′-position necessary for β-carboline formation. In contrast, palladium(0) treatment of **10** under conditions conducive to oxidative insertion[13] into aryl halide bonds provided the β-carboline **11** smoothly. The rationale for the study of this process, which may account for the success, was the accessible formation of the six-membered intermediate **i** which may precede a reductive elimination with formation of the aryl–nitrogen bond and β-carboline generation (eq

(9) Ratz, R.; Schroeder, H. *J. Org. Chem.* **1958**, *23*, 1931.
(10) Martin, J. C. *J. Org. Chem.* **1982**, *47*, 3761. Kende, A. S.; Lorah, D. P.; Boatman, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 1271. Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T.-T. *Ibid.* **1982**, *104*, 536.

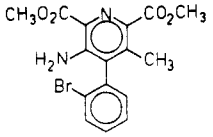
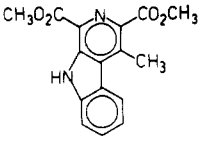
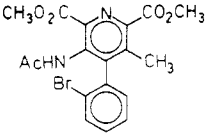
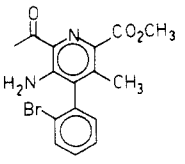
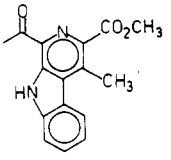
(11) Shiori, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203; *Tetrahedron* **1974**, *30*, 2151.
(12) (a) Kametani, T.; Ohsawa, T.; Ihara, M. *Heterocycles* **1980**, *14*, 277. (b) Kametani, T.; Ohsawa, T.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1978**, 460. Kametani, T.; Takahashi, K.; Ihara, M.; Fukumoto, K. *Ibid.* **1976**, 389. (c) Miller, R. B.; Stowell, J. G. *J. Org. Chem.* **1983**, *48*, 886. (d) Kauffmann, T.; Fischer, H. *Chem. Ber.* **1973**, *106*, 220. (e) Sahyun, M. R. V.; Cram, D. J. *Org. Syn.* **1965**, *45*, 89.
(13) Fitton, P.; Johnson, M. P.; McKeon, J. E. *J. Chem. Soc., Chem. Commun.* **1968**, 6. Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287.

Table I. [4 + 2] Cycloaddition of 3,5,6-Tris(ethoxycarbonyl)-1,2,4-triazine (6) with α-Aryl Enamines

entry	enamine	conditions: equiv enamine	solvent	temp, °C	time, h	product[a]	% yield[b,c]
1[d]	 5a	1.0	$CHCl_3$	60	19	 7a	28 (3.1:1)
		1.5	$CHCl_3$	60	20		51 (3.1:1)
		1.5	CH_2Cl_2	40	22		51 (6.5:1)
		2.5					54 (6.5:1)
		1.5		25	24		50 (7.5:1)
					48		45 (7.5:1)
2[d]	 5b	2.0	$CHCl_3$	45	24	7a	trace
		2.0	$CHCl_3$	60	20		58 (1:1)
3[d]	 5c	2.0	$CHCl_3$	50	24	 7c	52 (>95%)

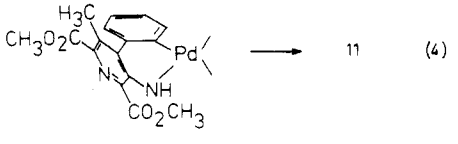
[a] Each product exhibited the expected ^1H NMR, IR, and MS characteristics consistent with the assigned structure, and each gave satisfactory CHN analyses or HRMS information. [b] Yields are based on pure material isolated by chromatography (SiO_2). [c] Ratio of regioisomers isolated from the reaction mixture. The ratio was determined by isolation of the pure isomers or by ^1H NMR integration or the separable $ArCH_3$ signals. [d] The enamine substrates **5a–c** were prepared from the corresponding propiophenones with the aid of $TiCl_4$, see: White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213.

Table II. Palladium(0)-Mediated β-Carboline Synthesis

entry	substrate	conditions: equiv $(Ph_3P)_4Pd$	solvent	temp, °C	time, h	product[a]	% yield[b]
1	 10a	1.0	THF	80	20[c]	 11	50
		1.2	THF	80	21[c]		81
		1.5	THF	80	21[c]		84
		1.2	dioxane	100	20		50
		1.5	dioxane	100	24		80
		1.2	toluene	100	24		43
		0.01	THF	80	24[c]		0
2[d]		1.2	dioxane	100	22	11[e]	50
3[d]		1.4	dioxane	100	10		60
		1.5	dioxane	100	36		87

[a] Each product exhibited the expected ^1H NMR, IR, and MS characteristics consistent with the assigned structure and each gave satisfactory CHN analyses or HRMS information. [b] Yields are based on pure material isolated by chromatography (SiO_2). [c] The reaction was run in a sealed (Teflon) Kontes vial. [d] A detailed procedure for the preparation of the substrate is described in the accompanying report.[6] [e] Deacylation of the β-carboline presumably occurs upon workup and purification.

4).[14] Table II details representative results of a study of this process.



11 (4)

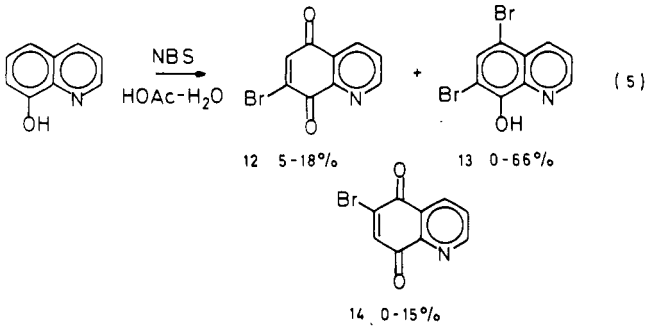
i

(14) (a) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444. Venanzi, A. I.; Pugin, B. *J. Organomet. Chem.* **1981**, *214*, 125. (b) Dillon, K. B.; Waddington, T. C.; Younger, D. *J. Chem. Soc., Dalton Trans.* **1975**, 790.

The cyclization reactions detailed in Table II may involve a nitrogen–palladium(II) reductive elimination with nitrogen–carbon bond formation, and the successful observation of such a process may be attributed to the reduced nucleophilicity of the aryl amine, the result of methoxycarbonyl delocalization, and a weakened N–Pd coordination.[14a] The rate of the cyclization reaction is consistent with the initial oxidative insertion reaction being operative and rate determining. The rate of oxidative addition reactions of palladium(0) with aryl bromides is comparable[13] to the rate of β-carboline formation, and trace amounts of debromo substrate have been detected if the cyclization reactions were quenched prior to the complete

consumption of substrate.[6] The requirement for stoichiometric $(Ph_3P)_4Pd$ for effective promotion of the β-carboline closure potentially arises from a competitive oxidative addition of liberated HBr with catalyst.[14b]

Studies on the Preparation of the AB Quinoline-5,8-quinone Ring System of Lavendamycin. Assured that the CDE ring system of lavendamycin could arise from a 4-arylpyridine generated through the use of an inverse electron demand [4 + 2] cycloaddition reaction of a 1,2,4-triazine, efforts focused on the preparation and utilization of an appropriately substituted amino aldehyde for use in a Friedlander condensation[15] and introduction of the AB 7-aminoquinoline-5,8-quinone ring system found in lavendamycin.[6] Initial studies which were conducted with 7-bromoquinoline-5,8-quinone (**12**), prepared in modest yield in a one-step oxidative bromination of 8-hydroxyquinoline (eq 5)[16] or by modification of a previ-



12 5-18% 13 0-66% (5)

14 0-15%

ously detailed three-step procedure,[17,18] secured the suitability of such a precursor for introduction of a 7-aminoquinoline-5,8-quinone (Scheme II).[17,18] Treatment of 7-bromoquinoline-5,8-quinone (**12**) with sodium azide,[19] a reaction that was found to be sensitive to the presence of excess reagent,[19b] followed by reduction of 7-azidoquinoline-5,8-quinone (**17**) with triphenylphosphine provided 7-aminoquinoline-5,8-quinone (**18**). The use of excess sodium azide (1.5 equiv) in the displacement reaction did lead to the predominant formation of 7-amino-6-azidoquinoline-5,8-quinone,[19] and initial attempts at reduction of 6-azidoquinoline-5,8-quinone (**17**) with sodium hydrosulfite[4a,19] failed to provide the 7-aminoquinoline-5,8-quinone (**18**) in acceptable yields (10–20%). In contrast, the use of stoichiometric sodium azide in the conversion of **12** to **17** and azide reduction with triphenylphosphine followed by mild, aqueous hydrolysis of the resulting phosphine imine[20] provided **18** in excellent yields without competitive quinone to hydroquinone reduction. The direct azide displacement of 7-bromoquinoline-5,8-quinone was confirmed by comparison of **18** with authentic 7-aminoquinoline-5,8-quinone of unambiguous structure.[17]

Assured that a 7-bromoquinoline-5,8-quinone could serve as an immediate precursor for the introduction of the lavendamycin AB 7-aminoquinoline-5,8-quinone ring system, the preparation of 2-amino-3-(benzyloxy)-4-bromobenzaldehyde (**23**) for use in a Friedlander condensation and 7-bromoquinoline-5,8-quinone introduction was investigated and is detailed in Scheme III.[21] The selection of **23** as the amino aldehyde component for use in a Friedlander condensation and subsequent lavendamycin AB quinoline introduction was based on the recognized observations that 6-substituted 2-aminobenzaldehydes, agents that possess two substituents ortho to the aryl aldehyde, participate in a Friedlander condensation in only low to modest yields.[15] Thus, the choice of **23** represents one in which the amino aldehyde possesses suitable functionality for introduction of the 7-aminoquinoline-5,8-quinone and one in which the Friedlander condensation would be expected to proceed in satisfactory yield.

Consistent with these expectations, condensation[15] of **23** with 2-acetylpyridine (**24**) provided 8-(benzyloxy)-7-bromo-2-(2′-pyridyl)quinoline (**25**) in excellent yield (Scheme IV). Deprotection of the phenol in **25**, which was most effectively accomplished with anhydrous hydrogen bromide in benzene,[22] provided **26**. Direct conversion of **26** to the 7-bromoquinoline-5,8-quinone **27** was effected with the use of potassium nitrosodisulfonate, Fremy's salt,[23] in an oxidation that was not especially sensitive to

(15) Cheng, C. C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37.

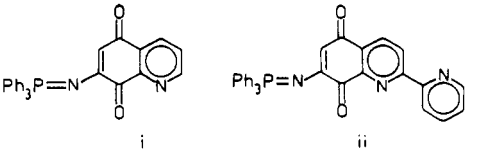
(16) (a) Heinzman, S. W.; Grunwell, J. R. *Tetrahedron Lett.* **1980**, *21*, 4305.

(17) (a) Petrow, V.; Sturgeon, B. *J. Chem. Soc.* **1954**, 571. (b) Authentic 7-aminoquinoline-5,8-quinone was also prepared by the sequence 70% HNO_3–H_2SO_4, 0–25 °C, 1 h, 75% [8-hydroxyquinoline to 5,7-dinitro-8-hydroxyquinoline]; H_2, 5% Pd/C, THF–EtOH, 25 °C, 48 h [5,7-dinitro-8-hydroxyquinoline to 5,7-diamino-8-hydroxyquinoline: ^1H NMR ($CDCl_3$, ppm) 8.85 (1 H, dd, J = 5, 1 Hz, C-2 H), 8.65 (1 H, dd, J = 9, 1 Hz, C-4 H), 7.54 (1 H, dd, J = 9, 6 Hz, C-3 H), 6.12 (1 H, s, C- H)]; 10 equiv of Fremy's salt, CH_3OH–0.05 M K_2HPO_4, 25 °C, 14–48 h and proved to be identical with the material prepared by the sequence detailed in Scheme II.

(18) Details of the preparation of **12** are provided in supplementary material.

(19) (a) Kuo, H. S.; Yoshina, S. *Yakugaku Zasshi* **1977**, *97*, 827. (b) In a related study, treatment of 2-bromo-1,4-naphthoquinone with 1.5 equiv of sodium azide (THF or DMF, 25 °C, 0.5–2 h) led to the predominant formation of 2-amino-3-azido-1,4-naphthoquinone: ^1H NMR ($CDCl_3$, ppm) 8.06–7.50 (4 H, m, aromatic), 5.07 (2 H, br s, NH_2); IR (KBr) ν_{max} 3470, 3264 (NH), 2120 (N_3), 1680 cm^{-1}; MS m/e 214 (M^+). The dissolution of sodium azide in water or methanol prior to addition to a solution of **12** resulted in a substantial increase in the isolated yield of **17**. The displacement reaction proceeds more rapidly (6 min, EtOH–H_2O, 25 °C, 87%; 12 min, THF–H_2O, 25 °C, 91%) than the studies of others imply [4a,19a] (1.5 equiv of NaN_3, 3 h, 25 °C), and a small amount of 7-aminoquinoline-5,8-quinone (**18**, 3–13%) is formed directly in the reaction of **12** with sodium azide. For related observations, see: Fieser, L. F.; Hartwell, J. L. *J. Am. Chem. Soc.* **1935**, *57*, 1482. (c) Treatment of *suspensions* of 7-bromoquinoline-5,8-quinone (**27**) in THF, CH_3OH, DMF, and HMPA with 1 equiv of NaN_3 (predissolved in H_2O or CH_3OH) afforded predominantly 7-amino-6-azido-2-(2-pyridyl)quinoline-5,8-quinone: ^1H NMR ($CDCl_3$, ppm) 8.89 (1 H, d, J = 8 Hz, C-4 H), 8.61 (2 H, rough d, J = 7.5 Hz, pyridyl C-3/C-6 H), 8.41 (1 H, d, J = 8 Hz, C-3 H), 7.82 (1 H, ddd, J = 8, 7.5, 1.5 Hz, pyridyl C-4 H), 7.47–7.22 (1 H, m, pyridyl C-5 H); IR (KBr) ν_{max} 3459, 3389 (NH), 2116 (N_3), 1688, 1619, 1586, 1451, 1402, 1375, 1312, 1291, 1264, 1244, 1181, 1148, 1107, 1076, 1055, 997 cm^{-1}; MS m/e 292 (M^+), 266 (M^+–N_2 + H_2), 264 (M^+ – N_2), 250 (M^+ – N_3). This results from an effective concentration of NaN_3 in excess of 1.0 equiv. The two-phase reaction conditions utilized in the conversion of **27** to **28** minimizes the effective concentration of sodium azide present in the organic phase and allows the reaction to be conducted under conditions in which the 7-bromoquinoline-5,8-quinone is soluble.

(20) (a) Mungall, W. S.; Greene, G. L.; Heavner, G. A.; Letsinger, R. L. *J. Org. Chem.* **1975**, *40*, 1659. (b) Corey, E. J.; Samuelsson, B.; Luzzio, F. A. *J. Am. Chem. Soc.* **1984**, *106*, 3682. The phosphine imine **i** was isolated by chromatography (SiO_2, 68%) upon treatment of **17** with Ph_3P (1.1 equiv, 25 °C, CH_2Cl_2, 1 h) and characterized. Hydrolysis of purified **i** (HOAc–H_2O–THF, 3:2:1, 25 °C) provided **18** (93%, 10 min; 48%, 2.7 h). Similarly, **ii** was isolated and characterized in the conversion of **28** and **29**.

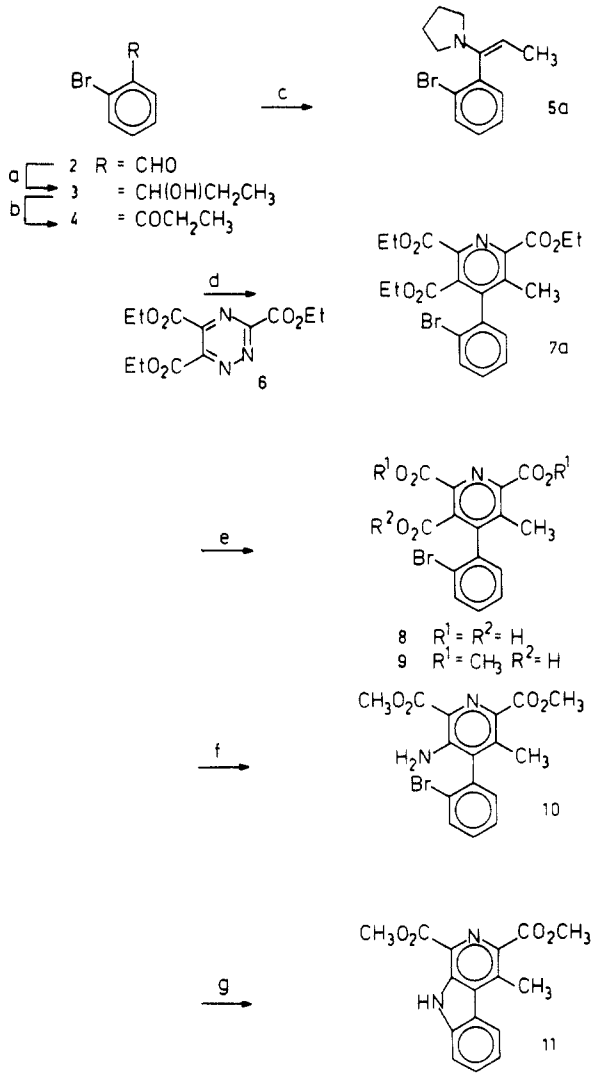


i ii

(21) Seela, F. *J. Med. Chem.* **1972**, *15*, 684. The yield of isolated product in the sodium hydrosulfite conversion of **22** to **23** decreases with increasing reaction time (93%, 0.5 h; 80%, 12 h) due to a slow, competing reduction of the aldehyde group.

(22) Initial efforts to remove the benzyl ether with CF_3CO_2H (neat, 60 °C, 7–17 h) were as effective (90–98%) but on occasion provided substantial or predominant amounts of the pyridinium *N*-benzyl derivative of **26**: ^1H NMR ($CDCl_3$, ppm) 4.33 (2 H, s, NCH_2Ph). For related observations, see: Marsh, J. P., Jr.; Goodman, L. *J. Org. Chem.* **1965**, *30*, 2491. Kiso, Y.; Isawa, H.; Kitagawa, K.; Akita, T. *Chem. Pharm. Bull.* **1978**, *26*, 2562. Deprotection of the phenol in CH_2Cl_2 [HBr(g), 25 °C, 1 h] was equally effective (95–100%).

Scheme I[a]



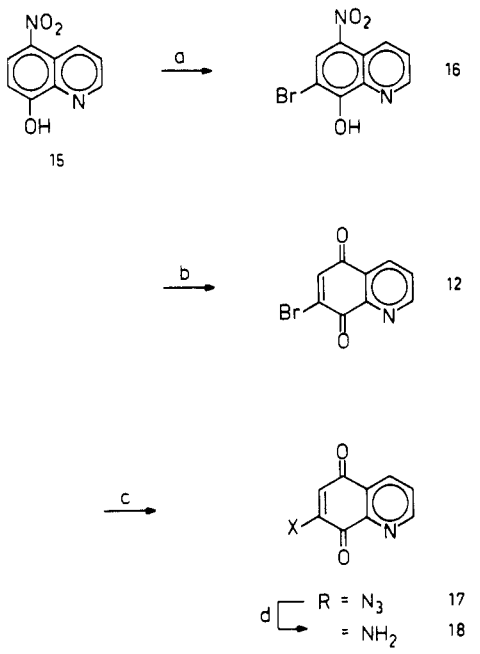
[a] (a) 1.0 equiv of EtMgBr, THF, −78 to +25 °C, 3.5 h; (b) 1.2 equiv of H_2CrO_4, Et_2O, 25 °C, 3.0 h, 94% from **2**; (c) 4 equiv of pyrrolidine, 0.5 equiv of $TiCl_4$, Et_2O, 0–25 °C, 12–16 h, 80–88%; (d) Table I; (e) 15 equiv of LiOH, THF-CH_3OH-H_2O (3:2:1), reflux, 28–30 h; 10% HCl-CH_3OH, 25 °C, 18–20 h, 67% from **7a**; (f) 2.2 equiv of $(PhO)_2P(O)N_3$, 2.2 equiv of Et_3N, benzene, reflux, 2.5 h; H_2O-benzene, reflux, 2 h, 72%; (g) Table II.

the substrate concentration.[22b,24]

Conversion of the reactive 7-bromoquinoline-5,8-quinone **27**[24] to 7-amino-2-(2-pyridyl)quinoline-5,8-quinone (**29**) followed the protocol described beforehand and is detailed in Scheme IV.

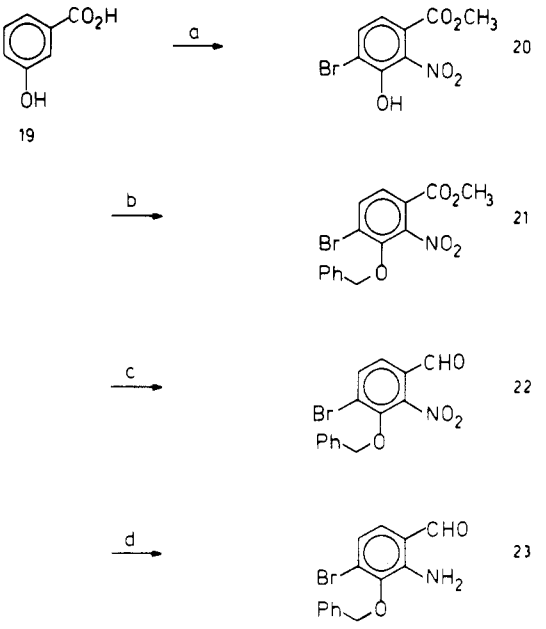
Application of these studies in the total synthesis of lavendamycin (**1**) is detailed in the accompanying report.[6] Current studies on the antimicrobial, cytotoxic, and antitumor properties of quinoline-5,8-quinones including the lavendamycin partial structures detailed herein will be reported separately.

Scheme II[a]



[a] (a) 1.05 equiv of NBS, THF, catalytic H_2SO_4, 25 °C, 2.5 h, 88%; (b) 5.0 equiv of $Na_2S_2O_4$, THF-H_2O, 60 °C, 10 min, 74%; 2.0 equiv of $K_2Cr_2O_7$, CH_2Cl_2-5% aqueous H_2SO_4, 25 °C, 30 min, 64%; (c) 1.1 equiv of NaN_3, THF-H_2O, 25 °C, 0.2 h, 91% **17** and 3% **18**; (d) 1.1 equiv of Ph_3P, CH_2Cl_2, 25 °C, 1 h, 68–79%; HOAc-H_2O-THF (3:2:1), 25 °C, 10 min, 93%.

Scheme III[a]



[a] (a) Br_2, HOAc; HNO_3; HCl, CH_3OH;[21] (b) 1.2 equiv of NaH, DMF, 0 °C, 10 min; 1.1 equiv of $PhCH_2Br$, 0–25 °C, 20 h, 85%; (c) 3.0 equiv of $LiBH_4$, THF, 25 °C, 21 h, 93–97%; 1.5 equiv of PDC, CH_2Cl_2, 25 °C, 11 h, 83%; (d) 5 equiv of $Na_2S_2O_4$, H_2O-THF, 60 °C, 0.5 h, 93%.

Experimental Section[25]

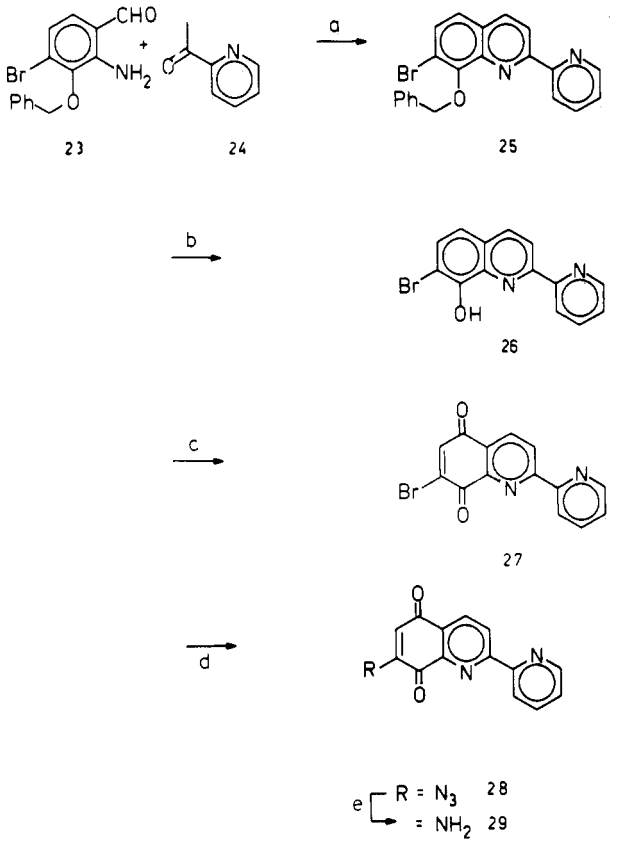
Triethyl 4-(2-Bromophenyl)-5-methylpyridine-2,3,6-tricarboxylate (7a). A solution of triethyl 1,2,4-triazine-3,5,6-

(23) (a) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229. (b) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2745. Attempts to convert **26** to **27** with ceric ammonium nitrate[4b] or potassium dichromate[4a,17] led to the consumption of **26** without product formation. No reaction was observed upon treatment of **26** with Fremy's salt (5–15 equiv, THF, 25 °C), HIO_4 (1.5 equiv, CH_3OH–$CHCl_3$, 2:1, 25 °C, 20 h) (see: Rao, K. V.; Kuo, H.-S. *J. Heterocycl. Chem.* **1979**, *42*, 232).

(24) Oxidations of **26** to **27** with Fremy's salt proceed well under a range of conditions (4–20 equiv of Fremy's salt, 0.07–0.002 M **26**, MeOH or acetone–0.05 M KH_2PO_4, 1.5–2.5 h, 53–100%). A two-phase Fremy's salt oxidation[4a] of **26** (20–40 equiv Fremy's salt, H_2O–CH_2Cl_2, 25 °C, 2–5 h) in the presence of $(n\text{-}Bu)_4NHSO_4$ (1.0 equiv) as a phase-transfer catalyst provided **27** (50–70%). The 7-bromoquinoline-5,8-quinone **27** is not completely stable to chromatography on silica gel.

(25) General experimental details are provided in the accompanying report.[6]

Scheme IV[a]



[a] (a) 4 equiv of Triton B, THF, 25 °C, 18 h, 81–90%; (b) HBr(g), C_6H_6, 60 °C, 7 h, 98%; (c) 20 equiv of $\cdot ON(SO_3K)_2$, acetone, 0.05 M KH_2PO_4, 25 °C, 2.0 h, 77% (100%);[24] (d) 1.1 equiv of NaN_3, CH_2Cl_2–H_2O, 23 h, 25 °C, 85% **28** and 8% **29**; (e) 1.0 equiv of Ph_3P, CH_2Cl_2, 1 h, 25 °C; HOAc–H_2O–THF (3:2:2), 25 °C, 0.3 h.

tricarboxylate[9,26] (**6**; 5.0 g, 16.8 mmol) in methylene chloride (60 mL) was treated with the pyrrolidine enamine **5a**[26] (6.77 g, 25.2 mmol, 1.5 equiv) in methylene chloride (5.0 mL) at 25 °C under N_2. The reaction mixture was stirred at 25 °C for 24 h and the solvent was removed in vacuo. MPLC (SiO_2, 25 × 500 cm, 30% ether–hexane eluant) afforded 3.90 g (7.79 g theor, 50%) of **7a** (7.5:1 regioisomer). For **7a**: ^1H NMR ($CDCl_3$) δ 7.74–7.09 (4 H, m, aromatic), 4.45 (2 H, q, J = 8 Hz, CH_2), 4.40 (2 H, q, J = 8 Hz, CH_2), 4.00 (2 H, q, J = 8 Hz, CH_2), 2.24 (3 H, s, $ArCH_3$), 1.44 (3 H, t, J = 8 Hz, CH_3), 1.40 (3 H, t, J = 8 Hz, CH_3), 0.97 (3 H, t, J = 8 Hz, CH_3); IR (film) ν_{max} 3025, 2985, 1725, (C=O), 1552, 1456, 1358, 1323, 1265, 1236, 1200, 1080, 1000, 892, 840, 735, 708 cm^{-1}; EIMS m/e (relative intensity) 464/466 (M^+, 1/1, 4), 420/418 (10), 392/390 (15), 385 (40), 384 (97), 356 (24), 331 (20), 319 (35), 318 (30), 316 (20), 311 (22), 310 (base), 282 (48), 238 (27), 210 (35), 209 (24), 194 (26), 167 (35), 166 (43), 165 (44), 164 (49), 140 (40), 139 (51), 138 (20), 116 (21); HRMS m/e for $C_{21}H_{22}BrNO_6$, calcd 463.0629, found 463.0590.

4-(2-Bromophenyl)-3-carboxy-2,6-bis(methoxycarbonyl)-5-methylpyridine (9). A solution of triethyl 4-(2-bromophenyl)-5-methylpyridine-2,3,6-tricarboxylate (**7a**; 560 mg, 1.2 mmol) in THF–MeOH (50 mL, 3:2) was treated with a solution of LiOH (762 mg, 18.1 mmol, 15.0 equiv) in H_2O (10 mL) at 25 °C under N_2. The resulting reaction mixture was warmed at reflux for 36 h. The reaction mixture was cooled, diluted with H_2O (30 mL), acidified to pH 2–3 using 1 N HCl, and extracted with EtOAc (2 × 40 mL). The organic extracts were washed with saturated NaCl, dried (Na_2SO_4), and filtered and the solvent was removed in vacuo. A solution of the crude triacid **8** in absolute MeOH (10 mL) was added to a stirred solution of 10% HCl–MeOH (40 mL) at 25 °C. The reaction was stirred at 25 °C (18 h). The solvent was removed in vacuo. Chromatography (SiO_2, 3% MeOH–$CHCl_3$ eluant) afforded 331 mg (489 mg theor, 67%) of pure **9** as a white foam:[29b] mp 250 °C dec; ^1H NMR ($CDCl_3$) δ 7.72–7.40 (1 H, m, aromatic), 7.38–7.05 (3 H, m, aromatic), 4.00 (3 H, s, CO_2CH_3), 3.93 (3 H, s, CO_2CH_3), 2.26 (3 H, s, $ArCH_3$); IR ($CHCl_3$) ν_{max} 3600–2400 (br, CO_2H), 3000, 2927, 1728, 1588, 1435, 1345, 1300, 1250, 1218, 1110, 1038, 1012 cm^{-1}; EIMS m/e (relative intensity) 392/390 (3), 364/362 (3), 343 (16), 342 (75), 297 (19), 296 (base), 268 (12), 264 (6), 252 (8), 237 (5), 236 (10), 225 (9), 224 (27), 209 (10), 208 (11), 207 (5), 194/192 (8), 193 (8), 181 (7), 180 (8), 167 (15), 166 (16), 165 (26), 164 (48), 153 (17), 152 (15), 140 (16), 139 (25), 138 (21), 137 (11), 127 (11), 126 (17), 115 (10), 114 (8), 100 (9), 99 (9), 89 (10), 88 (12).

Anal. Calcd for $C_{17}H_{14}BrNO_6$: C, 50.01; H, 3.45; N, 3.45. Found: C, 50.38; H, 3.09; N, 3.10.

3-Amino-4-(2-bromophenyl)-2,6-bis(methoxycarbonyl)-5-methylpyridine (10). A solution of 4-(2-bromophenyl)-3-carboxy-2,6-bis(methoxycarbonyl)-5-methylpyridine (**9**; 347 mg, 0.85 mmol) in dry benzene (15 mL) was treated with diphenyl phosphorazidate[11] (514 mg, 1.87 mmol, 2.2 equiv) and triethylamine (223 mg, 0.3 mL, 2.2 equiv) at 25 °C under N_2. The reaction mixture was warmed at reflux for 2.5 h and cooled, and H_2O (0.25 mL) was added. The reaction mixture was warmed at reflux for an additional 2.0 h. The solvent was removed in vacuo, and chromatography (SiO_2, 50% EtOAc–hexane eluant) afforded 232 mg (322 mg theor, 72%) of pure **10** as a white solid: mp 146–148 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$) δ 7.76 (1 H, dd, J = 10 Hz, J = 2 Hz, aromatic), 7.45–7.05 (3 H, m, aromatic), 5.82 (2 H, br s, $ArNH_2$), 3.98 (3 H, s, CO_2CH_3), 3.96 (3 H, s, CO_2CH_3), 2.24 (3 H, s, $ArCH_3$; ^{13}C NMR ($CDCl_3$) δ 166.0/164.5 (two s, CO_2CH_3), 145.9 (s, C3), 138.9 (s, C2), 136.1 (s, C6), 135.2 (s, C5), 133.9 (d, C10), 130.8/130.6 (two d, C9/C11), 130.5 (s, C4), 128.8 (d, C12), 125.3 (s, C7), 123.7 (s, C8, CBr), 53.6/52.5 (two q, CO_2CH_3), 17.3 (q, CH_3); IR ($CHCl_3$) ν_{max} 3510 and 3380 (NH_2), 3010, 2960, 1722, 1695, 1588, 1435, 1348, 1305, 1268, 1250, 1230, 1113, 895 cm^{-1}; EIMS m/e (relative intensity) 378/380 (M^+, 1/1, 30), 347 (11), 322/320 (55), 299 (39), 290/288 (32), 269 (11), 267 (33), 240 (19), 239 (96), 224 (12), 210/208 (20), 209 (base), 196 (4), 195 (9), 183 (7), 182 (20), 181 (30), 152 (24), 141 (11), 140 (18), 128/126 (21), 127 (36), 77 (40), 76 (15), 75 (13), 63 (20), 59 (16), 51 (16).

Anal. Calcd for $C_{16}H_{15}BrN_2O_4$: C, 50.67; H, 3.98; N, 7.38. Found: C, 50.59; H, 4.00; N, 7.20.

The conversion of **7a** (7.5:1 **7a**/regioisomer, 3.34 g, 7.2 mmol) to **10** without the prior separation of the **7a**/regioisomer mixture afforded **10** (1.50 g, 4.0 mmol, 56% overall). Separation of **10** from the isomeric product, dimethyl 3-amino-5-(2-bromophenyl)-4-methylpyridine-2,6-dicarboxylate[29a] (0.20 g, 7%), proved convenient at this stage.

1,3-Bis(methoxycarbonyl)-4-methyl-β-carboline (11). A solution of **10** (159 mg, 0.42 mmol) in 4.0 mL of dioxane was treated with tetrakis(triphenylphosphine)palladium(0) (728 mg, 0.628 mmol, 1.5 equiv) under an argon atmosphere and was warmed at 100 °C for 24 h. The reaction mixture was cooled and the solvent was removed in vacuo. Chromatography (SiO_2, 30% EtOAc–hexane eluant) afforded 100 mg (125 mg theor, 80%) of pure **11** as a yellow solid: mp 217–219 °C (EtOH); ^1H NMR ($CDCl_3$) δ 10.17 (1 H, br s, NH), 8.35 (1 H, d, J = 8 Hz, aromatic), 7.68–7.40 (3 H, m, aromatic), 4.11 (3 H, s, CO_2CH_3), 4.04 (3 H, s, CO_2CH_3), 3.22 (3 H, s, $ArCH_3$); ^{13}C NMR[27] ($CDCl_3$) δ 166.8 and 165.2 (CO_2CH_3), 141.5 (C-8), 137.3 (C-6), 135.8 (C-5), 132.8 (C-2), 129.8 (C-4), 128.6 (C-10), 128.4 (C-3), 123.6 (C-12), 123.4 (C-7), 120.7 (C-11), 113.1 (C-9), 52.10 and 52.08 (CO_2CH_3), 16.3 (CH_3); IR ($CHCl_3$) ν_{max} 3422 (NH), 3005, 2928, 1723, 1700, 1590,1490,

(26) Full details for the preparation are provided in the supplementary material.

(27) Assignments are based in part on a comparison with the ^{13}C NMR assignments of lavendamycin; see ref 3.

(28) Available from Aldrich Chemical Co.

(29) (a) For 3-amino-5-(2-bromophenyl)-2,6-bis(methoxycarbonyl)-4-methylpyridine: ^1H NMR ($CDCl_3$, ppm) 6.98–7.72 (4 H, m aromatic), 6.28 (2 H, br s, NH_2), 3.99 (3 H, s, CO_2CH_3), 3.71 (3 H, s, CO_2CH_3), 1.88 (3 H, s, CH_3); IR (KBr) ν_{max} 3457, 3353, 1728, 1694, 1611, 1476, 1435, 1358, 1300, 1233, 1206, 1163, 1113, 1021, 903, 793, 762 cm^{-1}, EIMS (relative intensity) m/e 378/380 (M^+, 1/1, 1), 299 (M^+ – Br, base), 240 (3), 223 (2). (b) Fischer esterification (10% HCl–CH_3OH), 25 °C, 18 h) of purified 4-(2-bromophenyl)-5-methylpyridine-2,3,6-tricarboxylic acid (**8**) afforded **9** in 78% yield.

(30) Salesin, E. D.; Gordon, L. *Talanta* **1960**, *4*, 75.

1458, 1438, 1342, 1297, 1272, 1241, 1098, 1062 cm^{-1}; mass spectrum m/e (relative intensity) 298 (M^+, 65), 267 (11), 266 (20), 241 (9), 240 (63), 239 (16), 238 (37), 209 (18), 208 (base), 207 (7), 206 (28), 181 (8), 180 (18), 179 (32), 178 (9); HRMS m/e for $C_{16}H_{14}N_2O_4$, calcd 298.0953, found 298.0940.

In the same manner, **10** (20 mg, 0.053 mmol) in 1.0 mL of THF was treated with $(Ph_3P)_4Pd$ (92 mg, 0.08 mmol, 1.5 equiv) and the reaction mixture was warmed at 80 °C in a sealed Kontes vial for 21 h. Chromatography (SiO_2, 30% EtOAc–hexane) afforded 13 mg (82%) of pure **11**.

7-Azidoquinoline-5,8-quinone (17). A stirred solution of 7-bromoquinoline-5,8-quinone (**12**; 26 mg, 0.11 mmol)[18] in 0.35 mL of THF was treated with a solution of sodium azide (8 mg, 0.12 mmol, 1.1 equiv) in 0.05 mL of H_2O at 25 °C under a N_2 atmosphere, and the mixture was stirred at 25 °C for 0.2 h. The solution was poured onto 5 mL of cold water and extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 1 × 13 cm, 50–100% ethyl acetate–hexane eluant; gradient elution) afforded 20 mg (22 mg theor, 91%) of **17** as an orange solid: mp 135–137 °C (lit.[19a] mp 136–138 °C); ^1H NMR ($CDCl_3$) δ 8.96 (1 H, rough d, J = 5 Hz, C-2 H), 8.38 (1 H, dd, J = 8, 1.5 Hz, C-4 H), 7.62 (1 H, dd, J = 5, 8 Hz, C-3 H), 6.48 (1 H, s, C-6 H); IR (KBr) ν_{max} 2132, 1698, 1653, 1578, 1323, 1260, 1136, 947 cm^{-1}. It also gave 1 mg (37 mg theor, 3%) of **18** as a red, crystalline solid identical with the material described below.

7-Aminoquinoline-5,8-quinone (18). A stirred solution of **17** (27 mg, 0.14 mmol) in dry CH_2Cl_2 (0.15 mL) under a N_2 atmosphere was treated with a solution of triphenylphosphine (39 mg, 0.15 mmol, 1.1 equiv) in 0.15 mL of CH_2Cl_2 with stirring. Evolution of nitrogen was visible within 1 min after addition of Ph_3P. Stirring was continued at 25 °C for 1 h. Concentration of the reaction mixture in vacuo gave 70 mg of dark brown residue. Chromatography (SiO_2, 1.5 × 17 cm, 60% ethyl acetate–hexane eluant) afforded 40.5 mg (60 mg theor, 68%) of the phosphine imine as a brown solid: mp 214–215 °C; ^1H NMR ($CDCl_3$) δ 8.68 (1 H, dd, J = 5, 1.5 Hz, C-2 H), 8.25 (1 H, dd, J = 8, 1.5 Hz, C-4 H), 7.12–7.91 (16 H, m, phenyl H and C-3 H), 6.47 (1 H, s, C-6 H); IR (KBr) ν_{max} 3434, 1686, 1620, 1584, 1437, 1331, 1285, 1267, 1065, 889 cm^{-1}; MS m/e (relative intensity) 434 (M^+, 42), 262 (base), 183 (79), 108 (25).

Similarly, a solution of **17** (12 mg, 0.06 mmol) in CH_2Cl_2 (0.1 mL) under a N_2 atmosphere was treated with a solution of Ph_3P (17.3 mg, 0.066 mmol, 1.1 equiv) in 0.1 mL of CH_2Cl_2 and stirred at 25 °C for 1 h. Rapid chromatography (SiO_2, 1 × 17 cm, 60–70% ethyl acetate–hexane gradient elution) afforded 20.6 mg (26.1 mg theor, 79%) of the phosphine imine.

A solution of the phosphine imine (36 mg, 0.083 mmol) in 0.3 mL of THF was treated with 0.9 mL of acetic acid and 0.6 mL of H_2O, and the solution was allowed to stir at 25 °C for 10 min. The reaction solution was diluted with 5 mL of H_2O, extracted with ethyl acetate (3 × 10 mL, 3 × 5 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 1.5 × 20 cm, 60% ethyl acetate–hexane eluant) and washing with ether to remove triphenylphosphine oxide afforded 13.5 mg (14.5 mg theor, 93%) of **18** as a red, crystalline solid: mp 263 °C (ethyl acetate, lit.[19a] mp 263 °C); ^1H NMR ($CDCl_3$) δ 8.88 (1 H, dd, J = 5, 1.5 Hz, C-2 H), 8.37 (1 H, dd, J = 8, 1.5 Hz, C-4 H), 7.59 (1 H, dd, J = 5, 8 Hz, C-3 H), 6.03 (1 H, s, C-6 H), 5.25 (2 H, br s, NH_2); IR (KBr) ν_{max} 3440, 3295, 1701, 1615, 1555, 1420, 1356, 1267, 1146, 1003, 818 cm^{-1}.

Methyl 3-(Benzyloxy)-4-bromo-2-nitrobenzoate (21). A solution of methyl 4-bromo-3-hydroxy-2-nitrobenzoate[21] (**20**; 1.80 g, 6.52 mmol) in dry DMF (40 mL) was cooled to 0 °C under N_2 and treated with sodium hydride (313 mg, 7.80 mmol, 1.2 equiv). The reaction mixture was stirred for 10 min (0 °C) before benzyl bromide (1.22 g, 7.20 mmol, 1.1 equiv) was added. The reaction mixture was allowed to warm to 25 °C (0.5 h), and stirring was continued for an additional 20 h. A solution of saturated NaCl (10 mL) was added, and the reaction mixture was further diluted with H_2O (60 mL). The aqueous layer was extracted with Et_2O (4 × 40 mL). The combined ether extracts were washed with H_2O (1 × 20 mL), washed with saturated NaCl (1 × 10 mL), and dried (Na_2SO_4), and the solvent was removed in vacuo. MPLC (SiO_2, 25 × 500 cm, 15% EtOAc–hexane eluant) afforded 2.02 g (2.38 g theor, 85%) of pure **21** as light yellow crystals: mp 85–87 °C (Et_2O–hexane); ^1H NMR ($CDCl_3$) δ 7.80 (1 H, d, J = 8 Hz, aromatic), 7.68 (1 H, d, J = 8 Hz, aromatic), 7.46–7.25 (5 H, m, Ph), 5.13 (2 H, s, OCH_2Ph), 3.90 (3 H, s, CO_2CH_3); IR (KBr) ν_{max} 2959, 1723, 1587, 1561, 1547, 1458, 1433, 1366, 1304, 1132, 1003, 903, 847, 752 cm^{-1}; EIMS m/e (relative intensity) 365/367 (M^+, 1/1, 1), 259/261 (19), 92 (base), 65 (72).

Anal. Calcd for $C_{15}H_{12}BrNO_5$: C, 49.19; H, 3.30, N, 3.82. Found: C, 48.89; H, 3.20; N, 3.78.

3-(Benzyloxy)-4-bromo-2-nitrobenzaldehyde (22). A solution of methyl 3-(benzyloxy)-4-bromo-2-nitrobenzoate (**21**; 1.20 g, 33.0 mmol) in THF (30 mL) was treated with $LiBH_4$ (216 mg, 9.90 mmol, 3.0 equiv) at 25 °C under N_2. The reaction mixture was stirred at 25 °C (21 h). Saturated ammonium chloride (10 mL) was added and the reaction mixture diluted with H_2O (50 mL) and extracted with EtOAc (2 × 25 mL). The organic extract was washed with saturated NaCl, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. MPLC (SiO_2, 15 × 250 cm, 10–15% EtOAc–hexane gradient elution) afforded 1.04 g (1.11 g theor, 93%, 93–97%) of pure 3-(benzyloxy)-4-bromo-2-nitrobenzyl alcohol as a beige solid: mp 65–67 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$) δ 7.69 (1 H, d, J = 8 Hz, aromatic), 7.44–7.34 (5 H, m, Ph), 7.20 (1 H, d, J = 8 Hz, aromatic), 5.13 (2 H, s, CH_2Ph), 4.64–4.57 (2 H, m, $ArCH_2OH$); IR (KBr) ν_{max} 3408, 2962, 1536, 1466, 1456, 1366, 1275, 1221, 1047, 1003, 762 cm^{-1}; EIMS m/e (relative intensity) 337/339 (M^+, 1/1, 1), 303/305 (1), 231/233 (1), 213/215 (1), 107 (9), 91 (base); HRMS m/e for $C_{14}H_{12}BrNO_4$, calcd 336.9948, found 336.9942.

A solution of 3-(benzyloxy)-4-bromo-2-nitrobenzyl alcohol (500 mg, 1.48 mmol) in CH_2Cl_2 (35 mL) was treated with pyridinium dichromate (835 mg, 2.22 mmol, 1.5 equiv) at 25 °C under N_2. The reaction mixture was stirred at 25 °C (11.0 h), filtered through Celite, washed with 5% aqueous HCl (1 × 15 mL) and saturated NaCl (1 × 15 mL), and dried (Na_2SO_4) and the solvent was removed in vacuo. MPLC (SiO_2, 15 × 250 cm, 10% EtOAc–hexane eluant) afforded 410 mg (497 mg theor, 82%) of pure **22** as a yellow solid: mp 92–94 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 9.89 (1 H, s, ArCHO), 7.90 (1 H, d, J = 8 Hz, aromatic), 7.59 (1 H, d, J = 8 Hz, aromatic), 7.39 (5 H, br s, Ph), 5.15 (2 H, s, CH_2Ph); IR (KBr) ν_{max} 3093, 2957, 2895, 1696, 1582, 1555, 1535, 1360, 1262, 895, 791, 695 cm^{-1}; CIMS (NH_3) m/e (relative intensity) 355/353 (M^+ + 18, 1/1, 1), 304 (3), 150 (5), 108 (10), 91 (base).

Anal. Calcd for $C_{14}H_{10}BrNO_4$: C, 50.02; H, 2.99; N, 4.16. Found: C, 50.18; H, 3.00; N, 4.13.

2-Amino-3-(benzyloxy)-4-bromobenzaldehyde (23). A solution of 3-(benzyloxy)-4-bromo-2-nitrobenzaldehyde (**22**; 1.0 g, 2.96 mmol) in THF (70 mL) was treated with a solution of sodium hydrosulfite (2.57 g, 14.8 mmol, 5.0 equiv) in H_2O (35 mL). The reaction mixture was warmed at 60 °C (0.5 h), cooled, poured onto H_2O (50 mL), and extracted with EtOAc (3 × 50 mL). The EtOAc layer was washed with saturated NaCl (1 × 30 mL) and dried (Na_2SO_4) and the solvent removed in vacuo. Chromatography (SiO_2, 10% EtOAc–hexane eluant) afforded 0.842 g (0.906 g theor, 93%) of **23** as a light yellow solid: mp 81.5–82.5 °C (Et_2O–hexane); ^1H NMR ($CDCl_3$) δ 9.83 (1 H, s, ArCHO), 7.48–7.30 (5 H, m, Ph), 7.14 (1 H, d, J = 6 Hz, aromatic), 6.81 (1 H, d, J = 6 Hz, aromatic), 6.34 (2 H, br s, $ArNH_2$), 4.99 (2 H, s, CH_2Ph); IR (KBr) ν_{max} 3466, 3346, 2962, 2841, 2804, 1663, 1601, 1538, 1462, 1445, 1380, 1221, 765, 737 cm^{-1}; EIMS m/e 304/306 (M^+, 1/1, 3), 226 (3), 214 (2), 186 (1), 107 (1), 106 (1), 91 (base), 78 (7), 65 (15); HRMS for $C_{14}H_{12}NO_2Br$, calcd 305.0050, found 305.0028.

Anal. Calcd for $C_{14}H_{12}NO_2Br$: C, 54.92; H, 3.96; N, 4.57. Found: C, 55.30; H, 3.99; N, 4.30.

8-(Benzyloxy)-7-bromo-2-(2′-pyridyl)quinoline (25). A solution of 2-acetylpyridine (**24**; 198 mg, 1.63 mmol, 1.0 equiv) in THF (17 mL) was treated with a 40% solution of *N*-benzyltrimethylammonium hydroxide (Triton-B,[28] 2.73 g, 6.52 mmol, 4 equiv) at 25 °C under N_2. A solution of **23** (0.50 g, 1.63 mmol) in THF (3.0 mL) was added to the reaction mixture. The reaction mixture was stirred at 25 °C (18 h), diluted with saturated ammonium chloride (1.5 mL), and further diluted with H_2O (20 mL) before being extracted into EtOAc (4 × 20 mL). The organic extract was dried (Na_2SO_4) and the solvent was removed in vacuo. Chromatography (SiO_2, 20% EtOAc–hexane eluant) afforded 0.516 g (0.638 g theor, 81%, 81–90%) of pure **25** as a beige solid: mp 91–92 °C (CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$) δ 8.71–8.41 (1 H, m, aromatic), 8.57 (1 H, d, J = 9 Hz, aromatic), 8.17 (1 H, d, J

= 9 Hz, aromatic), 7.38–7.17 (10 H, m, aromatic), 5.55 (2 H, s, CH_2Ph); IR (KBr) ν_{max} 2952, 1605, 1586, 1472, 1441, 1377, 1096, 1082, 1019, 739 cm^{-1}; EIMS m/e (relative intensity) 390/392 (M^+, 1/1, 5), 313/315 (13), 299/301 (12), 284/286 (7), 205 (17), 192 (14), 164 (4), 141 (5), 114 (4), 91 (base), 78 (10); HRMS m/e for $C_{21}H_{15}N_2OBr$ calcd 390.0366, found 390.0374.

7-Bromo-8-hydroxy-2-(2′-pyridyl)quinoline (26). A solution of 8-(benzyloxy)-7-bromo-2-(2-pyridyl)quinoline (**25**; 100 mg, 0.26 mmol) in benzene (4 mL) saturated with HBr gas was warmed at 60 °C for 7 h. The reaction mixture was cooled and diluted with CH_2Cl_2 (10 mL), and saturated $NaHCO_3$ (5 mL) was added, with stirring, until the yellow suspension had gone into solution. The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. Chromatography (SiO_2, 75% EtOAc–hexane eluant) afforded 75.7 mg (77 mg theor, 98%) of **26** as an off-white solid: mp 140–141 °C; ^1H NMR ($CDCl_3$) δ 8.74 (1 H, dd, J = 4.9, 1.3 Hz, C-6′ H), 8.64 (1 H, d, J = 8.6 Hz, C-4 H), 8.54 (1 H, d, J = 7.7 Hz, C-3′ H), 8.25 (1 H, d, J = 8.7 Hz, C-3 H), 7.89 (1 H, dt, J = 7.6, 1.8 Hz, C-4′ H), 7.62 (1 H, d, J = 8.8 Hz, C-6 H), 7.36 (1 H, ddd, J = 7.6, 4.8, 1.3 Hz, C-5′ H), 7.26 (1 H, d, J = 8.7 Hz, C-5 H); IR (KBr) ν_{max} 3379, 3055, 1589, 1558, 1475, 1398, 1331, 1257, 1113, 1068, 865, 785 cm^{-1}; EIMS m/e (relative intensity) 300/302 (M^+, 100/85), 272/274 (12/13), 221 (20), 193 (32), 192 (37), 166 (10), 141 (11), 137 (20), 136 (20), 89 (10), 87 (12), 83 (23), 78 (38), 63 (31), 62 (14); HRMS m/e for $C_{14}H_9BrN_2O$, calcd 299.9897, found 299.9900.

7-Bromo-2-(2′-pyridyl)quinoline-5,8-quinone (27). Fremy's Oxidation of 26. A solution of 7-bromo-8-hydroxy-2-(2-pyridyl)quinoline (**26**; 5.0 mg, 0.016 mmol) in acetone (2.0 mL) was added to a solution of potassium nitrosodisulfonate (Fremy's salt;[23] 89 mg, 0.33 mmol, 20 equiv) in 0.05 M KH_2PO_4 buffer (8.0 mL) at 25 °C. The reaction was stirred at 25 °C for 1.5 h. The reaction was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. Rapid chromatography[24] (SiO_2, 50% ethyl acetate–hexane eluant) afforded 5.2 mg (5.2 mg theor, 100%) of **27** as a yellow solid: mp 223 °C dec (yellow needles from CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 8.88 (1 H, d, J = 9 Hz, C-4 H), 8.76–8.56 (2 H, m, C-3′ H and C-6′ H), 8.50 (1 H, d, J = 9 Hz, C-3 H), 7.90 (1 H, dt, J = 9 Hz, 1 Hz, C-4′ H), 7.60 (1 H, s, C-6 H), 7.42–7.38 (1 H, m, C-5′H); IR (KBr) ν_{max} 3055, 1696, 1659, 1578, 1321, 1123 cm^{-1}; EIMS m/e (relative intensity) 314/316 (M^+, 1/1, base), 235 (15), 207 (57), 179 (78); HRMS m/e for $C_{14}H_7BrN_2O_2$, calcd 313.9690, found 313.9692.

In larger scale reactions, a solution of **26** (100 mg, 0.33 mmol) in acetone (30 mL) was added to a solution of Fremy's salt (1.78 g, 6.6 mmol, 20 equiv) in 0.05 M KH_2PO_4 buffer (100 mL) at 25 °C and stirred for 2.0 h. Chromatography (SiO_2, 50% ethyl acetate–hexane eluant) afforded 80.5 mg (105 mg theor, 77%) of **27**. Repetitive reactions (10–20 equiv of Fremy's salt, 2–5 h) provided **27** (75–85%).

Similarly, **26** (11.0 mg, 0.035 mmol) in MeOH (2.0 mL) was added to a solution of Fremy's salt (36.0 mg, 0.134 mmol, 4.0 equiv) in 0.05 M KH_2PO_4 buffer (3.0 mL) at 25 °C and stirred for 2.5 h. Chromatography (SiO_2, 50% ethyl acetate–hexane eluant) afforded 5.8 mg (11.0 mg theor, 53%) of **27**.

7-Azido-2-(2′-pyridyl)quinoline-5,8-quinone (28). A stirred solution of 7-bromo-2-(2′-pyridyl)quinoline-5,8-quinone (**27**; 6 mg, 0.019 mmol) in 0.15 mL of CH_2Cl_2 was treated with a solution of sodium azide (1.4 mg, 0.021 mmol, 1.1 equiv) in 0.02 mL of H_2O at 25 °C under a N_2 atmosphere, and the mixture was stirred at 25 °C for 23 h. Removal of the solvent in vacuo and chromatography (SiO_2, 1 × 16 cm, 50–60% ethyl acetate–hexane eluant; gradient solution) afforded 4.5 mg (5.3 mg theor, 85%) of **28** as an orange-yellow solid: ^1H NMR ($CDCl_3$) δ 8.82 (1 H, d, J = 8 Hz, C-4 H), 8.55–8.78 (2 H, m, C-3′ H and C-6′ H), 8.46 (1 H, d, J = 8 Hz, C-3 H), 7.96 (1 H, dt, J = 8 Hz, C-4′ H), 7.25–7.48 (1 H, m, C-5′ H), 6.50 (1 H, s, C-6 H); IR (KBr) ν_{max} 2124, 1696, 1651, 1597, 1580, 1451, 1356, 1325, 1266, 1196, 1129, 1096, 976 cm^{-1}; EIMS m/e (relative intensity) 251 (5), 249 ($M^+ - N_2$, 29), 221 (7), 195 (4), 182 (13), 154 (14), 78 (28).

A number of similar experiments (5–37 mg scale) provided **28** (70–85%).

7-Amino-2-(2′-pyridyl)quinoline-5,8-quinone (29). A stirred solution of **28** (49 mg, 0.177 mmol) in dry CH_2Cl_2 (1.0 mL) under a N_2 atmosphere was treated with a solution of triphenylphosphine (46.4 mg, 0.177 mmol, 1.0 equiv) in 0.5 mL of CH_2Cl_2 with stirring. Evolution of nitrogen was visible within 1 min after addition of Ph_3P. Stirring was continued at 25 °C for 1.0 h. Removal of the solvent in vacuo and chromatography (SiO_2, 1 × 10 cm, 60% ethyl acetate–hexane eluant) afforded 46.5 mg (90.5 mg theor, 51%) of the phosphine imine as a purple solid: ^1H NMR ($CDCl_3$) δ 8.62 (1 H, d, J = 7.5 Hz, C-4 H), 8.39 (1 H, d, J = 7.5 Hz, C-3 H), 8.42–8.65 (2 H, m, C-3′ H and C-6′ H), 7.12–7.97 (17 H, m, C-4′ H, C-5′ H, 3 Ph), 6.40 (1 H, s, C-6 H); IR (KBr) ν_{max} 3061, 1688, 1619, 1588, 1555, 1538, 1437, 1408, 1323, 1262, 1184, 1136, 1109, 1051, 1036, 9611, 849 cm^{-1}; EIMS m/e (relative intensity) 511 (M^+, 21), 262 (base), 183 (91), 108 (42).

A suspension of the phosphine imine (46.5 mg, 0.091 mmol) in 0.40 mL of THF was treated with 0.60 mL of acetic acid and 0.40 mL of H_2O, and the solution was allowed to stir at 25 °C for 0.3 h. Chromatography (SiO_2, 1 × 10 cm, 80–100% ethyl acetate–hexane gradient elution) and washing with ether to remove triphenylphosphine oxide afforded 22.5 mg (22.9 mg theor, 98%) of **29** as a red-orange solid: mp >300 °C (EtOAc); ^1H NMR (Me_2SO-d_6) δ 8.66 (1 H, d, J = 8 Hz, C-4 H), 8.25–8.68 (2 H, m, C-3′ H, C-6′ H), 8.35 (1 H, d, J = 8 Hz, C-3 H), 7.98 (1 H, dd, J = 8 Hz, C-4′ H), 7.38–7.60 (1 H, m, C-5′ H), 7.32 (2 H, br s, NH_2), 5.85 (1 H, s, C-6 H); IR (KBr) ν_{max} 3426, 3299, 1703, 1646, 1588, 1453, 1385, 1356, 1266, 1190, 1148, 1105, 1075, 1055, 752 cm^{-1}; EIMS m/e (relative intensity) 251 (M^+, 49), 224 (17), 195 (14), 182 (11), 156 (19), 78 (23); HRMS m/e for $C_{14}H_9N_3O_2$, calcd 251.0694, found 251.0704.

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Supplementary Material Available: Detailed procedures for the preparation of **3–5a**, 3,5,6-tris(ethoxycarbonyl)-1,2,4-triazine (**6**), **7c**, 7-bromoquinoline-5,8-quinone (**12**), **15**, and **16** (7 pages). Ordering information is given on any current masthead page.