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Stereo- and Regioselective Synthesis of (E,E)-Dienes: Evolution from the Transition-Metal Catalyzed Cross-Coupling to Titanium Alkoxide-Based Alkyne-Alkyne Reductive Coupling

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Abstract:
The pursuit of step- and atom-economy in natural product and complex molecule syntheses continuously inspires the development of synthetic methodologies. In this context, to enable efficient synthesis of (E,E)-dienes as common structural subunits in natural products, our lab has established robust protocols based on modified Negishi cross-couplings and evolved them to more concise titanium-mediated alkyne-alkyne reductive coupling. In this review, we summarize the natural product synthesis-driven methodology development and their applications in the total synthesis of complex molecules, focusing on the studies from our laboratory.
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2. Transition-Metal-Catalyzed Cross-Coupling in Natural Product Synthesis
3. Titanium Alkoxide-Mediated Reductive Coupling in Natural Product Synthesis
4. Summary

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Stereo- and Regioselective Synthesis of (*E*,*E*)-Dienes: Evolution from the Transition-Metal Catalyzed Cross-Coupling to Titanium Alkoxide-Based Alkyne-Alkyne Reductive Coupling

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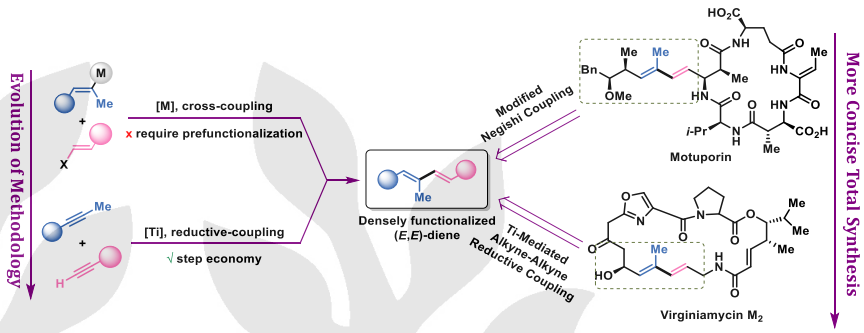

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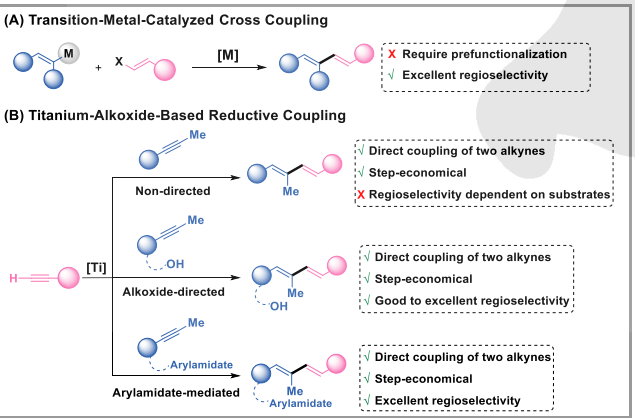
Key words cross coupling, reductive coupling, (*E*,*E*)-diene, titanium alkoxide-mediated, total synthesis

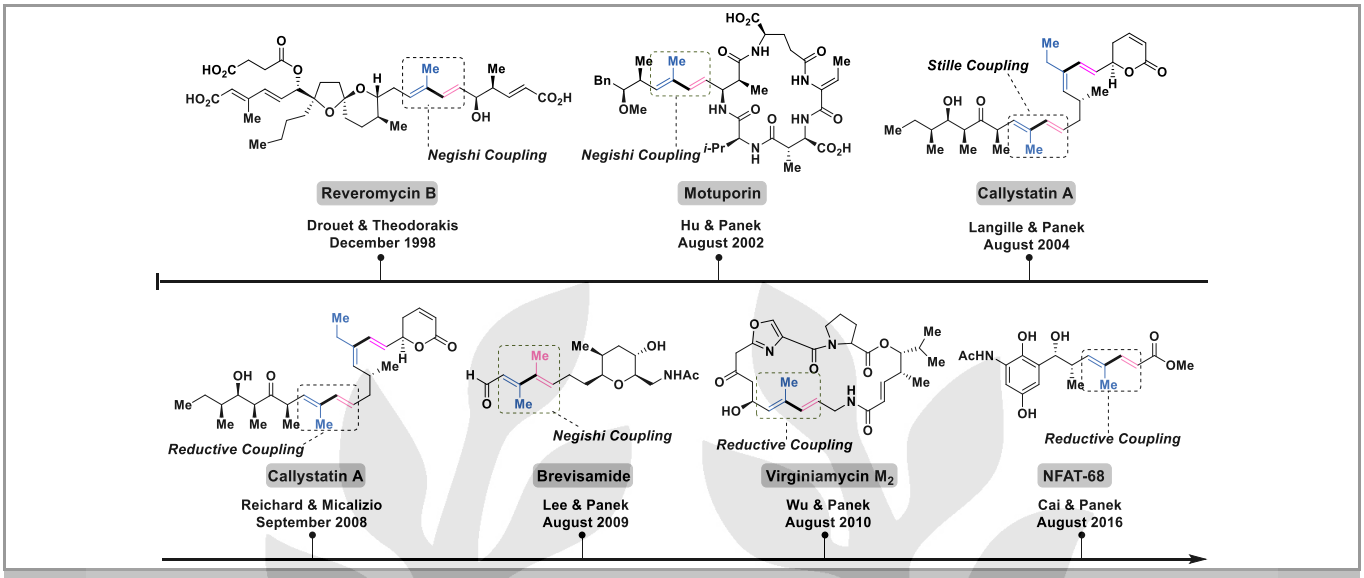
1 Introduction



Scheme 1 Evolution of coupling reactions to access (*E*,*E*)-dienes

Stereochemically well-defined, functionalized (*E*,*E*)-dienes are common structural features embedded in a vast number of natural products and pharmaceutical agents.[1-9] To construct such motif, conventional methods have relied on phosphorus-based olefination, and more recently palladium-catalyzed (sp^2-sp^2) cross coupling reactions,[10-16] which involve the use of prefunctionalized stereospecific vinyl halides and vinyl metallic reagents. Although excellent regioselectivity could be achieved, they involve redundant steps for pre-functionalization and transmetalation (Scheme 1A). On the other hand, reductive coupling between two alkynes provides a straightforward way to construct dienes, representing a step- and atom-economic carbon-carbon bond-forming reaction to access (*E*,*E*)-dienes (Scheme 1B). Research groups including Buchwald,[17-18] Montgomery,[19-20] Krische,[21-26] Jamison,[27-33] Sato,[34-35] Micalizio,[6-7, 36-42] and our own[15-16, 43-45] have made notable contributions in conquering challenges in the reaction reactivity and olefin selectivity. Since the first report of titanium alkoxide-based reductive coupling by Sato and co-workers,[34] Micalizio and co-workers and our group have developed alkoxide[46] and arylamidate directing group strategies[44] respectively to overcome the challenges associated with regioselectivities.

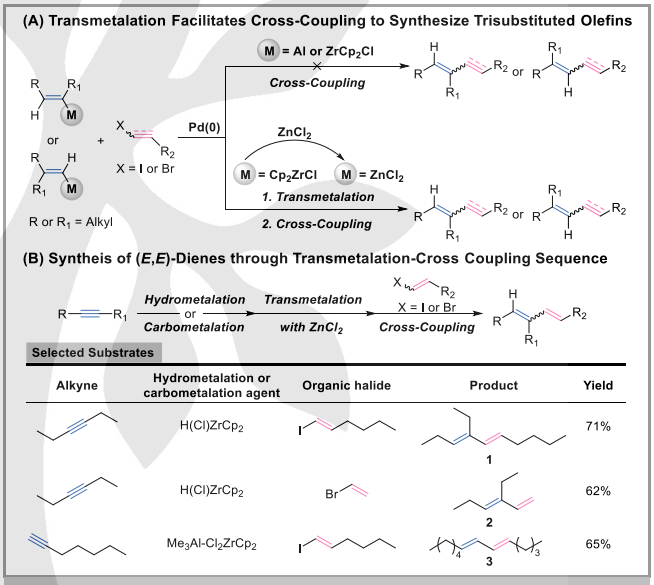
In this review, we focused on the chronological evolution of coupling reactions to access (*E*, *E*)-dienes, from a Negishi's palladium mediated coupling to titanium alkoxide-based alkyne-alkyne reductive couplings, in pursuit of better selectivities and their application in total synthesis. Seven natural products total syntheses (Scheme 2) were selected, where the transition-metal-catalyzed cross-coupling and the titanium-mediated reductive coupling served as the key strategies to enable efficient and convergent syntheses, with an emphasis on the contributions from our laboratory.



Scheme 2 Transition-metal-mediated cross-coupling reactions in the total synthesis of natural products containing (*E*,*E*)-dienes

2 Transition-Metal-Catalyzed Cross-Coupling in Natural Product Synthesis

Our group holds a long-standing interest in the development of useful synthetic methodologies and subsequent applications in complex natural product syntheses. Specifically, in the past three decades, we have developed a series of silicon-based bond construction methods to allow efficient, stereoselective synthesis of polyketide-derived polypropionates and heterocycles.[47-56] Since then, these enantio-enriched silicon-based reagents have been widely utilized in the asymmetric total syntheses of bioactive natural products and complex molecules. In the late 1990s, we initiated a program directed towards the asymmetric synthesis of natural product (–)-Motuporin, a protein phosphatase inhibitor.[13-14] Six of the eight stereogenic centers in this natural product were introduced by asymmetric crotylation using our crotylsilanes. To construct the trisubstituted (*E*,*E*)-diene in a stereoselective fashion, a transition-metal-mediated (sp^2-sp^2) cross-coupling reaction was employed. Inspired by the seminal work from Negishi and co-workers in the stereoselective synthesis of conjugated olefins,[57-58] we further modified this method for the expedient synthesis of configurationally pure (*E*,*E*)-, (*E*,*Z*)-, and (*Z*,*E*)-dienes bearing α- or α,β-stereogenic centers adjacent to the olefins.[11-12] The details of method development and its application in complex molecule synthesis will be discussed in the following sections.



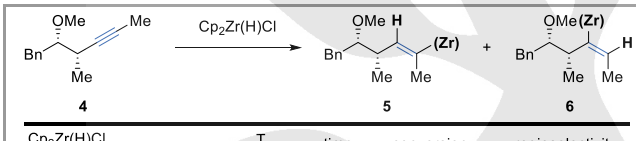
Scheme 3 Double-metal-catalysis in the synthesis of trisubstituted olefins by Negishi *et al.*

In 1978, Negishi and co-workers introduced the concept of double-metal-catalysis for the efficient synthesis of trisubstituted olefins.[57-58] In their early experiments, they found that vinylic aluminum and zirconium were reluctant to participate in the cross-coupling with alkenyl, aryl, or alkynyl halides. They postulated that the difficulty associated with these vinylic metallic reagents in participating in cross-coupling reactions could be due to the steric bulkiness of these metal species. Because the steric effect could accelerate the reductive elimination, the problem potentially arose from the transmetalation step. To address this problem, they proposed a double-transmetalation process or double-metal-catalysis, where one or two metals with low steric requirements and electronegativities were introduced in the transmetalation step. The kinetic basis for this proposal was that the rate

2.1 Synthesis of Branched Trisubstituted Conjugated Dienes by Negishi Coupling

enhancement could be achieved by lowering the overall activation energy. Practically, substituting a single transmetalation process of high energy barrier with two transmetalation processes of lower activation energy could result in an overall activation energy reduction leading to rate acceleration. Screening of various metal salts identified $ZnCl_2$ as the optimal metal source (Scheme 3A). Subsequent substrate scope evaluation employing this double-metal-catalysis concept provided satisfying results (Scheme 3B). For the scope of this review, we selected three examples where (*E*,*E*)-dienes were produced. Hydrozirconation of 3-hexyne using Schwartz's reagent, followed by transmetalation with $ZnCl_2$ and cross-coupling with either (*E*)-1-iodohex-1-ene or vinyl bromide, led to the formation of (3*E*,5*E*)-4-ethyldeca-3,5-diene **1** in 71% yield and (*E*)-3-ethylhexa-1,3-diene **2** in 62% yield respectively. Alternatively, carboalumination of hept-1-yne with Me_3Al-Cl_2ZrCp_2, followed by transmetalation with $ZnCl_2$ and cross-coupling with (*E*)-1-iodohex-1-ene, produced (*E*,*E*)-8-methyl-5,7-tridecadiene **3** in 65% yield. This work has laid a foundation for further methodology development and application in total syntheses of natural products that will be covered in this review.

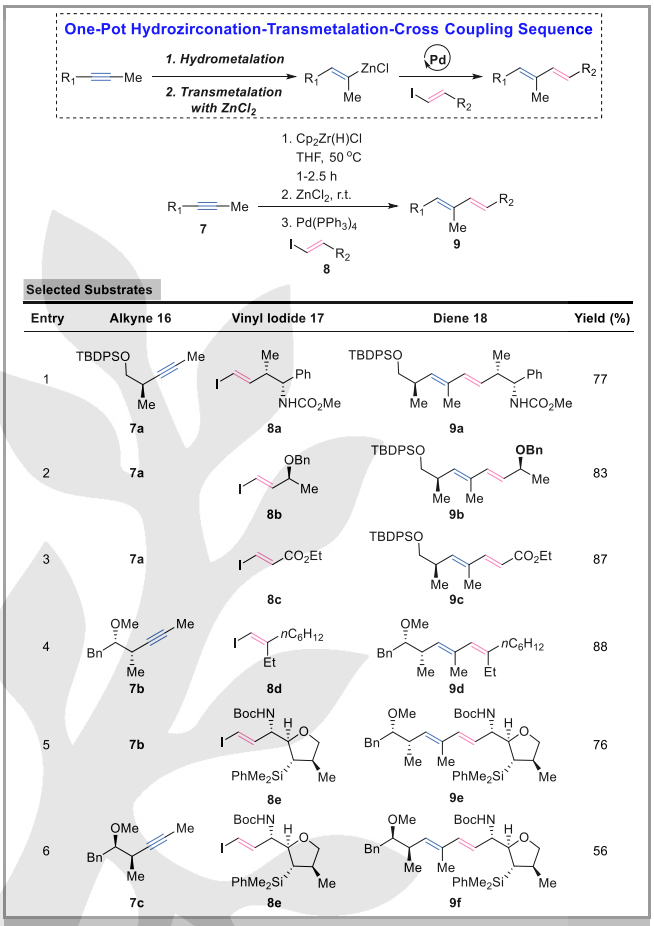
2.2 Stereo- and Regiocontrolled Synthesis of Branched Trisubstituted Conjugated Dienes by Modified Negishi Coupling



$Cp_2Zr(H)Cl$ (equiv)	solvent	T (°C)	time (h)	conversion (%)	regioselectivity **5/6**
1.2	toluene	45	2.0	92	63:37
2.5	benzene	r.t.	3.3	50	72:28
1.5	benzene	45	0.3	90	75:25
2.0	benzene	50	4.0	100	100:0
2.5	THF	rt	4.0	70	54:46
2.0	THF	50	0.4	100	87:13
2.0	**THF**	**50**	**1.0**	**100**	**100:0**

Scheme 4 Site-selectivity in hydrozirconation

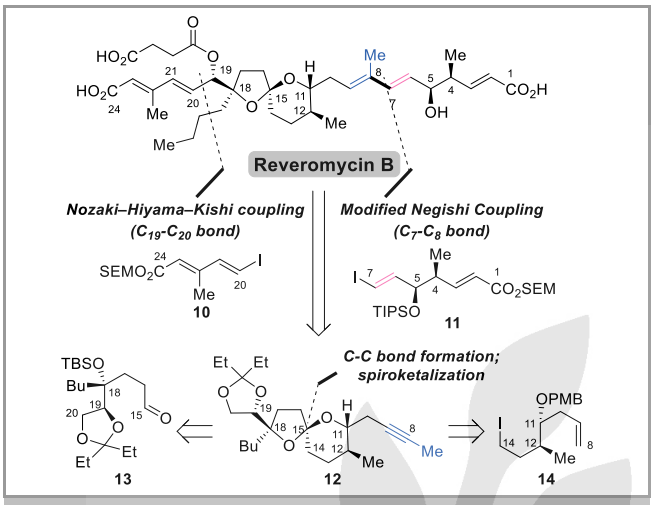
Inspired by Negishi's seminal work, in 1997, Hu and Panek reported the first extension of Negishi's work by applying the Pd(0)-catalyzed cross-coupling in the synthesis of highly functionalized and configurationally pure (*E*,*E*)-, (*E*,*Z*)-, and (*Z*,*E*)-dienes bearing adjacent stereogenic centers on the coupling fragments, which was applied in the total synthesis of (–)-Motuporin (Scheme 4).[11] The reaction involved a cascade hydrozirconation and cross-coupling, and initial efforts were focused on optimizing the hydrozirconation reaction to favor the formation of the thermodynamic product **5**. Reaction conditions screenings indicated that higher reaction temperature and an excess amount of Schwartz's reagent led to enhanced regioselectivity favoring terminal hydrozirconation product **5**. When the reaction was performed in THF at 50 °C with two equivalents of Schwartz's reagent, product **5** was obtained as a single regioisomer (Scheme 4, last entry). The fact that excess reagent gave thermodynamic product was consistent with the literature precedent from Schwartz[59-60] and may be rationalized by the reversible addition of a second equivalent of reagent to the initially formed vinylzirconium adduct. The use of THF as the reaction solvent allowed a one-pot hydrozirconation and cross-coupling sequence, simplifying the operational aspects of the process.



Scheme 5 Synthesis of functionalized (*E*,*E*)-dienes through one-pot hydrozirconation-transmetalation-cross coupling process.

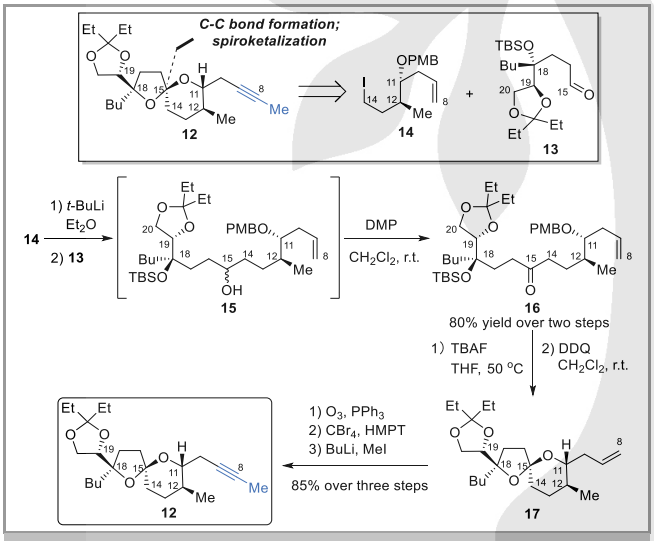
With the hydrozirconation process optimized, the subsequent transmetalation with $ZnCl_2$ and subsequent Pd(0)-catalyzed cross-coupling with a range of vinyl halides were evaluated. For the scope of this review, we presented only the results for the production of (*E*,*E*)-dienes (Scheme 5). All the coupled products were obtained as a single isomer of (*E*,*E*)-dienes with good to excellent yields, and the reactions were completed within 30 minutes. Notably, the selectivity and reactivity of this reaction were independent of the stereo- and electronic environment of both coupling partners. This reaction sequence represents a powerful method for the preparation of highly substituted (*E*,*E*)-dienes with wide application in complex molecule syntheses.

2.3 Enantioselective Total Synthesis of Reveromycin B by Drouet & Theodorakis



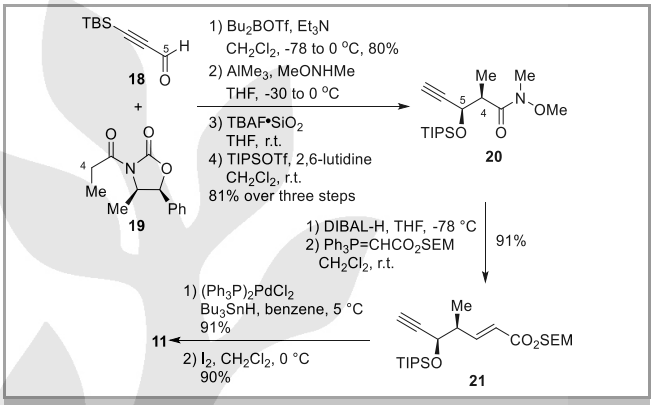
Scheme 6 Retrosynthetic analysis of Reveromycin B

The first application of the modified Negishi coupling in natural product total synthesis was reported by Drouet and Theodorakis at the University of California San Diego (UCSD) in 1999, for the synthesis of Reveromycin B (Scheme 6).[61] Retrosynthetically, the two key coupling reactions, Nozaki–Hiyama–Kishi coupling (C19-C20 bond) and Negishi coupling (C7-C8 bond), divided the molecule into three fragments (spiroketal **12**, vinyl iodide **10**, and vinyl iodide **11**) and greatly simplified the overall molecular complexity. Further disconnection of the highly substituted spiroketal **12** led to aldehyde **13** and iodide **14**, where a carbon-carbon bond formation and diastereoselective spiroketalization sequence generated the spiroketal **12**.



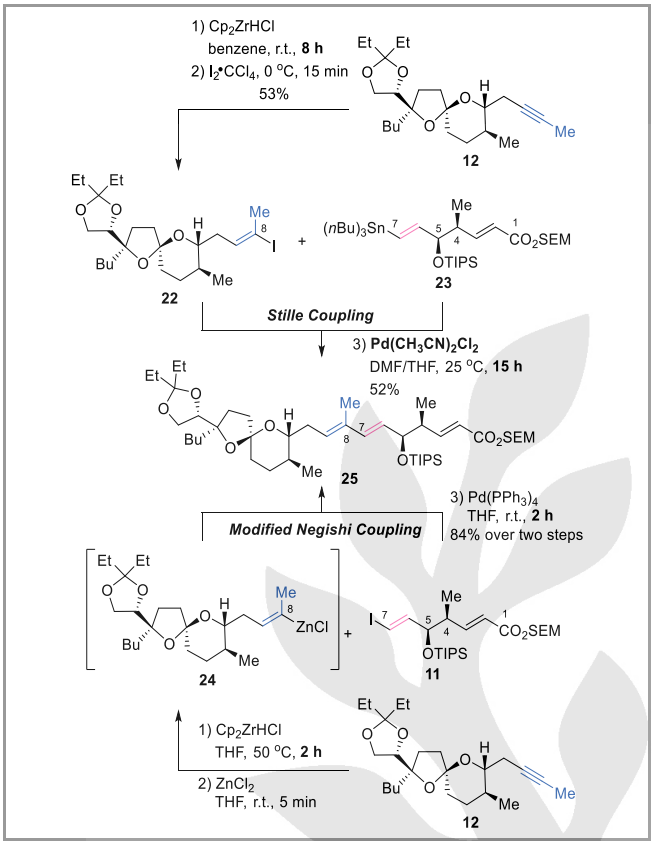
Scheme 7 Synthesis of the C8-C20 fragment **12** of Reveromycin B

The synthesis of Reveromycin B commenced with the construction of the central spiroketal fragment **12** (Scheme 7). Although the synthesis of intermediates **13** and **14** were not discussed in the original communication, it is worth noting that the two stereocenters in **13** and **14** were introduced efficiently.[63] The stereochemistry of diol in **13** was inherited from the commercially available L-ascorbic acid, and the chirality of tertiary alcohol was formed through a chelation-controlled Grignard addition of *n*-BuMgBr to an aldehyde (with a 4:1 dr) using the neighboring C19 alcohol as a directing element. For primary iodide **14**, the C11 and C12 stereocenters were introduced through a Brown's homoallylboration. With **13** and **14** in hand, lithiation of iodide **14** followed by addition to aldehyde **13** led to the secondary alcohol **15**, which was oxidized to form the ketone **16**. Subsequent deprotection of TBS and PMB group of C18 and C11 hydroxy groups delivered the spiroketal 17 as a single isomer. The internal alkyne **12** was formed through a sequence of ozonolysis of the terminal olefin followed by the modified Corey–Fuchs reaction.[63]



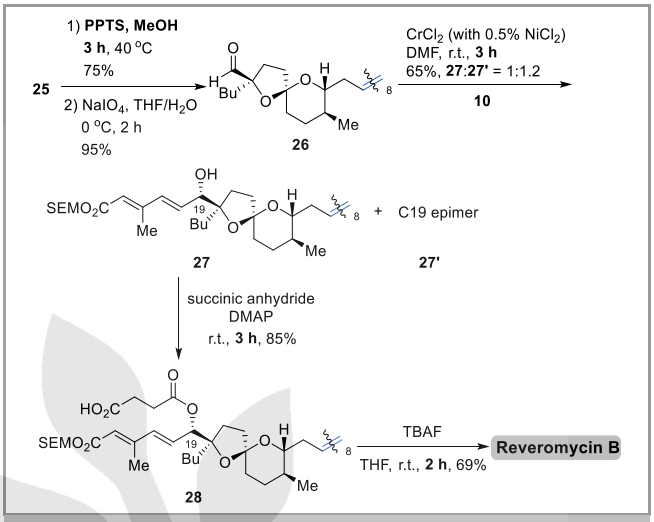
Scheme 8 Synthesis of the C1-C7 fragment **11** of Reveromycin B

The synthesis of C1-C7 fragment **11** proceeded with Evans' aldol reaction that set the C4 and C5 stereochemistry (Scheme 8). The aldol product was obtained as a single isomer with 80% yield. Subsequent Weinreb amide formation, TBS deprotection to form the terminal alkyne and TIPS protection of the secondary alcohol yielded the Weinreb amide **20**. Amide **20** was then subjected to DIBAL-H reduction to afford aldehyde, which was used to generate ester **21** via Horner–Wadsworth–Emmons olefination. Lastly, hydrostannylation followed by iodination of ester **21** produced fragment **11**.



Scheme 9 Comparison of Stille coupling and modified Negishi coupling to access the (*E*,*E*)-diene fragment **25**

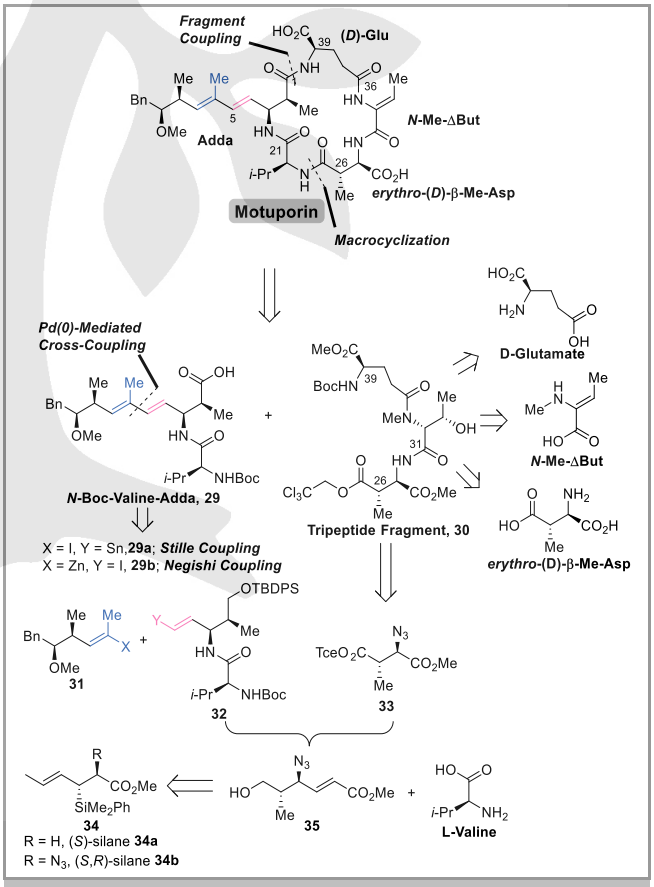
With both fragments **11** and **12** in hand, Drouet and Theodorakis evaluated the Pd(0)-mediated cross-coupling reaction to unify the two fragments (Scheme 10). The evaluation of both Stille and Negishi coupling reactions provides an excellent demonstration that the modified Negishi coupling reaction with double-metal-catalysis was more efficient and selective in constructing highly substituted conjugate olefins. In the case of Stille coupling, hydrozirconation and iodination of **12** resulted in poor selectivity with a regioisomeric ratio (r.r). of 2.5:1. Moreover, the subsequent Stille coupling proved to be quite challenging due to the low reactivity of the trisubstituted vinyl iodide toward oxidative addition, as evidenced by the major by-product to be protodestannylation or dimerization of stannane **23**. In contrast, the modified Negishi coupling, originally reported by Hu and Panek, was highly selective and efficient. The one-pot hydrozirconation of **12** with Schwartz reagent, followed by transmetalation with $ZnCl_2$ and cross-coupling with vinyl iodide **11,** delivered the (*E*,*E*)-diene **25** as a single isomer in a 84% yield.



Scheme 10 Completion of total synthesis of Reveromycin B

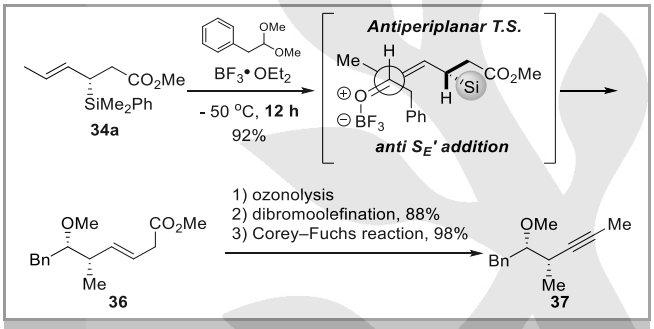
With the coupled product **25** in hand, deprotection of the acetonide with PPTS resulted in a diol, which was oxidatively cleaved to give the aldehyde **26**. An NHK coupling of **26** with diene **10** gave product **27**, with a 1.2:1 dr ratio at C19 and 30% yield. The secondary alcohol was then esterified with succinic anhydride to give compound **28**, which after TBAF-induced deprotection of the silyl group afforded natural product Reveromycin B in good yield.

2.4 Enantioselective Synthesis of the Protein Phosphatase Inhibitor (–)-Motuporin by Hu & Panek



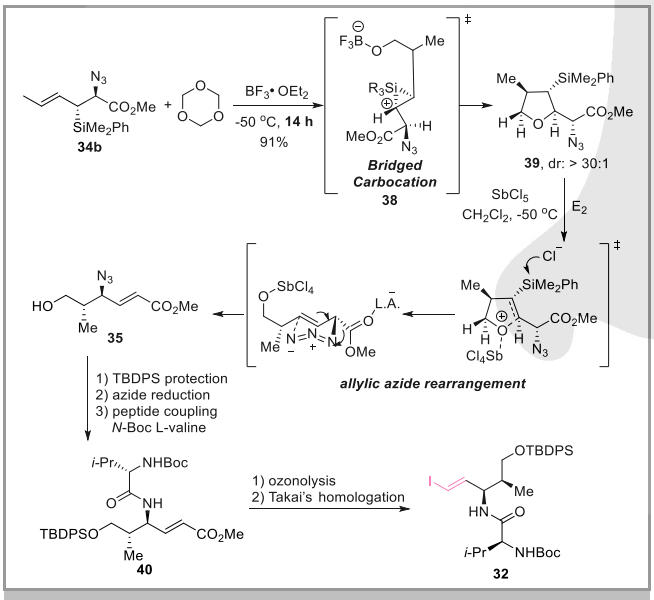
Scheme 11 Retrosynthetic analysis of (-)-Motuporin

The first application of the modified Negishi coupling in natural product synthesis from the Panek laboratory was reported in 2002 in the total synthesis of (-)-Motuporin.[13-14] In this synthesis, we demonstrated that the modified variant could be used to efficiently synthesize peptide fragments, where the presence of amides and heteroatoms did not affect the efficiency of the coupling reaction. Retrosynthetically (Scheme 11), the macrolactamization and amide coupling divided the natural product into two fragments, *N*-Boc-Valine-Adda **29** and tripeptide **30,** with similar molecular complexity. The tripeptide fragment **30** consists of three amino acids, D-Glutamate, *N*-Me-ΔBut and erythron-(D)-β-Me-Asp. As the Adda fragment **29** comprised of a trisubstituted (*E,E*)-diene, a Pd(0)-mediated cross-coupling was utilized to form the conjugated diene. Similar to Theodorakis' work, we evaluated both the Stille and Negishi coupling reactions. In addition to the utilization of the modified Negishi coupling, Panek's crotylsilane **34a** played a key role in setting the stereochemistry of six stereogenic centers.



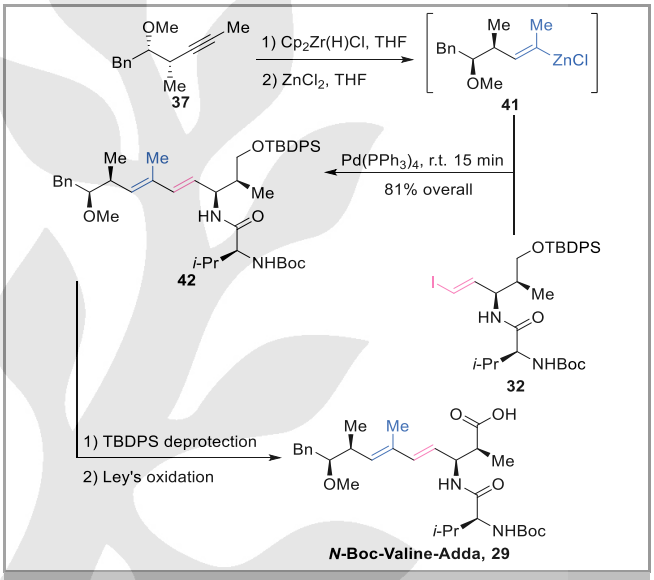
Scheme 12 Synthesis of internal alkyne **37** for Negishi coupling

To evaluate the Negishi coupling, we first synthesized internal alkyne **37**, which involved the crotylation of phenyl acetaldehyde dimethyl acetal with silane **34a**, which underwent an *anti* S_E' addition, to give homoallylic ether **36**. Subsequent ozonolysis, dibromoolefination of the aldehyde product and Corey–Fuchs reaction afforded internal alkyne **37**.



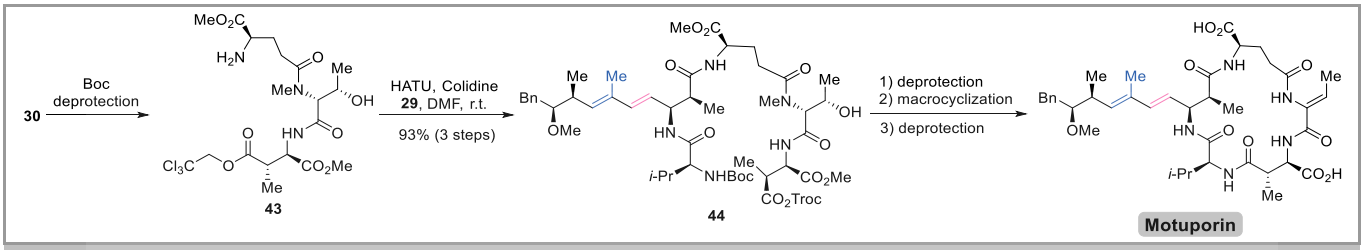
Scheme 13 Preparation of (*E*)-vinyl iodide **55** for Negishi coupling

The preparation of vinyl iodide **32** for Negishi coupling began with condensation reaction of silane **34b** with trioxane to give stereochemically pure tetrahydrofuran **39** as a single isomer (Scheme 13). This reaction presumably proceeded through a bridged carbocation intermediate **38**, where the stereochemical outcome of the reaction was dictated by the bridged silylium ion. A subsequent Lewis acid-mediated E_2-like elimination process followed by azide isomerization afforded allylic azide **35**. A series of functional group interconversion and peptide coupling with *N*-Boc-L-valine provided dipeptide **40**. Vinyl iodide **32** was obtained after ozonolysis of the alkene of compound **40** followed by Takai's homologation[64].



Scheme 14 Synthesis of the *N*-Boc-Valine-Adda fragment **29** based on modified Negishi coupling

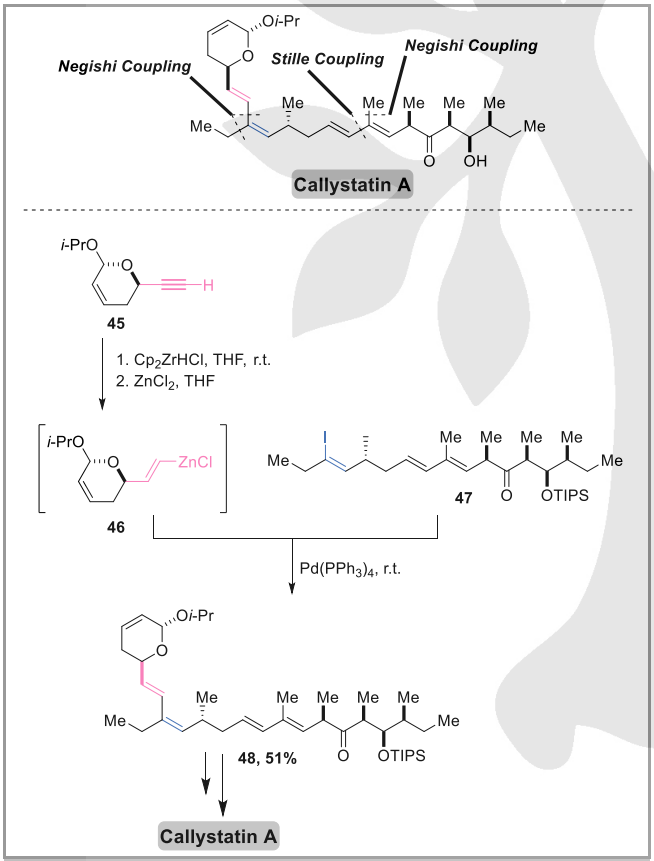
Initially, Hu and Panek evaluated the Stille coupling to form the (*E,E*)-diene of **29**. However, only moderate yield and poor stereoselectivity in the olefin formation were obtained. Indeed, when the strategy was switched to the modified Negishi coupling, the one-pot hydrozirconation-cross-coupling was highly efficient and afforded the (*E,E*)-diene **42** as a single isomer with 81% overall yield. Subsequent TBDPS deprotection and Ley's oxidation gave the *N*-Boc-Valine-Adda **29**. Once again, the success of this cross-coupling strategy was attributed to the double transmetalation process (Zr->Zn->Pd) of lower kinetic barrier compared with a single transmetalation process (Zr->Pd), leading to an overall rate enhancement.



Scheme 15 Completion of the synthesis of (-)-Motuporin

With both fragments **29** and **30** available in suitable amounts, a Boc deprotection of compound **30** gave free amine **43**, which underwent amide coupling with **29** to afford protected pentapeptide **44**. The trichloroethyl group of **44** was removed to give carboxylic acid, of which the Boc group was deprotected to afford the amine as a TFA salt. Subsequent macrocyclization using HATU and *N*-ethylmorpholine efficiently produced the macrocycle with a 79% yield. Finally, simultaneous methyl ester hydrolysis and in situ dehydration of *N*-methylthreonine was realized using Schreiber's conditions[65] (2 N $Ba(OH)_2$, H_2O/MeOH, 10:1) to give the natural product (-)-Motuporin.

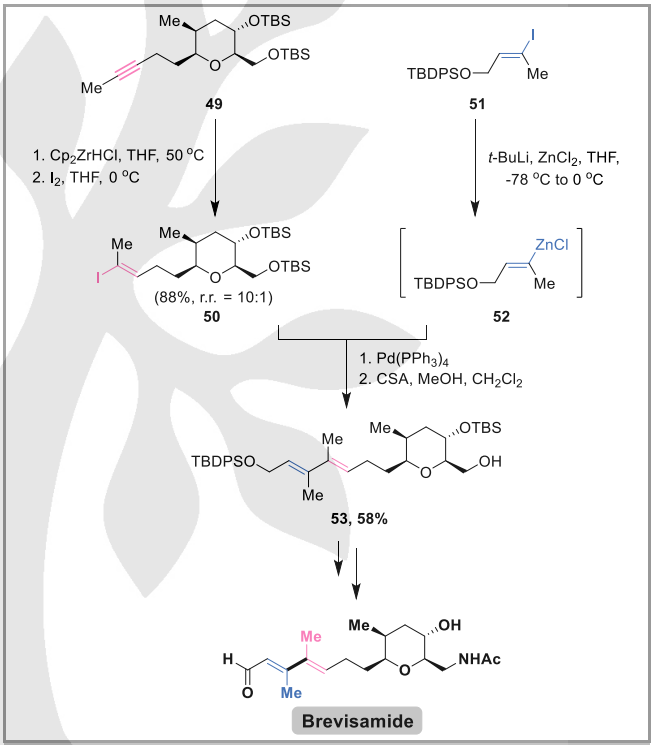
2.5 Total Synthesis of (-)-Callystatin A by Langille & Panek



Scheme 16 Synthesis of (-)-Callystatin A

(–)-Callystatin A, a polyketide-based natural product, is first isolated from a marine sponge *Callyspongia truncate* by Kobayashi's group in 1997.[5] Langille and Panek completed a total synthesis in 2004, where transition-metal-mediated cross-coupling reactions, such as Negishi and Stille coupling, were utilized extensively for the fragment coupling and conjugate olefin synthesis (Scheme 16).[66] The final fragment coupling used the modified Negishi coupling process and united the two structurally complex fragments **46** and **47** successfully to afford the trisubstituted (*E*,*E*)-diene **48**. Further functional group manipulations of compound **48** produced the natural product (–)-Callystatin A.

2.6 Total Synthesis of Brevisamide by Lee & Panek



Scheme 17 Synthesis of Brevisamide

The modified Negishi coupling was also applied in the total synthesis of marine toxin Brevisamide in the Panek laboratory.[67] This toxin is produced in nature by *Dinoflagellate Karenia brevis* and known to exhibit high potency in the neurological system, which causes open state of voltage-sensitive sodium channel (VSSC) and disturbs inactivation, and brevenal exhibits antagonism against toxic effects caused by brevetoxins.

The approach taken in this synthesis is similar to the previous two examples illustrated in both the synthesis of (–)-Callystatin A and (–)-Motuporin, where the modified Negishi coupling plays an important role in the preparation of conjugate dienes and fragment coupling. In this case, the internal alkyne **49** was first converted to a vinyl iodide through a sequence of hydrozirconation-iodination to yield the (*E*)-vinyl iodide **50**

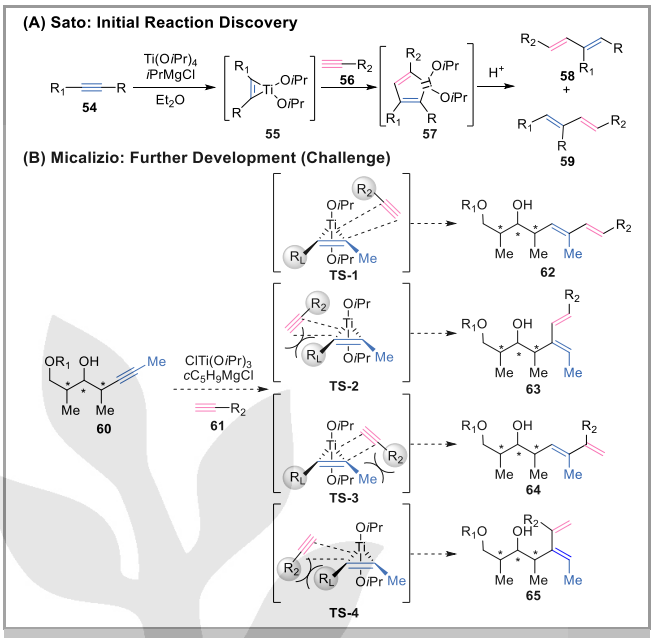
with an 88% yield and an *E/Z* ratio of 10:1. The other coupling partner **51** underwent a double transmetalation process (I->Li->Zn) to give the vinylzinc species **52**, which then participated in the Negishi coupling with iodide **50**. Subsequent deprotection of primary TBS ether afforded the diene **53** as a single isomer, which was followed by TBDPS removal and oxidation of the resulting alcohol provided the natural product Brevisamide.

3 Titanium Alkoxide-Mediated Reductive Coupling in Natural Product Synthesis

The one-pot hydrozirconation-transmetalation-Negishi cross coupling process developed by Hu and Panek to access (*E*,*E*)-dienes has enabled many convergent and efficient total syntheses of natural products as illustrated in Section 2. This process is not only highly efficient but also completely regioselective (Scheme 1A) and remains one of the most efficient methods to construct densely functionalized, trisubstituted conjugate dienes. In the past decades, the concept of atom- and step-economy become increasingly useful and has encouraged chemists to invent greener reactions that involve fewer steps and generate less waste.

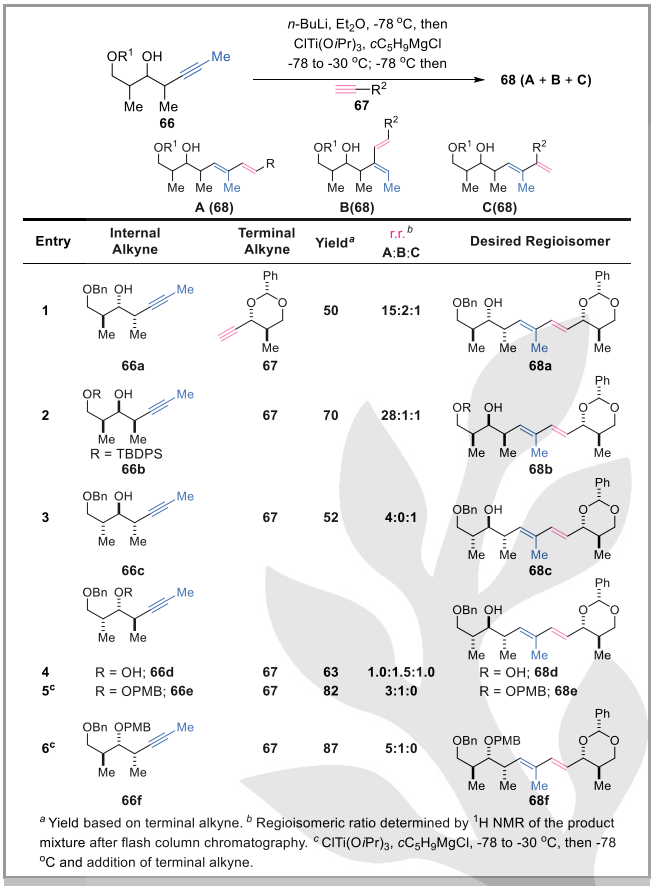
3.1 Titanium Alkoxide-Mediated Alkyne-Alkyne Reductive Coupling

In this context, transition-metal-mediated reductive coupling between two alkynes represents a straightforward way to access conjugate dienes, as only a single operation is required. In addition, compared with other transition metals, titanium is more abundant, inexpensive, and environmentally friendly. As such, the development of titanium-mediated reductive coupling is desirable (Scheme 1B). The earliest example that used titanium-alkoxide as a metal catalyst is from Sato and co-workers,[34] where they demonstrated that conjugate (*E*,*E*)-diene could be formed through the reductive coupling between an internal alkyne and terminal alkyne (Scheme 1B, non-directed). Although Sato's studies have established a firm foundation for titanium-mediated metallacycle-based bond constructions, the control of reactivity and selectivity in this process remained as unconquered barriers at that time. In early 2006, Micalizio and co-workers reported the concept of directed-carbometalation of internal alkynes,[46] where an in situ generated alkoxide was used as a directing group in the titanium-mediated alkyne-alkyne reductive coupling (Scheme 1B, alkoxide-directed). The strategic use of alkoxide as a directing group increases remarkably (1) the reactivity that allows an efficient coupling of internal alkynes with terminal or internal alkynes and alkenes, and (2) the regioselectivity that favors the production of (*E*,*E*)-dienes when unsymmetrical internal alkynes were coupled with unsymmetrical π-systems.



Scheme 18 Development of titanium alkoxide-mediated alkyne-alkyne reductive coupling by Sato and Micalizio

Mechanistically, the in situ generated Ti(II) species activates the internal alkyne **54** to form the presumed titanacyclopropene complex **55**. Upon the formation of **55**, the terminal alkyne coupling partner **56** adds in and couples with **55** to generate the second metal complex, titanacyclopentadiene complex **57**. Upon acidic quenching, conjugate dienes are formed (Scheme 18A). Importantly, the coupling process leading to complex **57** is regioselective, and the regioselectivity depends on the substitution pattern of the coupling partners. The complication associated with the coupling process is well explained by the transition state models proposed by Micalizio and co-workers (Scheme 18B),[8] where the terminal alkyne **61** could approach the Ti-complex in four different ways, leading to the formation of four different regioisomers (**62**-**65**).

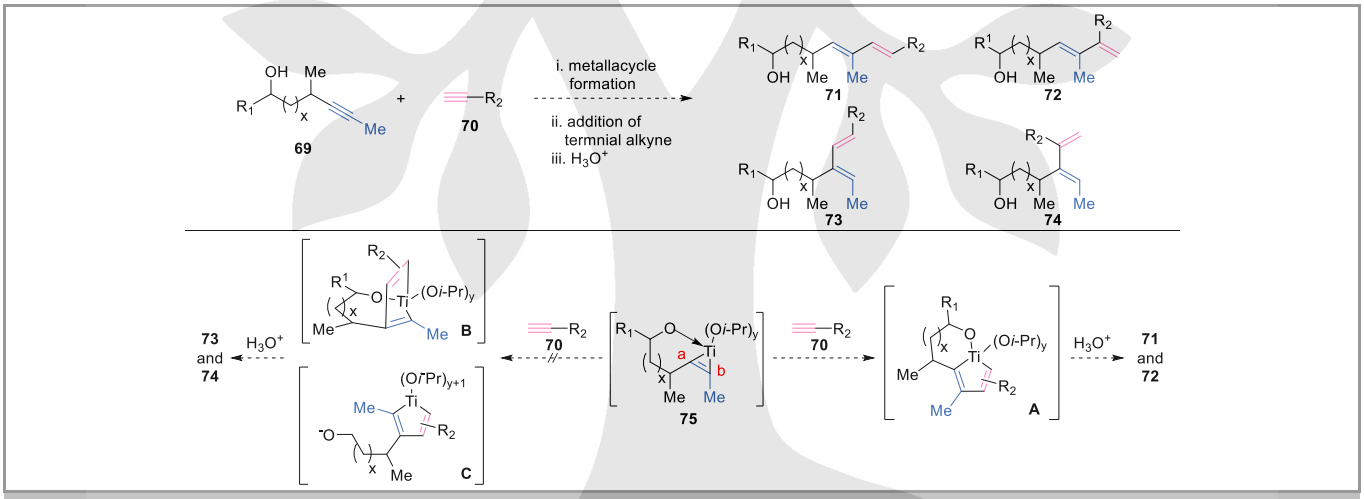


Entry	Internal Alkyne	Terminal Alkyne	Yield[a]	r.r.[b] A:B:C	Desired Regioisomer
1	**66a**	**67**	50	15:2:1	**68a**
2	R = TBDPS **66b**	**67**	70	28:1:1	**68b**
3	**66c**	**67**	52	4:0:1	**68c**
4	R = OH; **66d**	**67**	63	1.0:1.5:1.0	R = OH; **68d**
5[c]	R = OPMB; **66e**	**67**	82	3:1:0	R = OPMB; **68e**
6[c]	**66f**	**67**	87	5:1:0	**68f**

[a] Yield based on terminal alkyne. [b] Regioisomeric ratio determined by ^{1}H NMR of the product mixture after flash column chromatography. [c] $ClTi(OiPr)_3$, cC_5H_9MgCl, -78 to -30 °C, then -78 °C and addition of terminal alkyne.

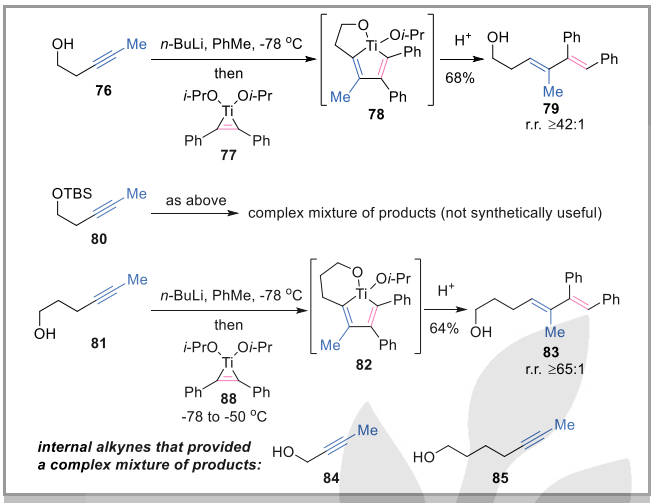
Scheme 19 Formation of complex polyketide containing (*E*,*E*)-diene through titanium-mediated regioselective alkyne-alkyne coupling

To address this challenge associated with regioselectivity, Micalizio and co-workers first studied the influence of the stereo- and electronic environment of substrate on the selectivity. Deprotonation of *syn-anti* homopropargylic alcohol **66**, followed by exposure to a mixture of $ClTi(OiPr)_3$ and cyclopentylmagnesium chloride, and addition of terminal alkyne **67** produced 1,3-diene **68a** in 50% yield with a 15:2:1 r.r. after aqueous workup. This r.r. is remarkable, especially given that both the coupling partners are highly substituted with complex stereoelectronic environment. Similarly, the couplings of diastereomeric homopropargylic alcohols **66b**, **66c** and **66d** with terminal alkyne **67** provided the 1,3-diene products (**68b**, **68c** and **68d)** with good yields and vary regioselectivities. Overall, this study (1) expands the role of titanium alkoxide in a new regioselective carbon-carbon bond-forming process for the synthesis of unsaturated polypropionates and (2) defines the impact of stereochemistry and the homopropargylic functional group on the regioselectivity of this coupling reaction.



Scheme 20 "Class I" alkoxide-directed titanium-mediated alkyne-alkyne reductive coupling by Micalizio and co-workers

In early 2006, Micalizio and co-workers introduced their development of directed carbometallation in titanium-mediated alkyne-alkyne reductive coupling, where an in situ generated alkoxide served as a directing group and directed the reaction to favor the formation of (*E*,*E*)-dienes.[46] This work represents the first directing group strategy reported in the titanium-mediated reductive coupling. Further exploration by Micalizio group led to the development of three modes of directed coupling processes, where they were defined as "class I", "class II", and "class III".[37] For the scope of this review, we focused only on the "class I" reaction. A design rationale or an empirical model was proposed to account for the preferred formation of (*E*,*E*)-dienes in this process (Scheme 20). The formation of products **73** and **74** were strongly disfavored due to significant unfavorable steric interactions between R_2 and the allylic substituent of metal complex **75** that incurred in the intermediates. Specifically, the intermediate (**B** or **C**) was destabilized due to the significant strain associated with the formation of a bridgehead alkene (via a carbometallation process that engaged bond "**a**" of **75**; see **B**) or the interruption of the tethering interaction ($\sigma_{Ti\text{-}O}$; *enroute* to **C**). Thus, the intermediate that led to the formation of **71** and **72** was the most stable and (*E*,*E*)-dienes were generally the major isomers.

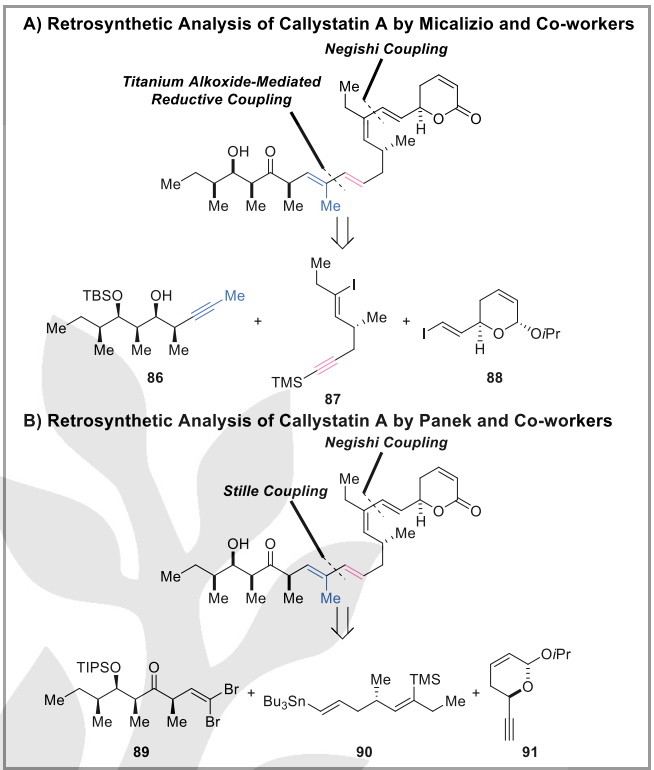


Scheme 21 Presence of a tethered alkoxide and the length of the tether influence reactivity as well as regioselectivity

The significant improvement of selectivity in the synthesis of **68a,** when compared with **68f,** illustrates the directing effect of a remote hydroxyl group in the titanium alkoxide-mediated alkyne-alkyne reductive coupling (Scheme 19). Further evidence for the apparent directing effect was provided in several control experiments (Scheme 21).[46] Deprotonation of homopropargylic alcohol **76**, followed by exposure to the preformed metallacyclopropene **77** (formed by treatment of diphenylacetylene with Ti(O*i*-Pr)$_4$ and *c*C_5H_9MgCl, PhMe, -78 to -50 °C) and aqueous workup, provided the stereodefined diene **79** with high regioselectivity (rs ≥ 42:1). In comparison, exposure of internal alkyne **80** without a free hydroxy group to the preformed titanium alkyne complex **77** led only to a complex mixture of products. In addition, evaluation of the impact of the tether length showed that bis-homopropargylic alcohol **81** provided similarly high level of regioselectivity, whereas alkynyl alcohols **84** and **85** displayed little to no regioselectivity, leading to a complex mixture of products.

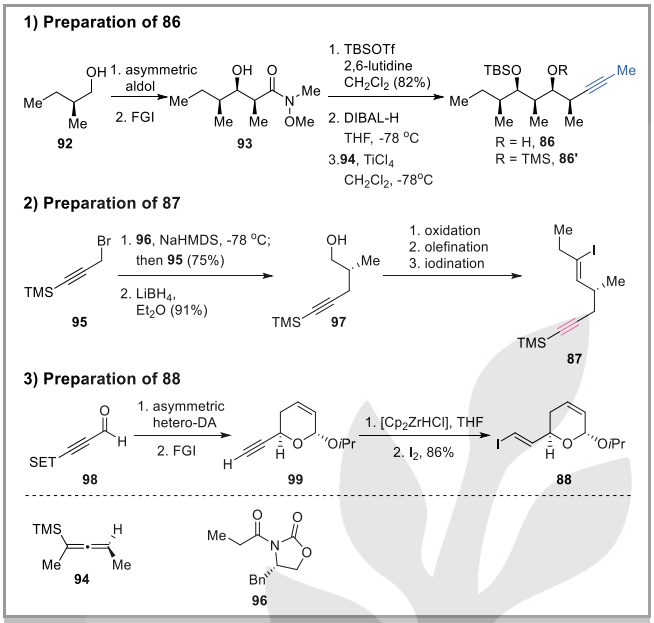
To demonstrate the synthetic applicability of the alkyne-alkyne reductive coupling method in complex molecule syntheses, both Micalizio group[68] and our operation[15-16] have independently reported the utilization of this method in the convergent total synthesis of natural products. In 2020, Cai and Panek have reported the first example of amide and carbamate directing effect in the titanium alkoxide-mediated reductive coupling[44] and its application in the small molecule synthesis as well as the generation of analogs of NFAT-68,[43] further expanding this underexplored reaction which will be discussed in the following sections.

3.2 Total Synthesis of Callystatin A by Reichard & Micalizio



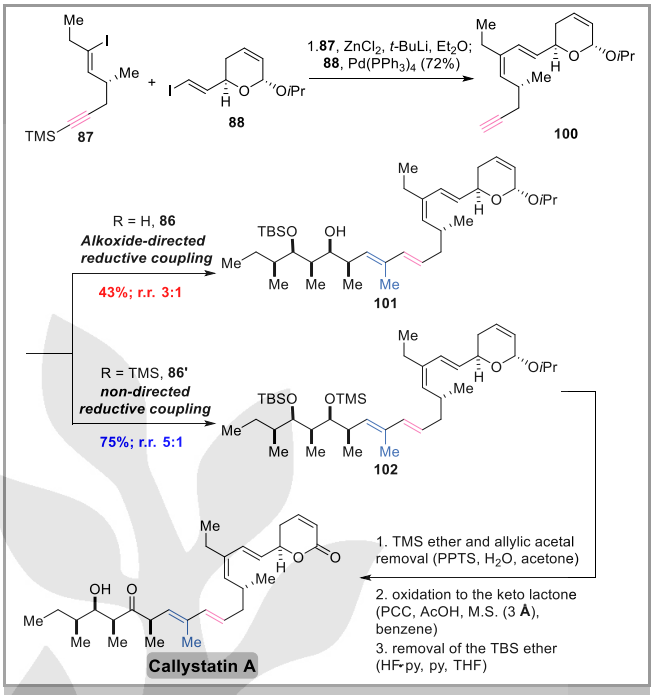
Scheme 22 Retrosynthetic analysis of Callystatin A based on titanium alkoxide-mediated reductive coupling: a comparison with Stille coupling

The first application of the titanium alkoxide-mediated alkyne-alkyne reductive coupling in natural product synthesis was reported by Micalizio and co-workers in 2008 in the total synthesis of Callystatin A.[68] A retrosynthetic analysis is shown comparing the two different strategies to construct the (*E*,*E*)-diene fragment is shown here to demonstrate the step- and atom economy of the reductive coupling (Scheme 22). Both syntheses are based on two key cross-coupling reactions that divide the molecule into three fragments with comparable molecular complexity. Micalizio's reductive coupling-based retrosynthesis gives two alkyne fragments **86** and **87**, where the desilylated **87** could directly couple with fragment **86** to form (*E*,*E*)-diene (Scheme 22A). In comparison, a Stille coupling-based retrosynthesis from Panek and co-workers requires multi-step functionalization of both coupling partners prior to cross coupling (Scheme 22B).[66]



Scheme 23 Preparation of the coupling partners **86-88**

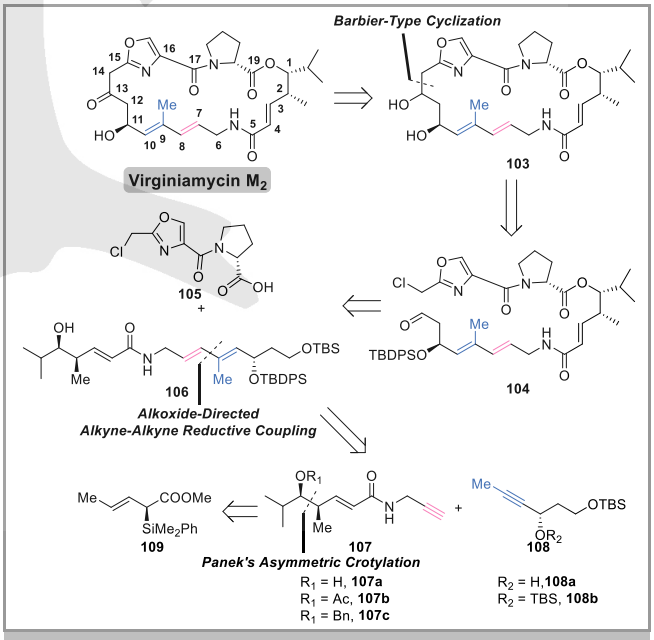
The synthesis commenced with the preparation of three coupling partners **86-88** (Scheme 23). The synthesis of internal alkyne **86** started with the oxidation of commercially available chiral alcohol **92** followed by an asymmetric aldol reaction and a functional group interconversion to obtain Weinreb amide **93**. TBS protection of the secondary alcohol, reduction of the Weinreb amide and asymmetric propargylation of the corresponding aldehyde provided alkyne **86**. The preparation of partner **87** started with an asymmetric alkylation of alkynyl bromide **95** using Evan's chiral auxiliary followed by a reduction to provide alcohol **97**. Oxidation of alcohol **97**, olefination of the aldehyde and an iodination gave the vinyl iodide **87**. Finally, the preparation of vinyl iodide **88** began with an asymmetric hetero-Diels-Alder (HDA) reaction of **98** to construct the central pyran ring. Notably, this HDA reaction, developed by Jacobsen and coworkers,[69] was highly selective and efficient. Subsequent functional group interconversion followed by a hydrozirconation and an iodination afforded the vinyl iodide **88**.



Scheme 24 Sequential cross-coupling and completion of a total synthesis of Callystatin A

With both fragments **87** and **88** in hand, a Negishi cross-coupling between them gave diene **100**, which then participated in the key titanium-mediated alkyne-alkyne reductive coupling. The authors tested both the alkoxide-directed and non-directed couplings, and demonstrated that in this case the non-directed or the TMS ether substrate gave a better regioselectivity (5:1 vs. 3:1) and yield. Although the directed reaction did not give useful levels of selectivity, it represents the first application of titanium-mediated alkyne-alkyne reductive coupling in natural product synthesis. Finally, subsequent functional group manipulation of compound **102** provided the natural product Callystatin A.

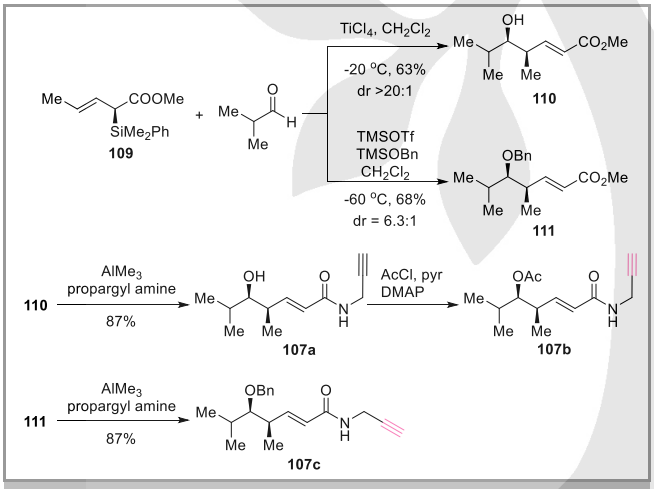
3.3 Total Synthesis of (-)-Virginiamycin M_2 by Wu & Panek



Scheme 25 Retrosynthetic analysis of Virginiamycin M_2 by Wu and Panek

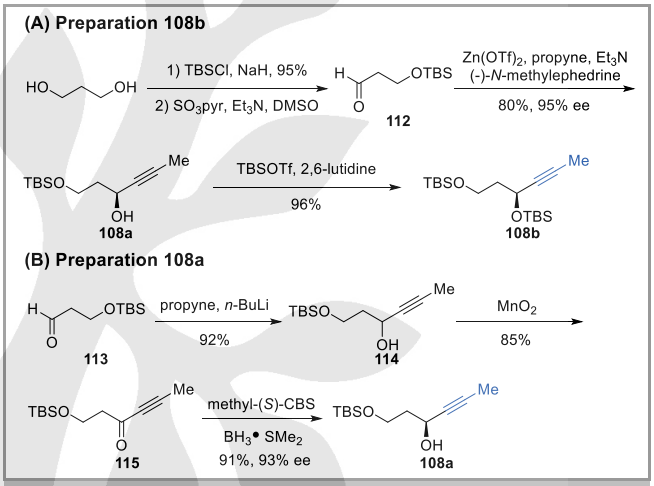
based on an alkoxide-directed alkyne-alkyne reductive coupling

The first successful application of an alkoxide-directed titanium-mediated alkyne-alkyne reductive coupling in natural product synthesis was reported in 2010 by Wu and Panek in their efficient and convergent synthesis of Virginiamycin M_2.[15-16] The ten-step (longest linear sequence from enantioenriched silane **109**) convergent synthesis takes advantage of (1) a late-stage SmI_2-mediated intramolecular Barbier/Reformatsky-type cyclization to construct the 23-membered macrocycle, a strategy that Panek et al. utilized for macrocyclization in the total synthesis of kendomycin[70], and (2) an efficient alkoxide-directed titanium-mediated alkyne–alkyne reductive coupling to assemble the highly substituted (*E*,*E*)-diene. These two operations significantly reduce the molecular complexity of the natural product to three fragments, carboxylic acid **105**, internal alkyne **108** and terminal alkyne **107;** and the two stereocenters and *trans*-olefin of fragment **107** can be accessed through Panek's asymmetric crotylation using chiral silane **109**. More recently in 2017, Li and Seiple from the University of California San Francisco disclosed a modular and highly convergent synthesis of Virginiamycin M_2, which features an asymmetric Mukaiyama-type vinylogous aldol reaction for the construction of C1 and C2 stereocenters and the C3-C5 α,β-unsaturated carbonyl fragment, and an intramolecular Stille macrocyclization to close 23-membered ring.[71-72] The synthesis is completed with a 15% yield over a longest linear sequence of eight steps. Compared with Li and Seiple's synthesis, Wu and Panek's work still represents the most efficient and step-economic synthesis to date.



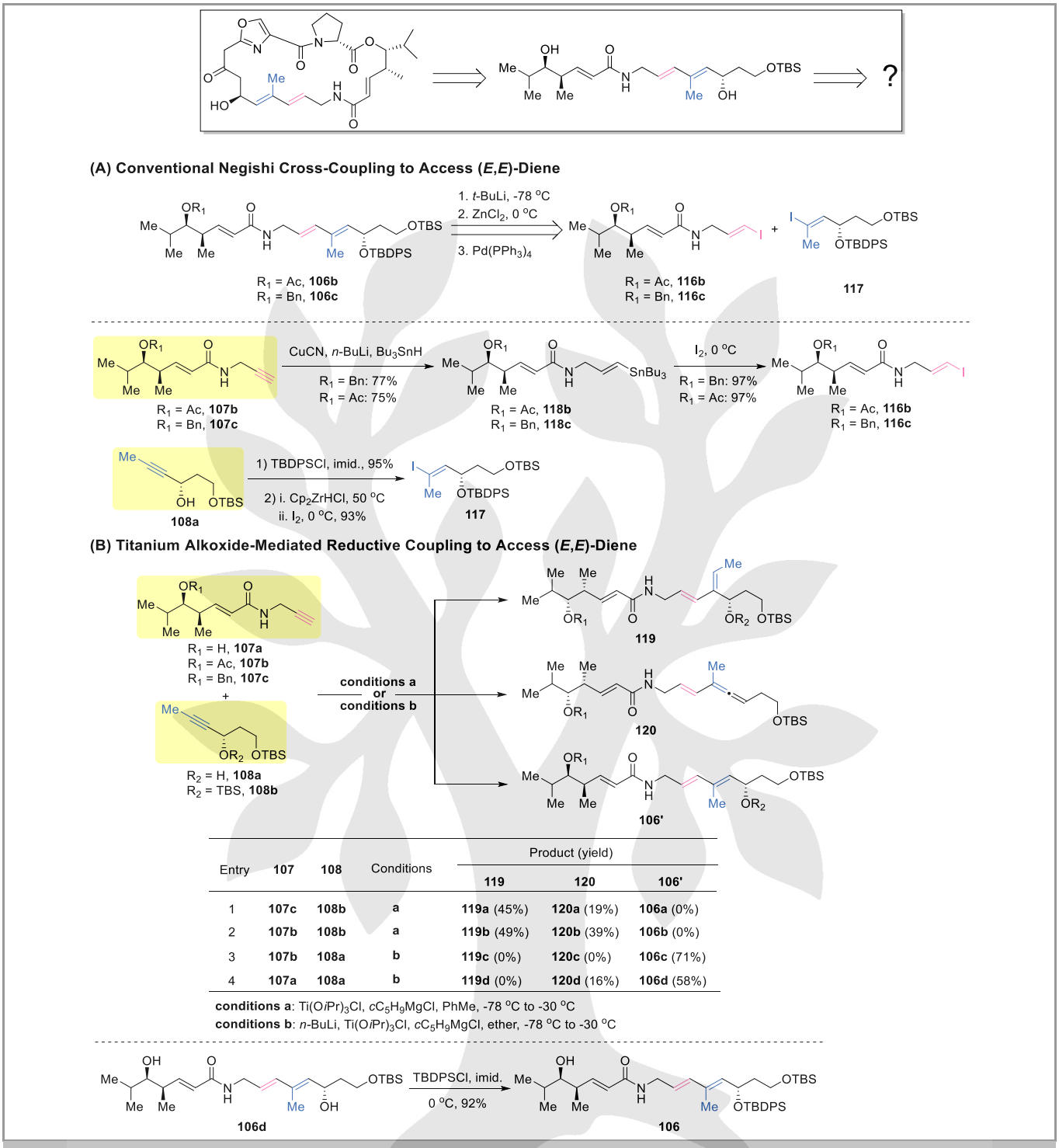
Scheme 26 Preparation of terminal alkynes **107**

The synthesis of Virginiamycin M_2 by Wu and Panek was initiated with the preparation of terminal alkyne **107**, including both the acetyl(Ac)-protected **107b** and benzyl(Bn)-protected **107c** (Scheme 25). A two-component asymmetric crotylation between silane **109** (obtained directly through a Cu-catalyzed asymmetric Si–H insertion[56]) and commercially available isobutyraldehyde provided the vinylogous product **110** with excellent diastereoselectivity (dr > 20:1) and enantiomeric excess (95% ee), whereas a three-component asymmetric crotylation between silane **109**, TMSOBn, and the aldehyde gave **111** with lower diastereoselectivity (dr = 6.3:1). Amidation of **110** and **111,** using the conditions reported by Weinreb, with propargylamine in the presence of $AlMe_3$ afforded amide **107a** and **107c** respectively with good yields. Acetylation of secondary alcohol **107a** gave **107b**. In this case, three different terminal alkynes with free hydroxy and protected hydroxy groups were prepared to evaluate the influences of protecting group in the regioselectivity of the alkyne-alkyne reductive coupling reactions.



Scheme 27 Preparation of internal alkynes **108**

The preparation of internal alkynes **108a** and **108b**, evaluated two asymmetric induction methods including Carreira's protocol (Scheme **27A**)[73] and an enantioselective ketone reduction using Corey's CBS reagent (Scheme **27B**) for operational simplicity when dealing with gaseous propyne. Both alkynes **108a** and **108b** were obtained with high enantiomeric excess.



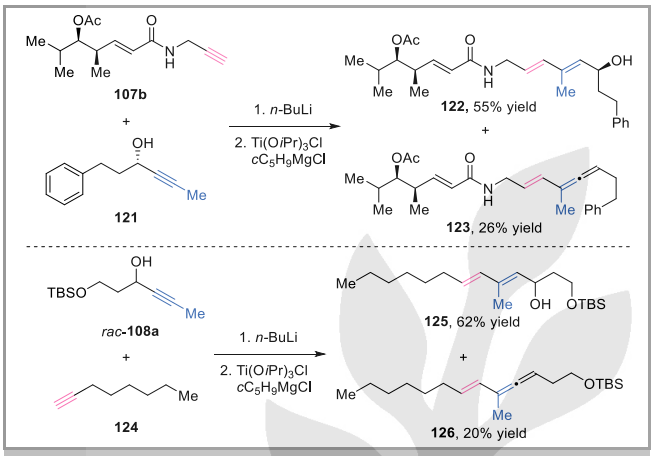
Entry	107	108	Conditions	Product (yield) 119	120	106'
1	107c	108b	a	119a (45%)	120a (19%)	106a (0%)
2	107b	108b	a	119b (49%)	120b (39%)	106b (0%)
3	107b	108a	b	119c (0%)	120c (0%)	106c (71%)
4	107a	108a	b	119d (0%)	120d (16%)	106d (58%)

conditions a: $Ti(O/Pr)_3Cl$, cC_5H_9MgCl, PhMe, -78 °C to -30 °C
conditions b: *n*-BuLi, $Ti(O/Pr)_3Cl$, cC_5H_9MgCl, ether, -78 °C to -30 °C

Scheme 28 Reductive coupling Vs. Negishi coupling to assemble the diene fragment **106**

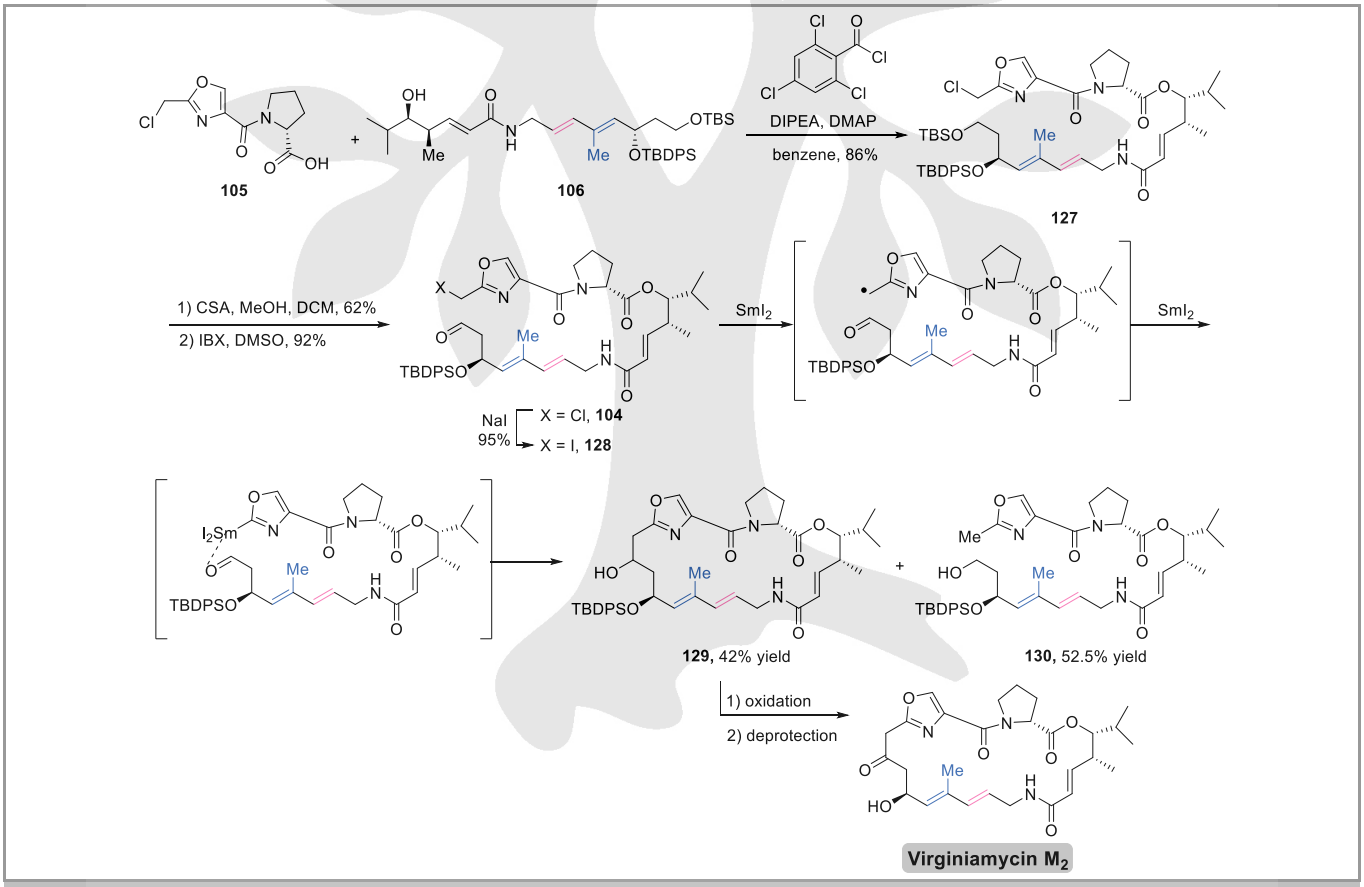
To assemble (*E*,*E*)-diene fragment **106**, the authors evaluated both the Negishi cross-coupling and the titanium-mediated reductive coupling, which serves as an excellent demonstration that the reductive coupling strategy evolves as a more efficient and atom-economic method (Scheme 28). Inspired by the earlier total synthesis of (-)-Motuporin,[13-14] Wu and Panek reported a one-pot hydrozirconation-transmetalation-cross coupling sequence as well. Regioselective hydrozirconation of internal alkyne **108a** with Cp_2ZrHCl (2 equiv, 50 °C) in THF afforded the (*E*)-vinyl zirconate as a single stereoisomer, and conversion to the zirconate with anhydrous $ZnCl_2$ followed by Pd(0)-catalyzed coupling with vinyl iodide **116c** furnished product **106c**. However, the yield of this sequence was low (20%), presumably due to the presence of a free hydroxy group in **108a**. Alternatively, the authors employed a two-step sequence to convert terminal alkyne **107** to (*E*)-vinyl iodide **116**: (i) a stannylcupration afforded exclusively (*E*)-terminal alkenyl stannane **118**; (ii) an iodination to obtain the vinyl iodide **116**. On the other hand, the vinyl iodide **117** was obtained through a sequence of hydroxy group protection, hydrozirconation with Schwartz's reagent (Cp_2ZrHCl, 2 equiv, 50 °C) and trapping the vinyl zirconium

intermediate with iodine. With both vinyl iodides available, the Negishi cross-coupling was executed by following a protocol of Li–I exchange, Zn–Li transmetalation, and Pd(0)-catalyzed coupling to give (*E*,*E*)-diene in high yield (Scheme 28A).



Scheme 29 Control experiments of alkoxide-directed alkyne–alkyne reductive coupling with propargylic alcohol

Because the titanium-mediated alkyne-alkyne reductive coupling offers an efficient solution for the generation of (*E*,*E*)-diene, the Panek group shifted its cross-coupling focus to reductive coupling strategy (Scheme 28B). As highlighted, the reductive coupling allows a direct coupling of the two alkyne fragments, **107** and **108**. In their detailed study, both the non-directed and alkoxide-directed coupling were evaluated, and the formation of three coupling products (*E*,*Z*)-diene **119**, allene **120**, and (*E*,*E*)-diene **106'** were observed. When the secondary hydroxy groups in **107** and **108** were protected, the reductive coupling produced only (*E*,*Z*)-diene **119** and allene **120** (Scheme 28B, entries 1 and 2). In comparison, when the hydroxy group of **108a** was deprotonated in situ using *n*-BuLi and served as a potential directing group in the reaction, the regioselectivity was reversed completely to favor the formation of (*E*,*E*)-diene **106'** (Scheme 28B, entry 3). A subsequent selective protection of the secondary alcohol as a TBDPS ether afforded fragment **106**. To this end, the reductive coupling route towards fragment **106** required only a total of seven steps as compared to the 13-steps using the Negishi cross-coupling strategy, hence illustrating the greater efficiency of reductive coupling without the requirements of numerous functional group manipulations. To validate that the reaction was indeed directed by alkoxide, the authors conducted several control experiments. Removing the steric and functional groups on the terminal alkyne and changing the steric- and stereo-environment on the internal alkyne part did not affect regioselectivity and produced (*E*,*E*)-diene as a single regioisomer with allene as by-product (Scheme 29).

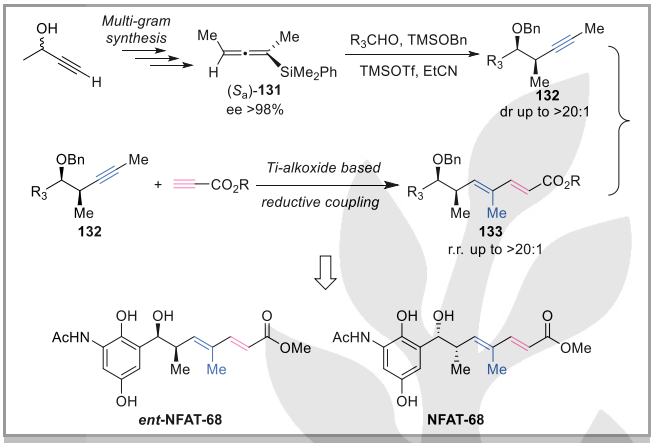


Scheme 30 Completion of the total synthesis of Virginiamycin M_2

With both fragments **105** and **106** in hand, a Yamaguchi esterification efficiently united them to provide the advanced intermediate **127**, which after TBS deprotection and an oxidation afforded aldehyde **104**. The chloride of **104** was converted to iodide, setting the stage for the key SmI_2-mediated Barbier/Reformatsky-type cyclization. After optimization, the authors were able to get a 45% yield of macrocycle **129** with 52.5% yield of reduction product **130**, which marked the largest

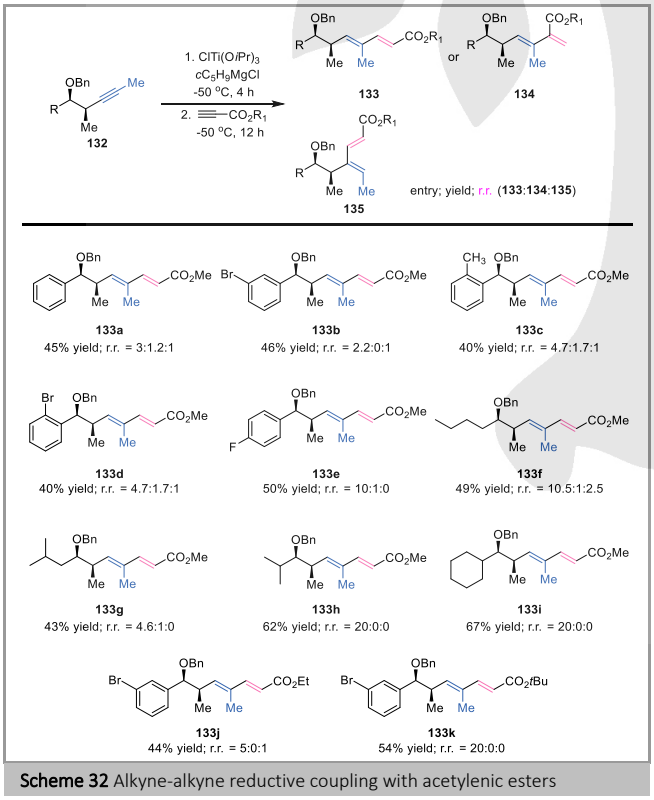
macrocycle (23-membered) formed among a SmI_2-mediated macrocyclizations to date. Subsequent oxidation of the alcohol and deprotection of TBDPS group of **129** led to the completion of the Virginiamycin M2 synthesis.

3.4 Total Synthesis of Nuclear Factor of Activated T-Cells-68 (NFAT-68) by Cai & Panek



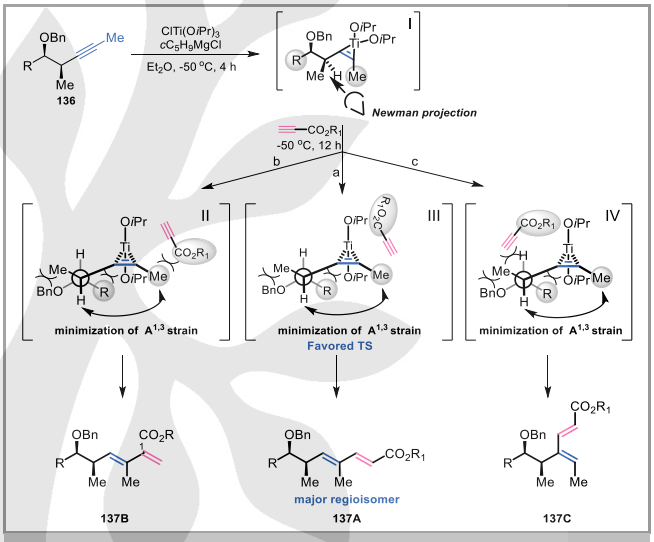
Scheme 31 Total synthesis of both enantiomers of NFAT-68 based on the sequential use of propargylation and Ti-mediated reductive coupling

Due to the continued interest in expanding the utility of the titanium-mediated reductive coupling and their organosilane chemistry in natural product synthesis, Cai and Panek selected the natural product NFAT-68 as a synthetic target (Scheme 31).[43] In this work, a new type of chiral allenylsilane[54, 74-77] was developed to facilitate the subsequent asymmetric three-component propargylation that set two stereocenters and generated an internal alkyne, which was participated in the subsequent titanium-mediated alkyne-alkyne reductive coupling.



Scheme 32 Alkyne-alkyne reductive coupling with acetylenic esters

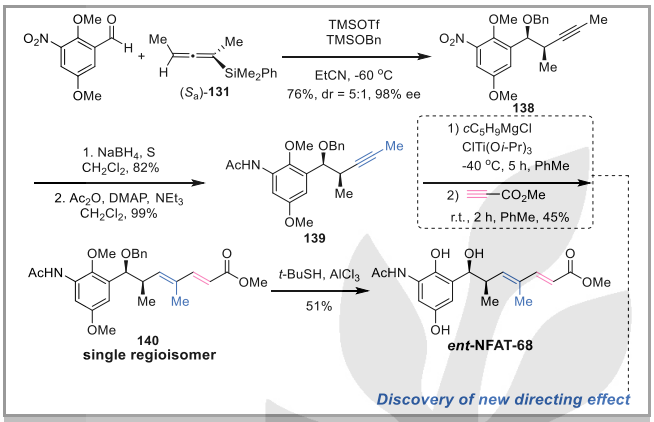
The reductive coupling with electronically activated acetylenic esters exhibited very different reactivity than that with electronically neutral terminal alkynes, which until that time was unprecedented in complex molecule synthesis. Furthermore, the observed regioselectivity with aromatic and aliphatic terminal alkynes exhibited an interesting dependence on the substitution patterns of the aromatic reaction partners and the steric bulk near the reaction centers for the aliphatic reaction partners, which was not reported previously. For example, *para*-fluoro substrate afforded diene **133e** with high regioselectivity (10:1); aliphatic substrates bearing tertiary carbons produced products **133h** and **133i** with complete regioselectivity. As for the terminal alkyne coupling partners, variation of the steric bulkiness on the ester group displayed a significant effect on the selectivity as well. For example, switching a methyl ester to an ethyl ester group (**133j**) resulted in a two-fold enhancement of selectivity, and the substitution with a *tert*-butyl group afforded the product as a single regioisomer (**133k**).



Scheme 33 Empirical transition state models for regiochemical course of reductive coupling

Cai and Panek then proposed the empirical transition state models to rationalize this interesting phenomenon of the regiochemical course of the reductive coupling (Scheme 33). Exposure of the internal alkyne to the Ti(II) species (generated in situ by reduction of $ClTi(OiPr)_3$ by cC_5H_9MgCl) led to the presumed titanocyclopropene complex I. Newman projection, which provides a clear comparison of how the direction of the approach of the terminal alkyne led to different regioisomers, was used as the basis of analysis. The lowest energy conformation of the titanium complex was presented by minimizing the gauche interactions between C4 and C5 substituents and the $A^{1,3}$ strain, and this analysis resulted in positioning the R group from internal alkyne in proximity to the titanium reacting center. The position of the R group in the transition state explains the observed influences of the steric bulk or the position of substituent on the aryl ring of the R group on the selectivity of the reaction by changing the steric environment of the titanium reaction center. Depending on how the terminal alkyne approaches the complex, the subsequent intermolecular carbometalation could proceed through three different pathways (a, b, c), leading to the three isomers. (*E*,*E*)-

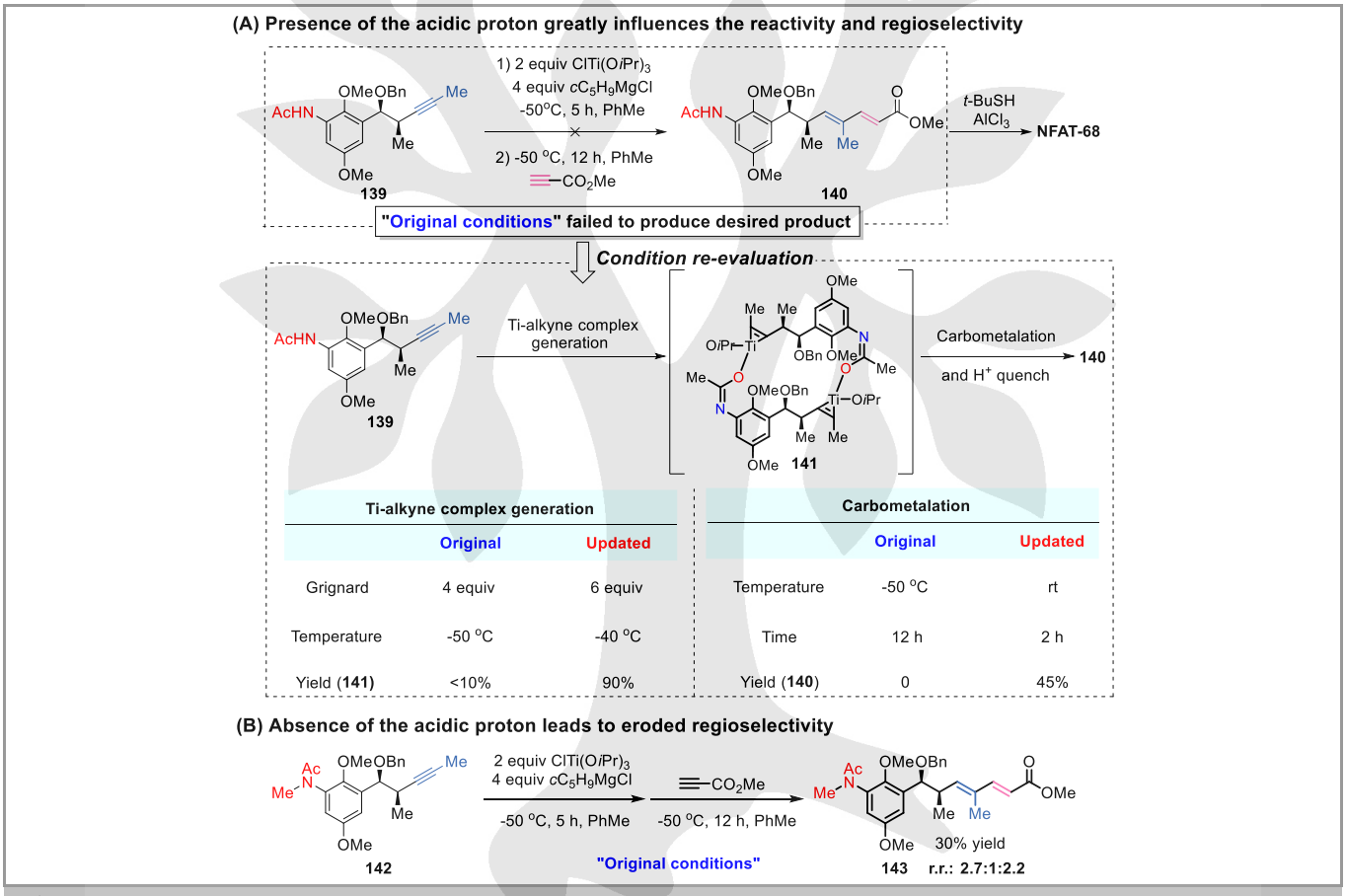
diene **137A** was formed as the major isomer, because transition state III had the least destabilizing steric interactions compared to the other two transition states and thus was energetically favored.



Scheme 34 Short synthesis of NFAT-68 and discovery of new directing effect

The synthesis of both enantiomers of NFAT-68 takes advantages of the propargylation and the reductive coupling reactions to rapidly set the stereochemistry and build the (*E*,*E*)-diene (Scheme 34). The synthesis was completed in five-steps with a 14% overall yield starting with allenylsilane. During the exploration of reductive coupling with acetamide, Cai and Panek discovered a new directing effect for the titanium-mediated reductive coupling, which will be discussed in the following section.[44]

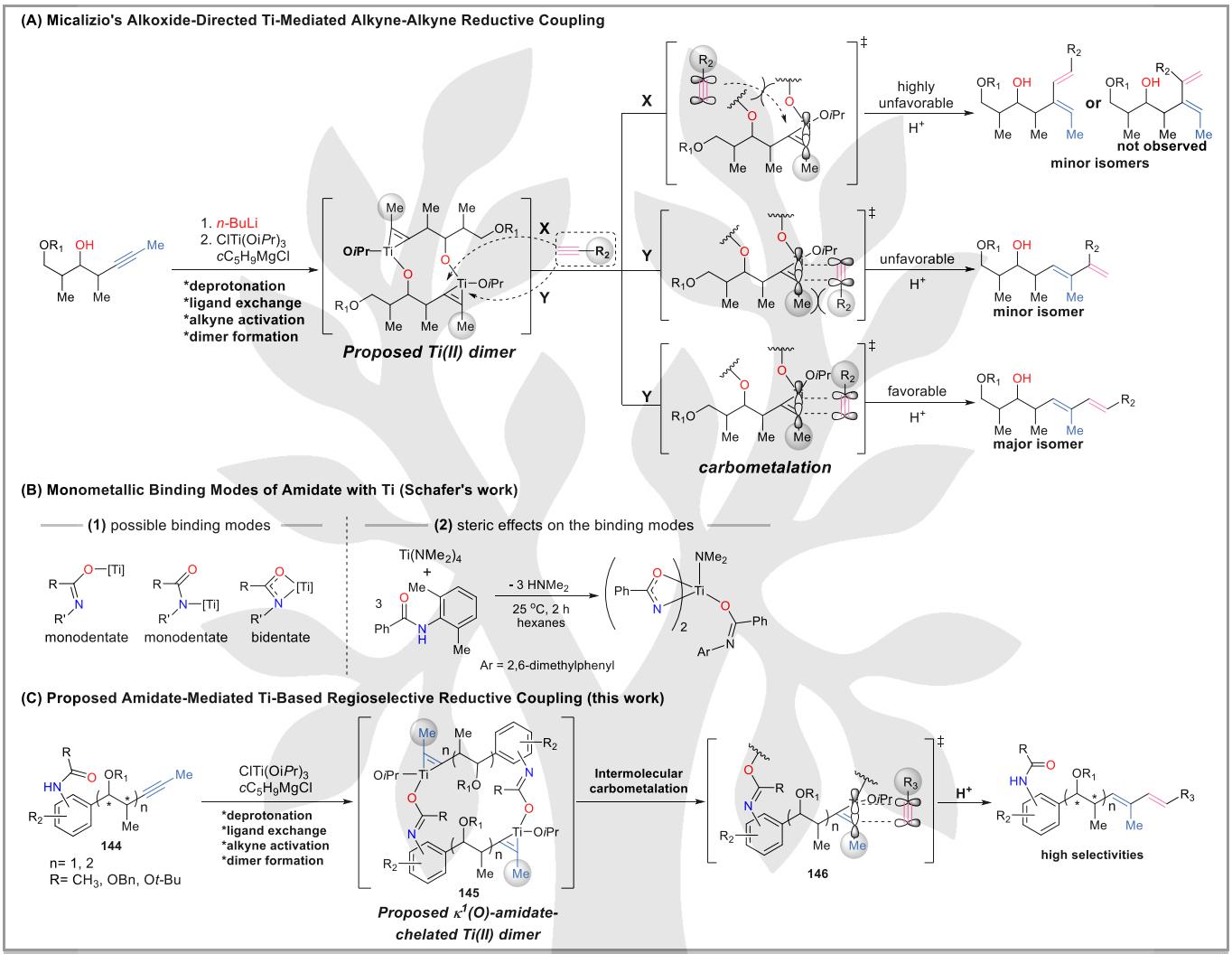
3.5 Titanium Alkoxide-Based Regioselective Alkyne-Alkyne Reductive Coupling Mediated by In Situ Generated Arylamidate



Scheme 35 Arylacetamide directing effect in alkyne-alkyne reductive coupling

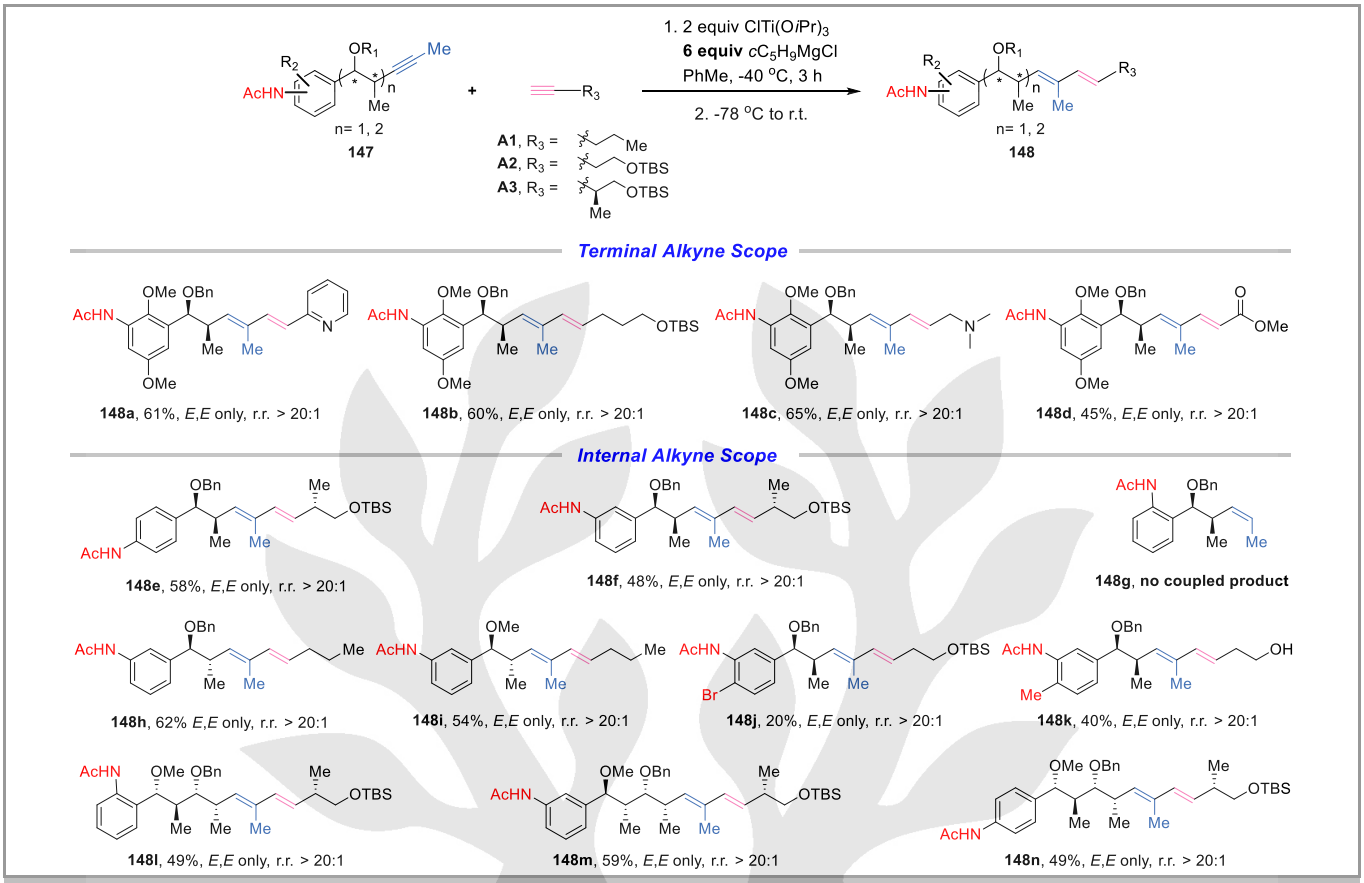
The development of new directing effect originated from the finding that previous reaction conditions ("original conditions") for the reductive coupling failed to produce the desired diene **140** using alkynyl acetamide **139** and methyl propiolate (Scheme 35) during the synthesis of NFAT-68. The authors reinvestigated the reaction conditions and carefully studied the two key transformations in the process, which are the formation of titanacyclopropene complex and the intermolecular carbometallation. Two important deviations from the "original conditions" were found for the generation of the presumed titanacyclopropene complex **141** (Scheme 35A). First, two additional equivalents (six vs four) of the Grignard reagent were required to achieve full conversion, where the excess amount of Grignard reagent was necessary for the deprotonation of the acetamide proton. Second, a higher reaction temperature was required to initiate the formation of complex **141**, where the thermodynamic effect of the deprotonated amide on the successful generation of Ti-alkyne

complex has not been previously described in reductive coupling reactions. The subsequent intermolecular carbometalation process displayed a different reaction profile as well. Elevated coupling temperature was needed for the complete consumption of **141**, and surprisingly the product was obtained as a single regioisomer. These two deviations suggested that the deprotonated acetamide had a pronounced impact on the reactivity and selectivity of the coupling reaction. Furthermore, the *N*-methylated counterpart **142** produced diene **143** with significantly reduced regioselectivity under the "original conditions" and gave only decomposition under the "updated conditions". This control experiment provided further evidence that the arylacetamide or the deprotonated acetamide may participate in the reaction and enhance the selectivity.



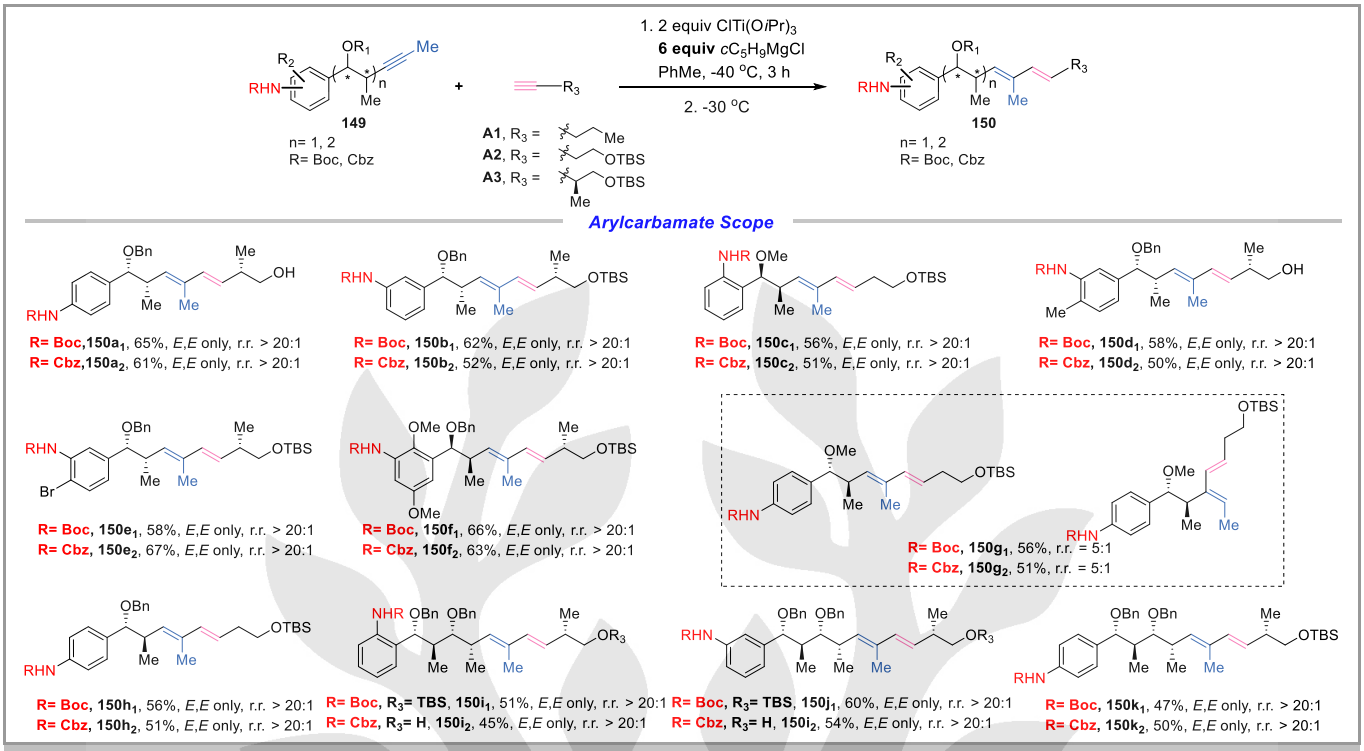
Scheme 36 Proposed arylamidate-mediated alkyne-alkyne reductive coupling

Encouraged by this early discovery, Cai and Panek hypothesized that the in situ-generated arylamidate might undergo ligand exchange with titanium and form an amidate-chelated dimer that can selectively undergo intermolecular carbometalation to deliver (*E*,*E*)-diene with high selectivity (Scheme 36C). Their hypothesis was based on the work from Micalizio,[7, 37, 46] Schafer[78-81] and their earlier work.[43] Micalizio group had carried out extensive studies and established a solid foundation in the mechanistic interpretation of operational intermediates and transition states leading to selective reductive coupling in the titanium-mediate reductive coupling (Scheme 36A).[7-8, 37, 40, 46] Central to Micalizio's proposal is the proposed Ti(II)-dimer. On the other hand, the Schafer group has established the coordination modes of amidates with Ti(IV) (Scheme 36B),[81] where the amidate can have three different binding modes with titanium depending on the steric environment. Taking both theories into consideration, Cai and Panek proposed a new type of dimer intermediate, where the chelation happens between amidate and titanium.



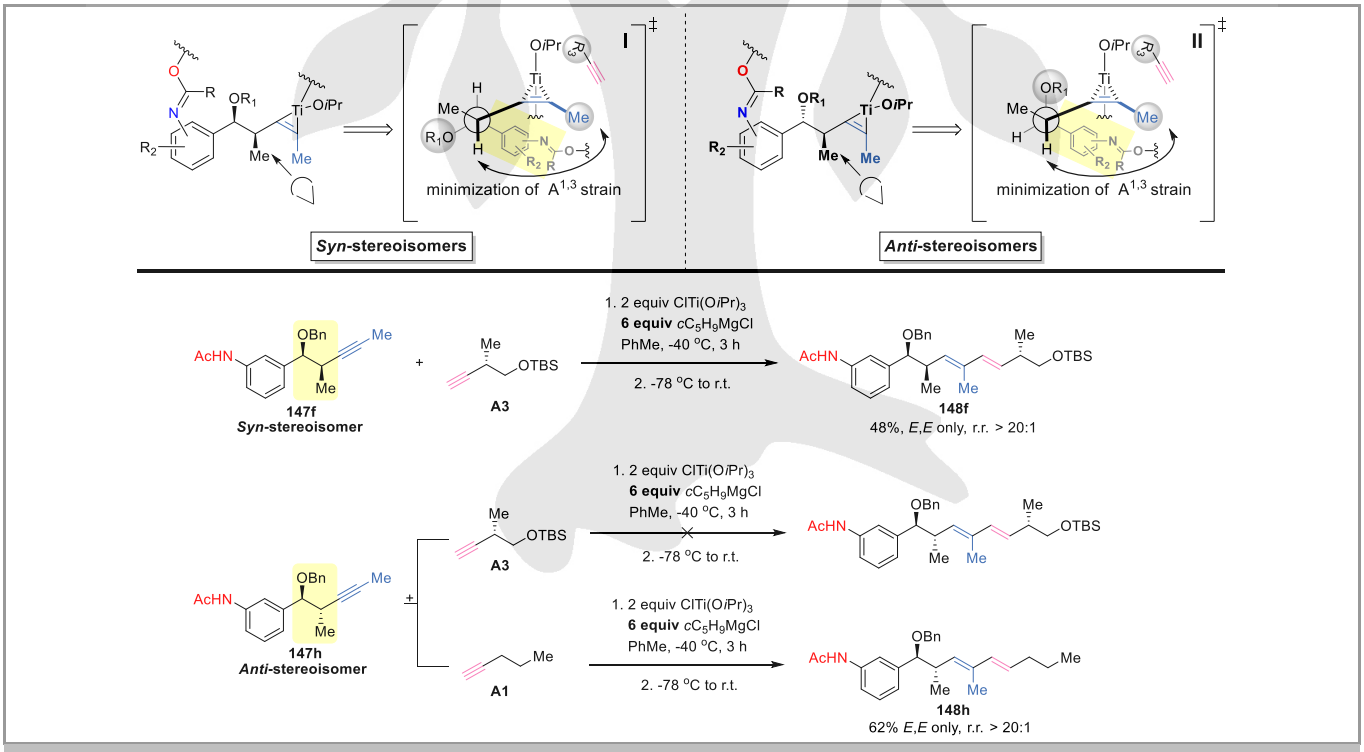
Scheme 37 Arylacetamide directing effect in alkyne-alkyne reductive coupling

To test the hypothesis, the authors first studied the alleged arylacetamide directing effect (Scheme 37). Indeed, the coupling reactions tolerated a variety of functional groups and provided the coupled products (*E*,*E*)-dienes as single isomer (terminal alkyne scope). Survey of the internal alkyne substrate scope revealed that: (1) *para*- and *meta*-substituted arenes gave excellent selectivity, but the *ortho*-substitution only led to reduction of alkyne to afford *Z*-alkene **148g**, and (2) variation of alcohol protecting groups, electronics on the aryl ring and tether length did not affect the selectivity, and all the coupled products were obtained as single isomers (**148h-148n**). These results strongly suggested that the arylacetamides had directing effects on the titanium alkoxide-mediated reductive couplings.



Scheme 38 Arylcarbamate directing effect in alkyne-alkyne reductive coupling

Encouraged by the success with acetamide directing effect, other commonly used amine protecting groups, such as *tert*-butyloxycarbonyl (Boc) and carboxybenzyl (Cbz), were explored. Indeed, both Boc and Cbz carbamate protecting groups displayed a similar directing effect as the acetamides (Scheme 38). The same variations on substrates were evaluated. All products were obtained as single regioisomers, except for the arene substrate with *para*-substituted and an *anti*-stereochemical relationship between benzylic methyl ether and homobenzylic methyl group.



Scheme 39 Stereochemical models for (*E,E*)-dienes with arylamidate as directing group

Not only the newly developed directing effect and excellent selectivity achieved for 37 examples were noteworthy, but the unprecedent reactivities were noteworthy. These events can be well rationalized by the proposed intermediate **145** and stereochemical models (Scheme 39). First, the use of arylamidate in their (Cai and Panek) case creates a more sterically crowed environment, which leads to better selectivities and lower reactivities compared with Micalizio's case. Second, as predicted by the transition state models I and II, the *anti*-isomer was less reactive than the *syn*-isomer in the coupling reaction. Indeed, *syn*-isomer **147f** couples readily with the sterically hindered terminal alkyne **A3**, whereas *anti*-isomer **147h** couples only with the least hindered alkyne **A1**.

4. Summary

The presence of an (*E*,*E*)-diene in various bioactive natural products has inspired our and others' laboratories to invent and develop novel chemistry to efficiently construct this motif in natural product synthesis. In the past three decades, Panek laboratory has devoted extensive efforts in this field, capitalizing on the initial development of the transition-metal-mediated sp^2-sp^2 cross-coupling or the modified Negishi coupling and the evolution of the strategy to titanium-mediated alkyne-alkyne reductive coupling. The advancement is driven by the desire to synthesize the bioactive natural products more efficiently, where the bond constructions are more atom-economic and the reactions are more selective.

Since the introduction of the concept of double-metal-catalysis and its application in the synthesis of trisubstituted, conjugate dienes by Negishi and co-workers,[58] it has seen a number of applications in natural product synthesis by research groups such as Theodorakis[61-62] and our group.[13-14, 67] The modified Negishi coupling reported by our own, an one-pot hydrozirconation-cross coupling process, allows the convenient assemble of (*E*,*E*)-dienes with high selectivity in the context of complex molecule synthesis. The first application of this methodology was realized by Theodorakis and co-workers in the asymmetric total synthesis of Reveromycin B in 1998, where they demonstrated that the Negishi coupling process was much more efficient than the Stille coupling. Subsequently, in 2002, Hu and Panek accomplished the total synthesis of (-)-Motuporin, where the Adda side chain was constructed efficiently using Negishi coupling.

The total synthesis of (-)-Callystatin A by Neil and Panek serves as a good example of using cross-coupling reactions for convergent fragment coupling.[66] The Negishi coupling was used to construct the (*E*,*Z*)-diene; the Stille coupling was used to assemble the (*E*,*E*)-diene; and another Negishi coupling was applied to install the C14-methyl group. These cross-coupling reactions proceeded smoothly with high yields and stereoselectivity, allowing the highly convergent synthesis of this natural product.

Although the modified Negishi coupling protocol assembles (*E*,*E*)-dienes with excellent regioselectivity, it requires multi-step functionalization of both the coupling partners and thus not step-economic. The development of a titanium-mediated alkyne-alkyne reductive coupling by Sato and Micalizio groups provides a more straightforward way to access (*E*,*E*)-dienes, where direct coupling of two alkynes to give (*E*,*E*)-dienes can be realized. Despite that the regioselectivity of this reaction is dependent on the stereo- and steric environment of the substrate, in 2008, Micalizio and co-workers accomplished the total synthesis of (-)-Callystatin A[68] using this reductive coupling technology. Compared with Panek's synthesis, the reductive coupling saves multiple steps that were required for pre-functionalization of coupling partners in the case of Negishi coupling, demonstrating the step-economy of the reductive coupling. To overcome the regioselectivity issue, in 2006, Micalizio and co-workers reported the first directing group strategy, an alkoxide-directed titanium-mediated reductive coupling.[46] This directed carbometalation process improves the selectivity for many cases, however the stereo- and steric environment of the substrates does influence on the level of selectivity.

In 2010, Wu and Panek reported the first application of an alkoxide-directed titanium-mediated alkyne-alkyne reductive coupling in the asymmetric total synthesis of Virginiamycin M_2.[15-16] The comparison of the Negishi coupling and the reductive coupling to assemble the (*E*,*E*)-diene fragment demonstrated that six steps can be saved and excellent selectivity can be achieved with the reductive coupling strategy. Following Wu's work, in 2016, Cai and Panek further explored this field and selected the natural product NFAT-68[43] as a target. With the newly developed allenylsilane, a variety of homopropargylic ethers can be accessed through the three-component propargylation reactions. These homopropargylic ethers served as good probe substrates and led to some interesting discoveries which were unprecedented. Transition state models were proposed to help understand and rationalize the dependence of the regioselectivity on the substitution pattern of substrate. These models pave way for the advancement of the arylamidate-mediated reductive coupling. This study is a good example of natural product synthesis-drive methodology development, where the inspiration came from the acetamide substrate in the synthesis of NFAT-68. The exploration of the reductive coupling for the synthesis of NFAT-68 provokes a new proposal and leads to the development of a new directing effect in the titanium alkoxide-mediated reductive coupling reported in 2020.[44]

The aryl-acetamide and -carbamate-mediated reductive coupling displays excellent regioselectivity towards a range of functional groups and perhaps more importantly the stereo- and steric environment of the substrates. Besides, new reactivity pattern was discovered, where the stereochemical relationship between the propargylic methyl group and the homopropargylic ether (*syn* vs. *anti*) and the position of the acetamide and the carbamate on the aryl ring could have profound effect on the reactivity. These new findings prompted the authors to propose a new titanium dimer intermediate, where the in situ generated amidate could chelate with titanium. More studies are needed to support the proposed intermediate. Future work will focus on expanding this methodology by exploring more amine protecting groups and a variety of alkyl amides and carbamates.

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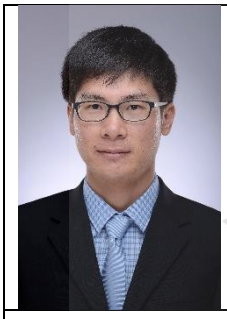
References

1. Burres, N. S.; Premachandran, U.; Hoselton, S.; Cwik, D.; Hochlowski, J. E.; Ye, Q.; Sunga, G. N.; Karwowski, J. P.; Jackson, M.; Whittern, D. N.; et al. *J. Antibiot. (Tokyo)* **1995**, *48* (5), 380.
2. Delpierre, G. R.; Eastwood, F. W.; Gream, G. E.; Kingston, D. G.; Sarin, P. S.; Todd, L.; Williams, D. H. *J. Chem. Soc. Perkin 1.* **1966,** *19*, 1653.
3. Desilva, E. D.; Williams, D. E.; Andersen, R. J.; Klix, H.; Holmes, C. F. B.; Allen, T. M. *Tetrahedron Lett.* **1992,** *33* (12), 1561.
4. Hamill, R. L.; Haney, M. E., Jr.; Stamper, M.; Wiley, P. F., Tylosin. *Antibiot Chemother (Northfield).* **1961,** *11*, 328.
5. Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S. *Tetrahedron Lett.* **1997,** *38*, 2859.
6. Micalizio, G. C.; Hale, S. B. *Acc. Chem. Res.* **2015,** *48*, 663.
7. Reichard, H. A.; McLaughlin, M.; Chen, M. Z.; Micalizio, G. C. *J. Org. Chem.* **2010,** *2010*, 391.
8. Shimp, H. L.; Micalizio, G. C. *Org. Lett.* **2005,** *7*, 5111.
9. Yoshida, M.; Kijima, M.; Akita, M.; Beppu, T. *J. Biol. Chem.* **1990,** *265*, 17174.
10. Zeng, X.; Qian, M.; Hu, Q.; Negishi, E. *Angew. Chem. Int. Ed. Engl.* **2004,** *43*, 2259.
11. Panek, J. S.; Hu, T. *J. Org. Chem.* **1997,** *62*, 4912.
12. Panek, J. S.; Hu, T. *J. Org. Chem.* **1997,** *62*, 4914.
13. Hu, T.; Panek, J. S. *J. Org. Chem.* **1999,** *64*, 3000.
14. Hu, T.; Panek, J. S. *J. Am. Chem. Soc.* **2002,** *124*, 11368.
15. Wu, J.; Panek, J. S. *Angew. Chem. Int. Ed. Engl.* **2010,** *49*, 6165.
16. Wu, J.; Panek, J. S. *J. Org. Chem.* **2011,** *76*, 9900.
17. Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989,** *111*, 2870.
18. Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987,** *109*, 2544.
19. Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004,** *126*, 3698.
20. Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004,** *126*, 15316.
21. Huddleston, R. R.; Jang, H. Y.; Krische, M. J. *J. Am. Chem. Soc.* **2003,** *125*, 11488.
22. Jang, H. Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004,** *126*, 466.
23. Kong, J. R.; Cho, C. W.; Krische, M. J. *J. Am. Chem. Soc.* **2005,** *127*, 11269.
24. Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006,** *128*, 16448.
25. Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem. Int. Ed. Engl.* **2009,** *48*, 6313.
26. Guo, Y. A.; Lee, W.; Krische, M. J. *Chemistry* **2017,** *23*, 2557.
27. Liu, P.; McCarren, P.; Cheong, P. H.; Jamison, T. F.; Houk, K. N. *J. Am. Chem. Soc.* **2010,** *132*, 2050.
28. Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004,** *126*, 15342.
29. Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004,** *126*, 4130.
30. Patel, S. J.; Jamison, T. F., *Angew. Chem. Int. Ed. Engl.* **2003,** *42*, 1364.
31. Luanphaisarnnont, T.; Ndubaku, C. O.; Jamison, T. F. *Org. Lett.* **2005,** *7*, 2937.
32. Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007,** (43), 4441.
33. Miller, K. M.; Huang, W. S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003,** *125*, 3442.
34. Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999,** *121*, 7342.
35. Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003,** *5*, 67.
36. Shimp, H. L.; Micalizio, G. C. *Org. Lett.* **2005,** *7*, 5111.
37. Perez, L. J.; Shimp, H. L.; Micalizio, G. C. *J. Org. Chem.* **2009,** *74*, 7211.
38. Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2005,** *127*, 3694.
39. Reichard, H. A.; Micalizio, G. C. *Angew. Chem. Int. Ed. Engl.* **2007,** *46*, 1440.
40. Reichard, H. A.; Micalizio, G. C. *Chem. Sci.* **2011,** *4*, 573.
41. Greszler, S. N.; Reichard, H. A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012,** *134*, 2766.
42. Jeso, V.; Aquino, C.; Cheng, X.; Mizoguchi, H.; Nakashige, M.; Micalizio, G. C. *J. Am. Chem. Soc.* **2014,** *136*, 8209.
43. Cai, B.; Evans, R. W.; Wu, J.; Panek, J. S. *Org. Lett.* **2016,** *18*, 4304.
44. Cai, B.; Panek, J. S. *J. Am. Chem. Soc.* **2020,** *142*, 3729.
45. Wu, J.; Pu, Y.; Panek, J. S. *J. Am. Chem. Soc.* **2012,** *134*, 18440.
46. Ryan, J.; Micalizio, G. C. *J. Am. Chem. Soc.* **2006,** *128*, 2764.
47. Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995,** *95*, 1293.
48. Huang, H. B.; Panek, J. S. *J. Am. Chem. Soc.* **2000,** *122*, 9836.
49. Huang, H. B.; Spande, T. F.; Panek, J. S. *J. Am. Chem. Soc.* **2003,** *125*, 626.
50. Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991,** *113*, 9868.
51. Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996,** *118*, 12475.
52. Hu, T.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **2002,** *124*, 12806.
53. Wrona, I. E.; Gabarda, A. E.; Evano, G.; Panek, J. S. *J. Am. Chem. Soc.* **2005,** *127*, 15026.
54. Brawn, R. A.; Panek, J. S. *Org. Lett.* **2007,** *9*, 2689.
55. Lee, J.; Panek, J. S. *Org. Lett.* **2011,** *13*, 502.
56. Wu, J.; Chen, Y.; Panek, J. S. *Org. Lett.* **2010,** *12*, 2112.
57. Vanhorn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978,** *100*, 2252.
58. Negishi, E. O., N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978,** *100*, 2254.
59. Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975,** *97*, 679.
60. Schwartz, J.; Labinger, J. A. *Angew. Chem. Int. Edit.* **1976,** *15*, 333.
61. Drouet, K. E.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1999,** *121*, 456.
62. Drouet, K. E.; Theodorakis, E. A. *Chem. Eur. J.* **2000,** *6*, 1987.
63. Coery, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

64. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986,** *108*, 7408.
65. Valentekovich, R. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1995,** *117*, 9069.
66. Langille, N. F.; Panek, J. S. *Org. Lett.* **2004,** *6*, 3203.
67. Lee, J.; Panek, J. S. *Org. Lett.* **2009,** *11*, 4390.
68. Reichard, H. A.; Rieger, J. C.; Micalizio, G. C. *Angew. Chem. Int. Ed. Engl.* **2008,** *47*, 7837.
69. Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem. Int. Ed. Engl.* **1999,** *38*, 2398.
70. Lowe, J. T.; Panek, J. S. *Org. Lett.* **2008,** *10*, 3813.
71. Li, Q.; Seiple, I. B. *J. Am. Chem. Soc.* **2017,** *139*, 13304.
72. Li, Q.; Seiple, I. B. *Tetrahedron* **2019,** *75*, 3309.
73. Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000,** *122*, 1806.
74. Brawn, R. A.; Panek, J. S. *Org. Lett.* **2009,** *11*, 4362.
75. Brawn, R. A.; Panek, J. S. *Org. Lett.* **2009,** *11*, 473.
76. Brawn, R. A.; Panek, J. S. *Org. Lett.* **2010,** *12*, 4624.
77. Brawn, R. A.; Welzel, M.; Lowe, J. T.; Panek, J. S. *Org. Lett.* **2010,** *12*, 336.
78. Leitch, D. C.; Beard, J. D.; Thomson, R. K.; Wright, V. A.; Patrick, B. O.; Schafer, L. L. *Eur. J. Inorg. Chem.* **2009,** (18), 2691.
79. Payne, P. R.; Thomson, R. K.; Medeiros, D. M.; Wan, G.; Schafer, L. L. *Dalton T.* **2013,** *42*, 15670.
80. Yim, J. C. H.; Bexrud, J. A.; Ayinla, R. O.; Leitch, D. C.; Schafer, L. L. *J. Org. Chem.* **2014,** *79*, 2015.
81. Ryken, S. A.; Schafer, L. L. *Acc. Chem. Res.* **2015,** *48*, 2576.

Biosketches

	Bin Cai was born in Suzhou, China. He received his Ph.D. in organic chemistry at Boston University in August 2018 under the guidance of Prof. James S. Panek. He is now a Postdoctoral Associate with Prof. Dale L. Boger at the Scripps Research, CA, USA, working on total synthesis of Vinblastine.
	Ren Wei Toh was born in Singapore and received his Ph.D. in organic chemistry at National University of Singapore in November 2021 under the guidance of Prof Wu Jie. He continues working as Postdoctoral Researcher with Prof Wu and is working on the derivatives of eosin Y synthesis and their biological activities.
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