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Ni-Catalyzed Cross-Electrophile Coupling for the Synthesis of Skipped Polyenes

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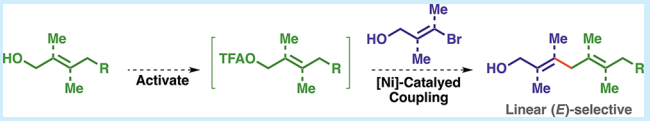
Supporting Information

ABSTRACT: Skipped polyenes featuring high (*E*)-selectivity and varying methyl substitution patterns are synthesized using a nickel-catalyzed cross-coupling reaction between allyl trifluoroacetates and vinyl bromides. The utility of this cross-electrophile coupling is showcased in part by the synthesis of the RST fragment of the marine ladder polyether, maitotoxin. Construction of this fragment is particularly challenging due to the alternating methyl substitution pattern.



Skipped polyenes featuring various methyl substitution patterns are commonly found in biologically active natural products with anticancer, antibacterial, and antiviral properties.[1] These molecules can also provide efficient entry to the fused cyclic ether skeletons of marine ladder polyether natural products by way of epoxide ring opening cascade reactions.[2a]

Given their significance, researchers have developed a number of individualized syntheses[2] of skipped polyenes as well as more generalized methods, but those are limited by particular substitution and unsaturation patterns. The Trost group, for example, recently reported the ruthenium-catalyzed synthesis of 1,3,6-trienes via the coupling of propene with two alkyl-substituted alkynes (Figure 1a).[3a] The Micalizio lab, alternatively, demonstrated a titanium-mediated coupling reaction of vinylcyclopropanes and alkynes to generate 1,4-dienes and 1,4,7-trienes (Figure 1b).[3b]

Herein, we describe a more flexible approach to polyene synthesis that proceeds via the Ni-catalyzed cross-electrophile coupling of activated allyl alcohol **3** with vinyl bromide **4** (Figure 1c). Linear polyenes, including those that display a variety of methyl substitution patterns, are readily accessed with high (*E*)-selectivity while tolerating a free alcohol group. Among the polyenes synthesized using this strategy is the all-linear (*E*)-pentaene **7**, which we use to prepare the RST fragment of the ladder polyether natural product, maitotoxin, via an epoxide opening cascade reaction (Figure 1d).[2,4]

Few examples of Ni-catalyzed cross-electrophile reductive couplings between allyl and sp^2 electrophiles are described in the literature, and those that are described provide mixtures of branched products, linear (*E*)-products, and linear (*Z*)-products.[5] To achieve high linear (*E*)-selectivity, our aim was to limit alkene isomerization by choosing coupling partners that react quickly under mild conditions and have excellent cross-selectivity. While there are other metals that catalyze allyl vinyl couplings,[6] we were inspired by the Gong group[5b] who reported the Ni-catalyzed coupling of aryl halides and allyl acetates (Figure 2a). We thus began our investigations by applying similar reaction conditions to the coupling of vinyl

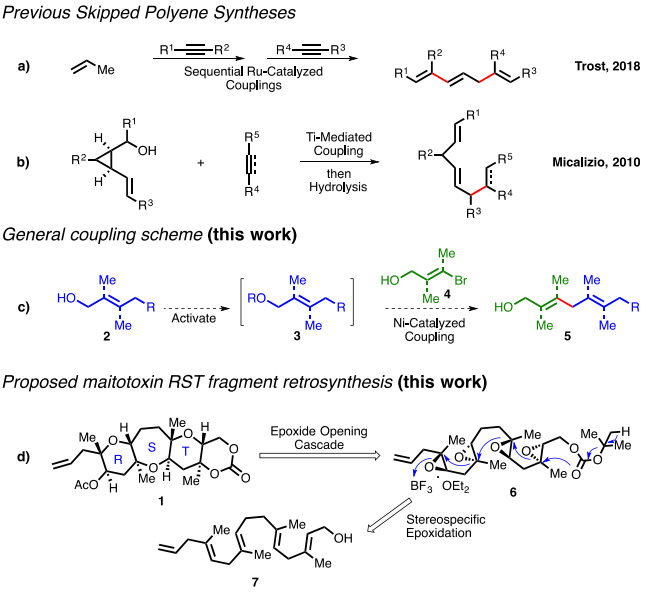


Figure 1. Skipped polyene syntheses by the (a) Trost and (b) Micalizio groups. (c) Proposed polyene synthesis described herein. (d) Synthetic plan for the RST fragment of maitotoxin via pentaene **7**.

bromide **9** and compound **8** featuring allyl acetate (**8a**), allyl pivalate (**8b**), and allyl trifluoroacetate (**8c**) activating groups (Figure 2b). Nickel(II) bromide (10 mol %) and 2,2-bipyridine (10 mol %) served as the catalyst and ligand, respectively, while zinc acted as the metal reductant. The addition of magnesium chloride and pyridine to the reaction mixture was found to be essential as similarly noted by the Gong group.[5b] While each of the three Ni-catalyzed reactions examined provided only the desired linear coupled products **10**/**11** (i.e., no branch product), the highly reactive **8c**

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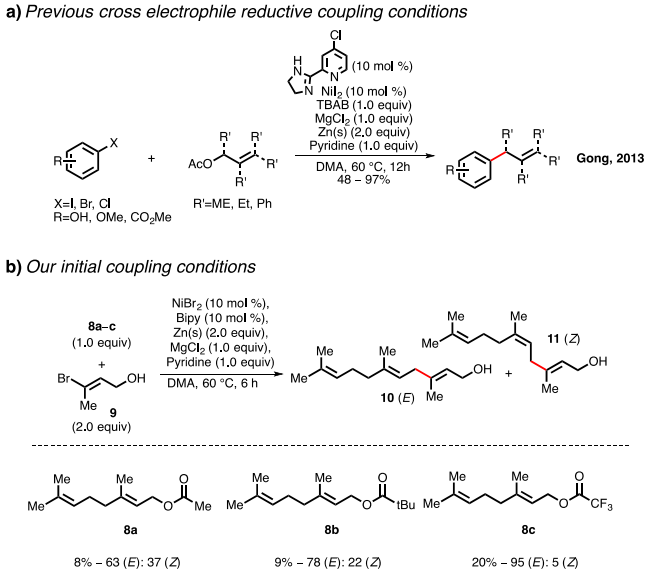


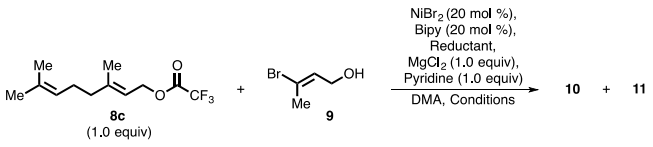
Figure 2. (a) Allyl–aryl coupling conditions developed by the Gong group. (b) Effect of the activating groups of **8** on product (*E*)-selectivity.

provided the best (*E*)-selectivity (**10**:**11**, *E*:*Z*, 95:5). Examination of the ^{1}H NMR spectrum of the crude reaction mixture revealed complete consumption of **8c** but the formation of homocoupled and hydrolyzed side products, thereby accounting for the low yield of **10**/**11** (20%).[7]

Accordingly, we next conducted optimization studies to further improve the reaction outcome. Because we observed a slight increase in the yield of **10**/**11** (23%) upon doubling the equivalents of nickel(II) bromide and 2,2-bipyridine (i.e., from 10 to 20 mol %) under otherwise identical conditions shown in Figure 2b, we maintained the use of this higher catalyst and ligand loading throughout our optimization studies. As shown in entries 1–4 of Table 1, decreasing the reaction time from 6 to 1 h and the reaction temperature from 60 to 40 °C significantly enhanced the product (*E*)-selectivity (>99:1) and yield (40%). Utilizing manganese rather than zinc as the reductant (entries 5 and 6) and increasing the equivalents of vinyl bromide **9** from 2.0 to 3.0 (entries 6 and 7) provided an additional improvement in product yield (~63%) without affecting the (*E*)-selectivity. Notably, decreasing the equivalents of manganese from 4.0 to 2.0 had little impact (Table 1, entries 7 and 8). Although we observed near exclusive (*E*)-selectivity, the yield of this transformation was not improved beyond 63% until we noted the dramatic impact of the reaction stir rate as a result of the heterogeneity of the manganese reductant. Reaction stir rates of ~600 rpm, for example, consistently provided product yields of approximately 50–60%, whereas a stir rate of 945 rpm led to an 86% product yield (Table 1, entry 9). Increasing the stir rate beyond 945 rpm had no additional effect.

As shown in Table 2, we then examined the scope of the vinyl halide coupling partners using the optimized conditions established in entry 9 of Table 1. We found that vinyl bromides substituted at the α position (entries 1, 2, and 6–8) resulted in moderate to good yields of the corresponding products (56–87%). Vinyl halides with α,β-substitution (entries 3 and 4), β-substitution (entry 5), and β,β-substitution (entry 9) provided a similar product yield range (48–72%).

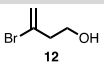
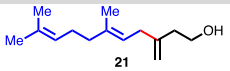
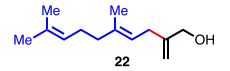
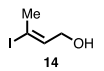
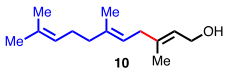
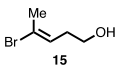
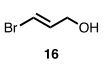
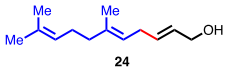
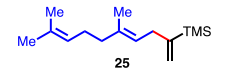
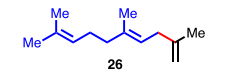
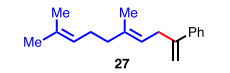
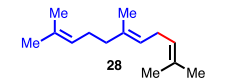
Table 1. Optimization of the Coupling between 8c and 9[a]



entry	**9** (equiv)	reductant (equiv)	*T* (°C)	*t* (h)	stirring rate (rpm)	yield (%) (**10**:**11**)
1	2.0	$Zn_{(s)}$ (2.0)	60	6	600	23% (96:4)
2	2.0	$Zn_{(s)}$ (2.0)	60	3	600	32% (97:3)
3	2.0	$Zn_{(s)}$ (2.0)	60	1	600	30% (97:3)
4	2.0	$Zn_{(s)}$ (2.0)	40	1	600	40% (>99:1)
5	2.0	$Zn_{(s)}$ (4.0)	40	1	600	41% (>99:1)
6	2.0	$Mn_{(s)}$ (4.0)	40	1	600	52% (>99:1)
7	3.0	$Mn_{(s)}$ (4.0)	40	1	600	63% (>99:1)
8	3.0	$Mn_{(s)}$ (2.0)	40	1	600	62% (>99:1)
9	3.0	$Mn_{(s)}$ (2.0)	40	1	945	86% (>99:1)

[a]Yields are determined via NMR using 1,3,5-trimethoxybenzene as an internal standard.

Table 2. Coupling of 8c with Vinyl Halides 12–20 under Optimized Conditions[a]

entry	vinyl halide	product	yield
1	 **12**	 **21**	77%
2	 **13**	 **22**	66%
3	 **14**	 **10**	60%
4	 **15**	 **23**	72%
5	 **16**	 **24**	48%
6	 **17**	 **25**	87%
7	 **18**	 **26**	76%
8	 **19**	 **27**	56%[b]
9	 **20**	 **28**	54%

[a]Yields are determined via NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Reaction time of 30 min.

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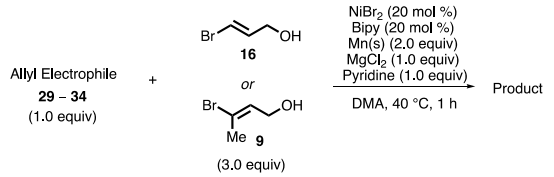
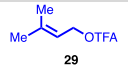
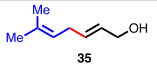
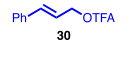
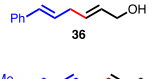
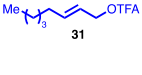
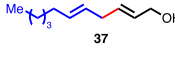
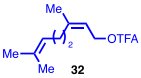
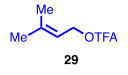
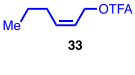
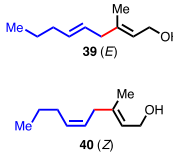
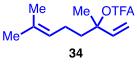
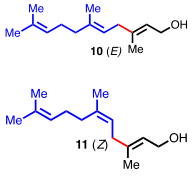
Next, we explored a range of allyl trifluoroacetate coupling partners (Table 3). Both di- and trisubstituted allyl

Table 3. Coupling of Vinyl Bromide 16 or 9 with Allyl Electrophiles 29−34 under Optimized Conditions[a]



entry	allyl electrophile	vinyl bromide	product(s)	yield (*E*:*Z*)
1	 **29**	**16**	 **35**	40%
2	 **30**	**16**	 **36**	12%
3	 **31**	**16**	 **37**	46%
4	 **32**	**9**	 **10**	52%
5	 **29**	**9**	 **38**	61%
6	 **33**	**9**	 **39** (*E*) **40** (*Z*)	51% (0.4:0.6)
7	 **34**	**9**	 **10** (*E*) **11** (*Z*)	37% (2:1)

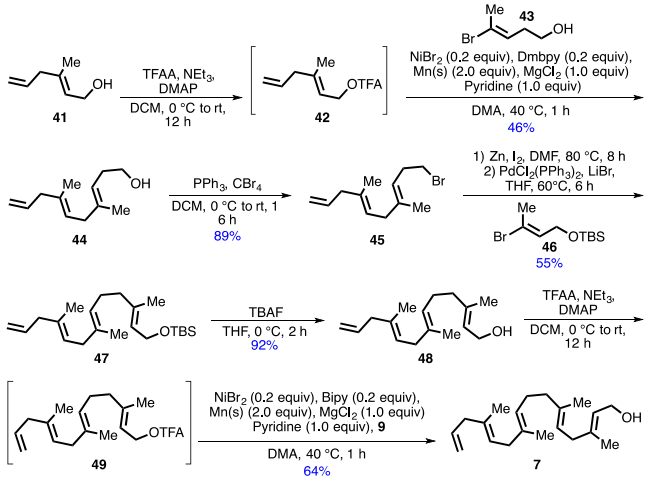
[a]Yields are determined via NMR using 1,3,5-trimethoxybenzene as an internal standard.

trifluoroacetates (entries 1−3) were coupled with vinyl bromide **16** without observing isomerization in low to moderate yields (12−46%). In addition to the desired product, we observed both homocoupling and hydrolysis of the trifluoroacetate starting materials, which accounted for the lower yields in some of these reactions. Trisubstituted allyl trifluoroacetates **32** and **29** coupled with vinyl bromide **9** in good yields (entries 4 and 5, 52−61%). Interestingly, nerol **32** isomerized when coupled with vinyl bromide **9** to give linear (*E*)-product **10** (entry 4). Due to the incomplete isomerization of **33** and **34** during the coupling to **9**, we observed *E*/*Z* product mixtures as shown in entries 6 and 7.

To further demonstrate the utility of this cross-electrophile coupling reaction, we implemented it in the construction of pentaene **7**. This intermediate was then used to synthesize the RST fragment of maitotoxin via an epoxide opening cascade reaction (Figure 1d). Maitotoxin is a member of the polyether marine biotoxin class of natural products and has been reported to exhibit anticancer activity.[8] The synthesis of the RST fragment is particularly challenging due to its alternating methyl substitution pattern and 6−7−6 ring structure. While a previous synthesis of the QRSTU ring fragment of maitotoxin was reported by the Nicolaou group in 2010, they found the installation of the alternating methyl substituents to be cumbersome and challenging.[9]

As presented in Scheme 1, we commenced the synthesis of pentaene **7** by activating known compound **41** with trifluoro-

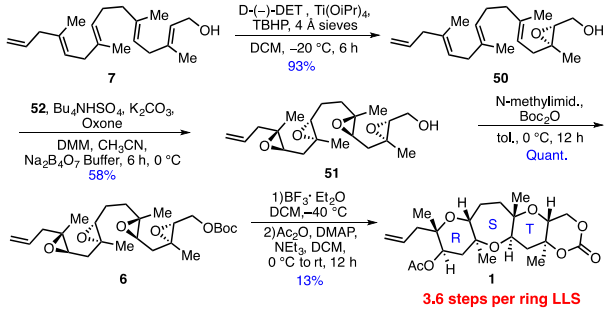
Scheme 1. Synthesis of Pentaene 7



acetic anhydride. After aqueous workup, **42** was immediately coupled with vinyl bromide **43** to furnish the desired product **44** in 46% yield. Notably, the use of 4,4′-dimethoxy-2,2-bipyridine in this coupling reaction minimized hydrolysis of the trifluoroacetate electrophile. Alcohol **44** was then transformed to alkyl bromide **45** and coupled to vinyl bromide **46** using a Negishi cross-coupling reaction.[10] Although we attempted to synthesize **48** from alcohol **44** using a nickel-catalyzed cross-electrophile coupling methodology, we could obtain only inseparable *E*/*Z* mixtures of the desired product. Following the formation of **47**, the primary alcohol was then deprotected and activated to generate **49**. A final coupling reaction under our developed nickel-catalyzed conditions provided the desired pentene **7**.

As illustrated in Scheme 2, a Sharpless epoxidation followed by Shi epoxidation was next implemented to chemoselectively and enantioselectively oxidize four of the five alkenes of

Scheme 2. Epoxidation of Pentaene 7 Followed by a Tetraepoxide Opening Cascade for the Formation of the RST Fragment of Maitotoxin 1



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pentane **7**. The free alcohol of the resulting product **51** was subsequently activated by forming the corresponding *tert*-butyl carbonate **6**. The final tetraepoxide opening cascade reaction was then initiated in the presence of the $BF_3{\cdot}OEt_2$ catalyst at −40 °C.[4] Following acetylation of the secondary alcohol, RST fragment **1** of maitotoxin was obtained. To the best of our knowledge, this is the first tetraepoxide opening cascade that has been performed to synthesize a natural product fragment containing both six- and seven-membered rings.

In conclusion, we have demonstrated the Ni-catalyzed cross-electrophile coupling of activated allyl alcohols with vinyl bromides as a general strategy for constructing skipped polyenes displaying high (*E*)-selectivity. This method has been applied to the synthesis of the all-(*E*), all-linear pentaene **7**, which we have further shown is a viable precursor for the synthesis of the challenging RST fragment of maitotoxin **1**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01019.

Experimental procedures and spectral data for polyenes **10**, **21**−**28**, and **35**−**40** and compounds **42**−**51**, **7**, **6**, and **1** (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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