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Allene–alkyne cross-coupling for stereoselective synthesis of substituted 1,4-dienes and cross-conjugated trienes

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Dedicated to Professor John Hartwig on his receipt of the Tetrahedron Prize

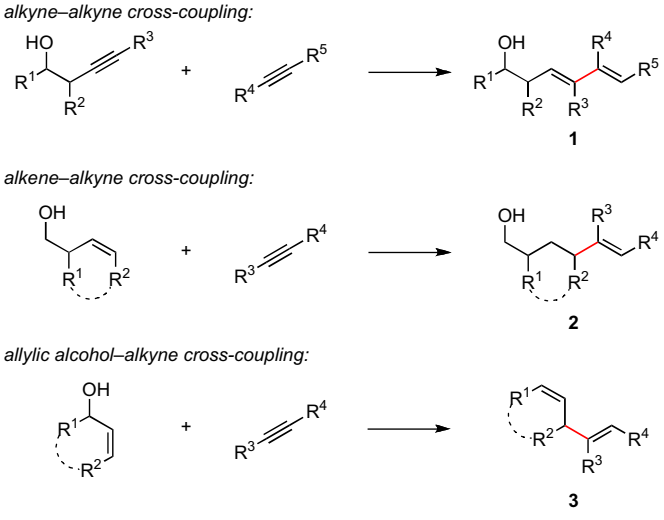
Abstract

Titanium-mediated cross-coupling of allenic alcohols with alkynes has been investigated. Divergent reaction pathways were discovered that provide either stereodefined 1,4-dienes or substituted cross-conjugated trienes. In short, allene substitution plays a critical role in the determination of reaction pathway.

1. Introduction

The direct cross-coupling of unactivated π-systems could represent a powerful strategy for the convergent synthesis of complex molecules. Such processes provide an advantage over metal-catalyzed cross-coupling reactions[1] that typically require the use of activated coupling partners (i.e., functionalized organometallic reagents and organic halides), as these 'starting materials' often require numerous stoichiometric reactions for their preparation. While numerous examples of metal-mediated coupling reactions of unactivated π-systems have been described in intramolecular settings, few reports describe the success of such processes for intermolecular C–C bond formation.[2] Where, in intramolecular C–C bond forming reactions, reactivity and selectivity are controlled by the enforced proximity of the reacting π-systems, the analogous bimolecular processes are significantly more complex. To realize such intermolecular cross-coupling reactions, one must be able to control site-selectivity (in the functionalization of each reacting π-component) and facial selectivity, while overcoming barriers associated with general reactivity.

Recently, we have described a variety of titanium-mediated cross-coupling reactions for the fusion of substituted and unactived π-systems (Scheme 1).[3] While these coupling reactions have provided a convergent pathway to the synthesis of stereodefined tetrasubstituted 1,3-dienes (**1**), branched allylic systems (**2**) and 1,4-dienes (**3**), they represent only a small



Scheme 1. Directed cross-coupling reactions of unactivated π-systems.

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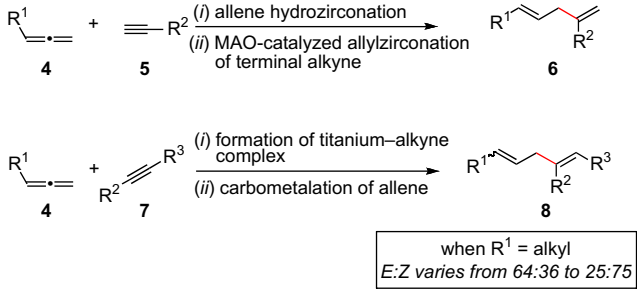
sample of the potential cross-coupling reactions possible based on the reactivity of metal–π complexes.

Metal-mediated allene–alkyne cross-coupling is a relatively underdeveloped process.[4] In the context of convergent synthesis of dienes, this mode of cross-coupling is known to be effective with only a limited subset of coupling partners, providing access to di- and trisubtituted products (Scheme 2). For example, allene hydrozirconation followed by MAO-catalyzed allylzirconation of terminal alkynes provides a regio- and ste-



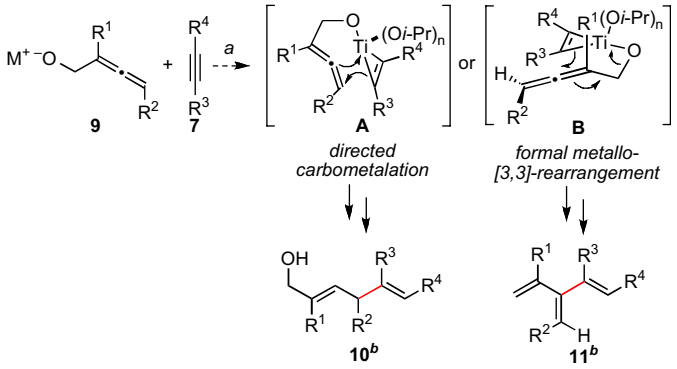
Scheme 2. Known pathways to 1,4-dienes based on allene–alkyne cross-coupling.

reoselective route to 1,4-disubstituted 1,4-dienes (**4**+**5**→**6**).[4d,e] For more highly substituted products, cross-coupling between preformed titanium–alkyne complexes and monosubstituted allenes has been reported to provide trisubstituted 1,4-dienes, albeit with varying degrees of stereoselection (**4**+**7**→**8**).[4a] While cross-coupling of an alkyl substituted allene bearing a tethered benzyl ether (R^1=$(CH_2)_2OBn$) with a symmetrical alkyne (R^2 and R^3=Bu) provides 1,4-dienes with a slight preference for the formation of the *E*-disubstituted olefin (*E*:*Z*=64:36), selectivity is a complex function of the nature of the alkyne. For example, coupling of the same allene with a TMS substituted alkyne provides 1,4-diene products with a modest preference for the formation of the *Z*-olefin-containing 1,4-diene (*E*:*Z*=25:75).

Major challenges that exist in the development of a general allene–alkyne cross-coupling reaction include the following:

(1) control in the functionalization of di- and trisubstituted allenes,
(2) regioselection (for the functionalization of each π-component: allene and alkyne), and
(3) stereoselection (in the formation of the substituted olefins resident in the products).

To address these issues, we initiated studies aimed at defining an alkoxide-directed allene–alkyne cross-coupling reaction.[5] As depicted in Scheme 3, it was anticipated that formation of a titanium complex of **7**, followed by exposure to a preformed allenic alkoxide (**9**) would afford a mixed titanate ester in a transient fashion. This reactive intermediate could then rearrange via directed carbometalation (**A**→**10**) or formal metallo-[3,3] rearrangment (**B**→**11**).[6] Here, we describe titanium-mediated cross-coupling reactions between allenes and alkynes that provide either 1,4-dienes (**10**) or cross-conjugated trienes (**11**) in a stereoselective fashion.



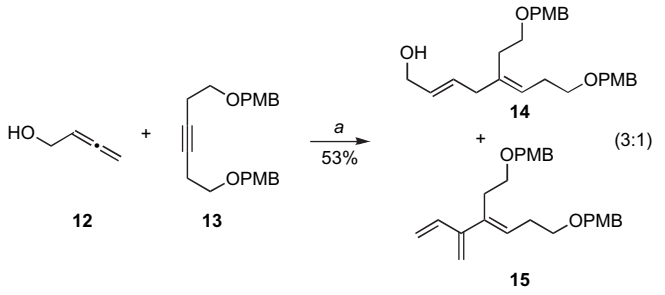
a = formation of a titanium–alkyne complex followed by introduction of the allenic alkoxide.
b = obtained after aqueous work up.

Scheme 3. A titanium-mediated, alkoxide-directed allene–alkyne cross-coupling reaction.

2. Results

2.1. Synthesis of stereodefined 1,4-dienes

Our studies began with examination of the cross-coupling reaction between 2,3-butadiene-1-ol **12** and the symmetrical alkyne **13**. As illustrated in Scheme 4, preformation of the metal–alkyne complex of **13**, followed by addition of the



a = alkyne (1.0 equiv), $ClTi(O\text{-}Pr)_3$ (2.0 equiv), $c\text{-}C_5H_9MgCl$ (4.0 equiv), PhMe (–78 to –30 °C), cool to –78 °C, then add lithium alkoxide of allene (0.7 equiv) (–78 to 0 °C).

Scheme 4. A stereodefined 1,4-diene and cross-conjugated triene from an alkoxide-directed allene–alkyne coupling.

lithium alkoxide of allene **12** and aqueous work-up provided a 3:1 mixture of coupled products in 53% yield. The major component of this mixture, identified as the stereodefined 1,4-diene **14**, was accompanied by a a small amount of a cross-conjugated triene (**15**). This initial result was viewed as quite promising, as no stereoisomeric 1,4-dienes were detected in the product mixture. Further, the stereoselection observed was consistent with a directed C–C bond forming process in preference to a non-directed process (the expected product from a non-directed cross-coupling is a 1,4-diene bearing a *Z*-allylic alcohol;[4a] not shown).

Cross-conjugated triene **15** was reasoned to be derived from a competition between the directed carbometalation pathway (**A**) and a formal metallo-[3,3] rearrangement process (**B**) (Scheme 3). In considering this competing pathway, it was

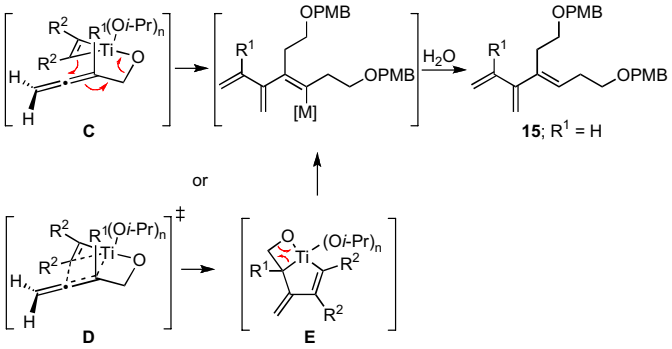
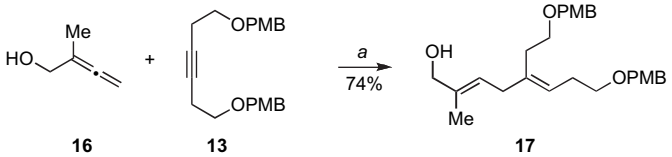


Figure 1. Possible origins of the cross-conjugated triene product **15**.



a = alkyne (1.4 equiv), $ClTi(O\textit{i}\text{-}Pr)_3$ (2.1 equiv), *c*-C_5H_9MgCl (4.3 equiv), PhMe (–78 to –30 °C), cool to –78 °C, then add lithium alkoxide of allene (1 equiv) (–78 to 0 °C).

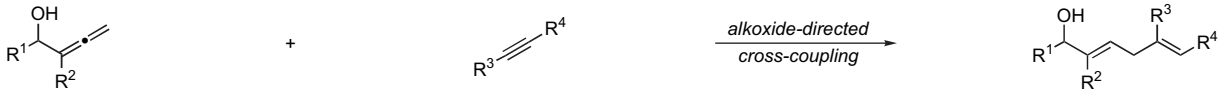
Scheme 5. Cross-coupling of 1,1-disubstituted allenes with internal alkynes proceeds with high levels of site-selectivity.

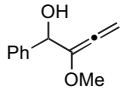
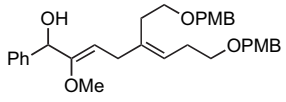
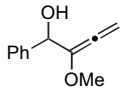
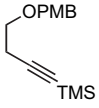
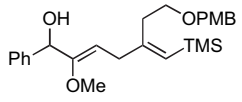
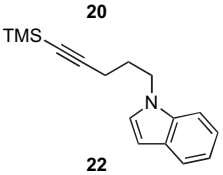
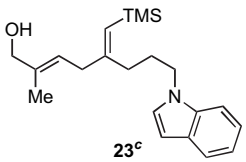
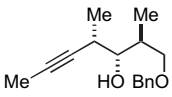
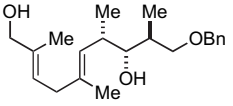
reasoned that the mechanism of the reaction could derive from a pathway whereby C–C bond formation occurs in concert with C–O bond breaking (**C**; Fig. 1),[7] or by a pathway where directed carbometalation provides an intermediate bicyclo[3.2.0] metallacyclopentane, which then undergoes *syn* elimination (**D**→**E**→**15**).

If production of the cross-conjugated triene proceeded by a pathway that involved full, or partial, C–Ti bond formation in the transition state (i.e., **D**), then allene substitution proximal to the alkoxide (R^1=alkyl) was anticipated to greatly impact the viability of this pathway. With R^1=alkyl, progression through **D** would require formation of a tertiary metal–carbon bond, a fact which was anticipated to greatly disfavor this pathway, and hence formation of a cross-conjugated triene. Alternatively, the reaction pathway for production of 1,4-dienes was not anticipated to be adversely affected by such substitution (see **A**; Scheme 3). In accord with these expectations, cross-coupling of 2-methyl-2,3-butadiene-1-ol **16** with alkyne **13** proceeds with good efficiency, and high selectivity for the formation of the *E*,*E*-1,4-diene **17** (Scheme 5). In this reaction, no evidence was found for the production of a cross-conjugated triene, or a stereoisomeric coupling product.

Table 1 illustrates that the 1,4-diene-selective cross-coupling of 1,1-disubstituted allenes with internal alkynes can be accomplished with a variety of functionalized substrates. For example, coupling of the methoxy-substituted allene **18** with symmetrical alkyne **13** affords the stereodefined enol ether-containing 1,4-diene **19** in 87% yield with ≥20:1 selectivity for the establishment of each stereodefined olefin (entry

Table 1



Entry[a]	Allene	Alkyne	Yield (%)	*E*:*Z*[b]	1,4-Diene
1	 **18**	**13**	87	≥1:20	 **19**
2	 **18**	 **20**	66	≥1:20	 **21**[c]
3	 **16**	 **22**	48	≥1:20	 **23**[c]
4	 **16**	 **24**	62	≥20:1	 **25**[d]

[a] Typical reaction conditions: alkyne (1.4 equiv), $ClTi(O\textit{i}\text{-}Pr)_3$ (2.1 equiv), *c*-C_5H_9MgCl (4.2 equiv), PhMe (−78 to −30 °C), cool to −78 °C, then add allenyl alkoxide (1 equiv) (−78 to 0 °C).

[b] Selectivity refers to the olefin formed from the allene coupling partner.

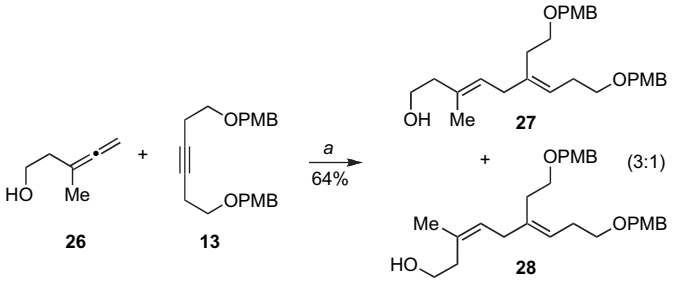
[c] rs=4:1.

[d] rr=2:1.

1). In a more complex example, allene **18** can be coupled to the unsymmetrical alkyne **20** in a site- and stereoselective manner. In this case, the 1,4-diene **21**, containing both a stereodefined enol ether and vinylsilane, is produced in 66% yield (entry 2). Although no evidence was found for the production of a stereoisomeric diene or cross-conjugated triene in this reaction, a minor isomer derived from regioisomeric functionalization of the TMS-alkyne was observed (rs=4:1). This observation speaks to the complexity of the present cross-coupling reaction, where site- and stereoselective functionalization of each unsymmetric π-system is accomplished simultaneously.

As depicted in entry 3, the heterocycle-containing TMS-alkyne **22** is also a suitable substrate for this cross-coupling process. Reaction with allene **16** provides the 1,4-diene product **23** as a single isomer (48% isolated yield). As observed previously, a minor isomer derived from regioisomeric functionalization of the unsymmetrical alkyne was generated (rs=4:1). Finally, cross-coupling of allene **16** with the unsymmetrically substituted internal alkyne **24** provides 1,4-diene **25** in 62% yield (entry 4). This example demonstrates that site- and stereoselective C–C bond formation proceeds with free hydroxyl functionality tethered to each reacting π-system.

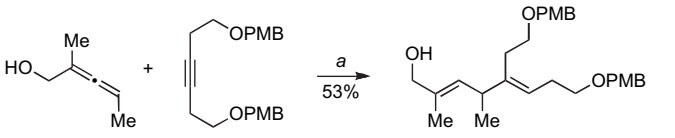
While allenic alkoxides uniformly provide 1,4-diene products with high levels of stereoselection in coupling reactions with internal alkynes (regio- and diastereoselection is ≥20:1), the homoallenic alkoxide derived from **26** does not provide high levels of stereoselection in cross-coupling reactions with alkyne **13** (Scheme 6). Whereas the 1,4-diene **27** is the major product in this coupling reaction, the isomeric diene **28** is formed as a minor product (**27**:**28**=3:1). This erosion in selectivity, from allenic alcohol to homoallenic alcohol, is presumed to derive from a competition between directed and non-directed C–C bond forming processes (Fig. 2).



a = alkyne (1.4 equiv), ClTi(O*i*-Pr)$_3$ (2.1 equiv), *c*-C$_5$H$_9$MgCl (4.2 equiv), PhMe (–78 to –30 °C), cool to –78 °C, then add lithium alkoxide of allene (1 equiv) (–78 to 0 °C).

Scheme 6. Cross-coupling of homoallenic alcohols with alkynes leads to diminished stereoselection.

Trisubstituted allenes are also useful substrates in this stereoselective cross-coupling reaction. As depicted in Scheme 7, coupling of allene (±)-**29** with the symmetrical alkyne **13** provides the highly substituted, stereodefined *E*,*E*-1,4-diene **30** in 53% yield. While the yield of the substituted diene is sufficient to render this reaction useful for the synthesis of highly substituted 1,4-dienes, unlike previously described cross-couplings, this reaction produces a significant amount of cross-conjugated triene (31%).



a = alkyne (1.4 equiv), ClTi(O*i*-Pr)$_3$ (2.1 equiv), *c*-C$_5$H$_9$MgCl (4.2 equiv), PhMe (–78 to –30 °C), cool to –78 °C, then add lithium alkoxide of allene (1 equiv) (–78 to 0 °C).

Scheme 7. Cross-coupling of trisubstituted allenes with internal alkynes.

2.2. Convergent synthesis of stereodefined poly-substituted cross-conjugated trienes

2.2.1. Background to the utility of cross-conjugated trienes in complex molecule synthesis

Cross-conjugated trienes are a functional group with great potential in complex molecule synthesis.[8] Since Blomquist and Verdol's synthesis of 2-vinyl-1,3-butadiene (**32**), and subsequent demonstration of its diene-transmissive Diels–Alder reaction with maleic anhydride,[9] many have explored the potential of cross-conjugated trienes in carbocycle and heterocycle construction (Scheme 8).[4h,10]

Despite great interest in the use of this reactive structural motif, barriers still exist in the preparation of highly substituted and stereodefined cross-conjugated trienes. Whereas cyclic cross-conjugated trienes are accessible via

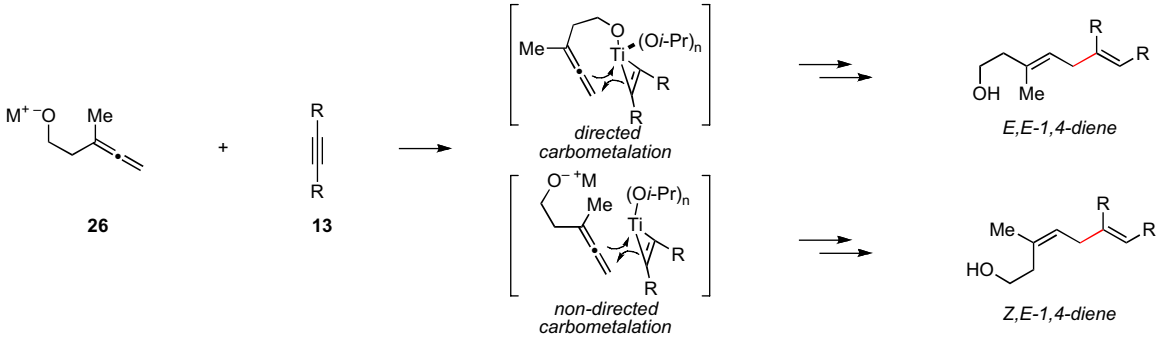
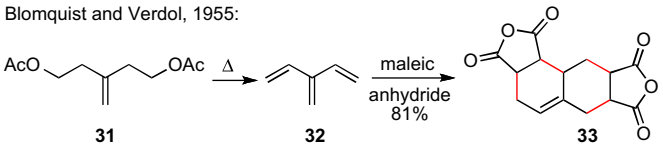


Figure 2. Competition between directed and non-directed carbometalation.



Scheme 8. Synthesis of 2-vinyl-1,3-butadiene and its diene-transmissive Diels–Alder reaction with maleic anhydride.

metal-mediated cycloisomerization processes,[11] the synthesis of acyclic cross-conjugated trienes is limited to the preparation of a small subset of sparsely substituted trienes.[9,12] In such processes, issues concerning stereoselection in the generation of the substituted olefins of the cross-conjugated triene are pronounced.

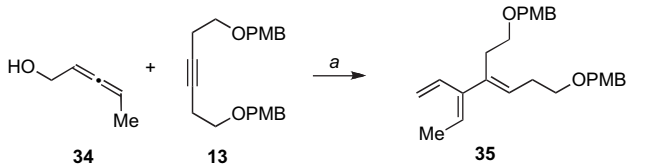
Based on the potential utility of substituted cross-conjugated trienes in complex molecule synthesis, and the lack of general convergent pathways for their synthesis, we focused our attention on optimizing the allene–alkyne cross-coupling reaction for the synthesis of stereodefined cross-conjugated trienes.

2.2.2. Synthesis of cross-conjugated trienes

The decreased regioselection observed in cross-coupling of trisubstituted allene **29** with alkyne **13** could be derived from a destabilization of the transition state for directed carbometalation in pathway **F** (Fig. 3). This destabilization would likely be based on the required build-up of non-bonded 1,2-steric interactions in the development of the intermediate bicyclo[3.3.0] metallacycle. Cross-coupling by C–C bond formation at the central carbon of the allene would avoid these destabilizing interactions, yet would require the formation (partial or full, depending on the mechanism) of a tertiary metal–carbon bond (**G**). Following this analysis, we reasoned that the reaction pathway for cross-coupling of allenes with alkynes could be diverted from the production of 1,4-dienes to stereodefined cross-conjugated trienes if the requirement of generating a tertiary metal–carbon bond was removed, while retaining the substitution at the terminus of the allene.

In line with this expectation, we were pleased to find that coupling of (±)-2,3-pentadiene-1-ol **34** with alkyne **13** affords the stereodefined cross-conjugated triene **35** (41% post HPLC; Scheme 9). Although this unoptimized coupling reaction did not proceed with high efficiency, no evidence was found for the production of a 1,4-diene.

A variety of substituted allenes and alkynes can be employed in this site- and stereoselective cross-conjugated triene synthesis. As depicted in entry 1 of Table 2, coupling of the



a = alkyne (1.4 equiv), $Ti(O\textit{i}\text{-}Pr)_4$ (2.1 equiv), *c*-C_5H_9MgCl (4.2 equiv), PhMe (–78 to –30 °C), cool to –78 °C, then add lithium alkoxide of allene (1 equiv) (–78 to 0 °C).

Scheme 9. Coupling of (±)-2,3-pentadiene-1-ol **34** with alkyne **13**.

isopropyl-substituted allenic alcohol **36** with alkyne **13** provides the substituted triene **37** in 69% yield with ≥20:1 selectivity for the formation of each stereodefined trisubstituted olefin. Entry 2 demonstrates that this convergent coupling reaction can be employed to generate tetrasubstituted olefins. In this case, triene **39** can be prepared as a single isomer in 62% yield.

Aside from controlling olefin geometry and site-selectivity in allene-functionalization, one can also control site-selectivity in the functionalization of unsymmetrical alkynes. As illustrated in entry 3, the branched alkyne **40** can be selectively coupled to allene **36**. In this reaction, C–C bond formation occurs preferentially distal to the branched architecture of alkyne **40**, and affords cross-conjugated triene **41** in 57% yield (rs=3:1, *E*:*Z* ≥20:1). The stereochemistry of these products was assigned on the basis of spectroscopic data, as depicted for **37** (Fig. 4).

Similarly, entries 4–7 demonstrate that selective functionalization of silyl-substituted alkynes is possible.[8] In these cases, the cross-conjugated triene products **43**, **45**, **46** and **48** can be generated in >70% yield, with high levels of stereoselection (regioselection with respect to alkyne functionalization=4:1).

The stereoselectivity observed in these reactions is consistent with C–C bond formation occurring *anti* to the distal alkyl substituent of the allene via geometry **B** (Scheme 3). To further explore the validity of this model, the cross-coupling reaction of a diastereomerically pure chiral allene, bearing a secondary hydroxyl directing group, with a symmetrical alkyne was investigated (Scheme 10). Coupling of allene **49** with alkyne **13** provides triene **50** in 50% yield. The observed stereoselection is consistent with reaction by way of a boat-like geometry **H**,[3d] where C–C bond formation occurs *anti* to the terminal butyl substituent of the allene, with the allenic substituent (R^1) occupying an equatorial position.

The highly substituted cross-conjugated trienes produced from this cross-coupling reaction have great potential for

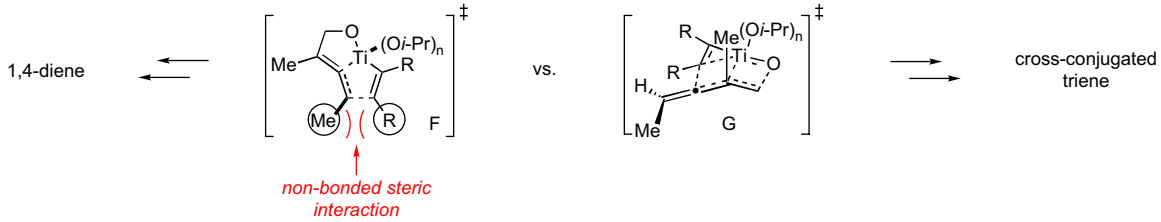
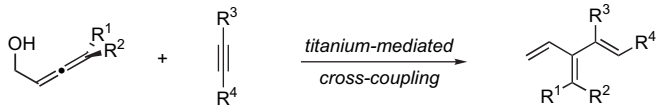
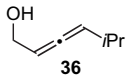
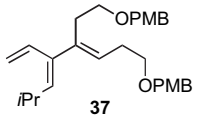
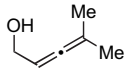
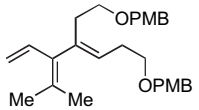
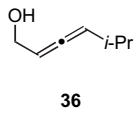
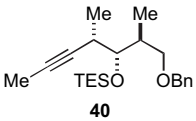
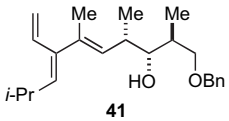
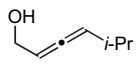
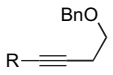
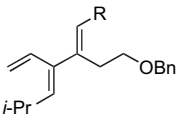
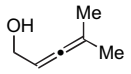
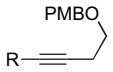
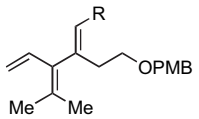


Figure 3. Competition between directed carbometalation and formal metallo-[3,3] rearrangement with trisubstituted allenes.

Table 2



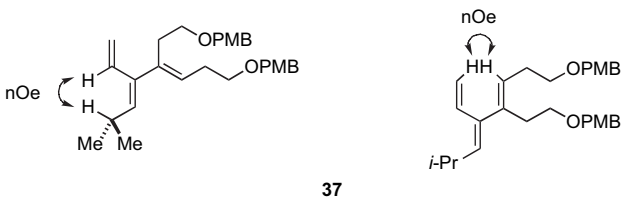
Entry[a]	Allene	Alkyne	Yield (%)	*E*:*Z*[b]	rs[c]	Product
1	 **36**	**13**	69	≥20:1	—	 **37**
2	 **38**	**13**	62	—	—	 **39**
3	 **36**	 **40**	57[d]	≥20:1	3:1	 **41**
						
4	**36**	**42**; R=TMS	75	≥20:1	4:1	**43**; R=TMS
5		**44**; R=TIPS	82	≥20:1	4:1	**45**; R=TIPS
						
6	**38**	**20**; R=TMS	71	—	4:1	**46**; R=TMS
7		**47**; R=TIPS	74	—	4:1	**48**; R=TIPS

[a] Typical reaction conditions: alkyne (1.4 equiv), ClTi(O*i*-Pr)$_3$ or Ti(O*i*-Pr)$_4$ (2.1 equiv), *c*-C_5H_9MgCl (4.2 equiv), PhMe (−78 to −30 °C), cool to −78 °C, then add allenyl alkoxide (1 equiv) (−78 to 0 °C).

[b] Refers to the establishment of the substituted olefin derived from the allene (the other stereodefined olefin, derived from the alkyne is formed as a single isomer).

[c] Refers to the site of alkyne functionalization.

[d] Yield after deprotection with TBAF (see supplementary data for details).



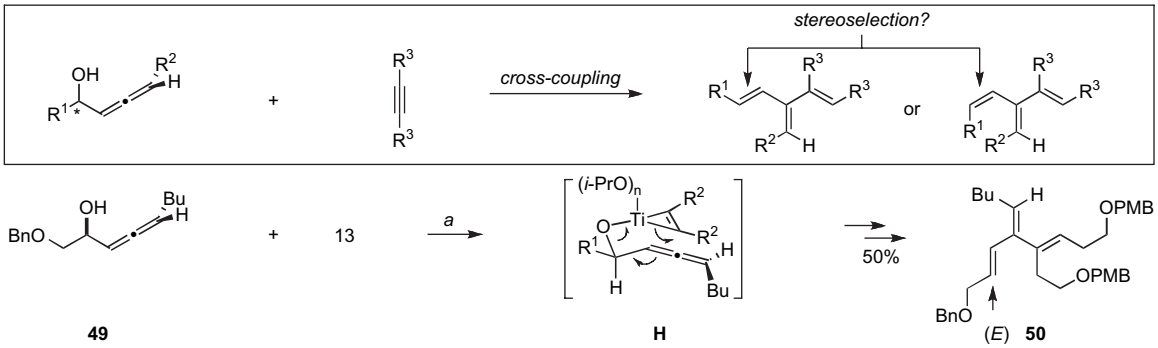
37

Figure 4. Stereochemical assignment of the cross-conjugated triene products was accomplished by analysis of NOE data as depicted for **37**.

facilitating the syntheses of complex carbocyclic and heterocyclic ring systems via site- and stereoselective cycloaddition processes. Whereas the reactivity of less-substituted acyclic cross-conjugated trienes is difficult to control in bimolecular [4+2] cycloadditions, as multiple cycloadditions often predominate,[4h,9,10,12] the substituted trienes generated here cleanly undergo mono-cycloaddition with activated dienophiles. For example, heating a toluene solution of **37** with maleimide **51** provides the cycloadduct **52** in 50% yield (*endo*:*exo*=6:1; Scheme 11). This reactivity pattern is consistent with the decreased reactivity of (*Z*)-dienes in Diels–Alder reactions.[13]

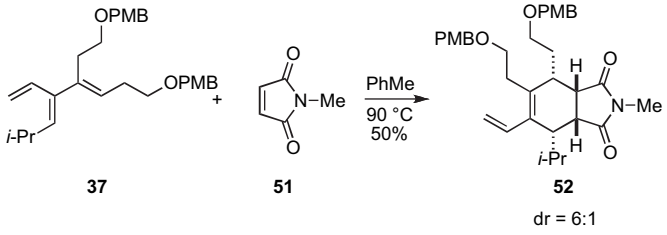
3. Conclusion

The cross-coupling of allenic alcohols with alkynes can be accomplished in a highly regio- and stereoselective manner. Applying an alkoxide-directed coupling reaction, tetrasubstituted 1,4-dienes are prepared by titanium-mediated coupling of 1,1-disubstituted allenes with internal alkynes. In these cases, stereoselection is consistent with the proposition that these processes proceed through the formation of bicyclo[3.3.0] metallacyclopentenes, protonation of which affords 1,4-dienes **55** (Scheme 12). Alternatively, alkoxide-directed cross-coupling of 1,3-disubstituted allenes with internal alkynes provides a general strategy for the synthesis of

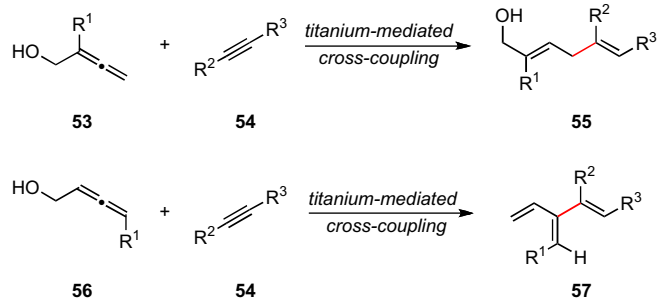


a = alkyne **9** (1.4 equiv), $Ti(O\textit{i}\text{-}Pr)_4$ (2.1 equiv), *c*-C_5H_9MgCl (4.3 equiv), PhMe (–78 to –30 °C), cool to –78 °C, then add allenyl alkoxide (1 equiv) –78 °C to 0 °C.

Scheme 10. Allene–alkyne coupling for the synthesis of stereodefined tetrasubstituted cross-conjugated trienes.



Scheme 11. Thermal intermolecular site- and stereoselective Diels–Alder reaction of a trisubstituted cross-conjugated triene and an activated dienophile.



Scheme 12. Allene–alkyne cross-coupling for the synthesis of 1,4-dienes or cross-conjugated trienes.

substituted cross-conjugated trienes **57**. These stereodefined substituted cross-conjugated trienes are useful intermediates in the synthesis of complex polycyclic systems, as they undergo site- and stereoselective mono [4+2] cycloaddition with activated dienophiles. Overall, these highly site-selective cross-coupling reactions provide stereoselective convergent access to structural motifs that are anticipated to be of great utility in the synthesis of complex molecules. Research directed at exploring these processes, both mechanistically and in the context of target-oriented synthesis, is underway.

4. Experimental section

4.1. General experimental information

All reactions were conducted in flame-dried glassware under nitrogen using anhydrous solvents. Toluene and tetrahydrofuran were distilled from sodium/benzophenone ketyl before use. Diethyl ether was used after passing through an activated alumina column. Titanium(IV) isopropoxide was used after distillation of the commercially available reagent. $ClTi(O\textit{i}\text{-}Pr)_3$ was purchased as a 1 M solution in hexanes from Aldrich and was used without further analysis or purification. All other commercially available reagents were used as received.

4.2. Representative procedure for the stereoselective synthesis of 1,4-dienes

4.2.1. Synthesis of (2E,5Z)-8-(4-methoxybenzyloxy)-5-(2-(4-methoxybenzyloxy)ethyl)-2-methylocta-2,5-dien-1-ol, ***17***

To a −78 °C solution of alkyne **13** (200 mg, 0.56 mmol) in 3.7 mL of PhMe were added 850 μL of $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in hexanes, 0.85 mmol) and 860 μL of *c*-C_5H_9MgCl (1.96 M in Et_2O, 1.69 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned dark reddish brown while warming slowly to −30 °C over 1 h. The reaction mixture was stirred at −30 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **16** (69 mg, 0.39 mmol) in 1.0 mL PhMe was added 160 μL of *n*BuLi (2.45 M in hexanes, 0.39 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath, and added to the −78 °C titanium solution dropwise via cannula. After warming slowly to 0 °C over 2 h, the reaction was quenched with 5 mL of satd NH_4Cl solution. The mixture was warmed to room temperature before extracting with EtOAc (3×15 mL). The combined organic layer was washed with satd $NaHCO_3$ solution (1×30 mL), brine (1×30 mL) and dried over anhydrous Na_2SO_4. Flash column chromatography of the crude material (20% EtOAc/hexanes, then 50% EtOAc/hexanes) provided 127 mg (74%) of diene **17** as a clear, colorless oil. A small portion was further purified by HPLC [EtOAc/hexanes: gradient from 35% to 55% (0–20 min, 25 mL/min) on a Microsorb (Si 80-120-C5 H410119) column] to obtain a sample for analytical characterization. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.23 (m, 4H), 6.89–6.85 (m, 4H), 5.42–5.37 (m, 1H), 5.24 (t, J=7.1 Hz, 1H), 4.42 (s, 2H), 4.41 (s, 2H), 4.00 (d, J=5.8 Hz, 2H), 3.80 (s, 3H), 3.80 (s, 3H), 3.46–3.39 (m,

4H), 2.75 (d, J=7.3 Hz, 2H), 2.34 (dt, J=14.7, 7.6 Hz, 2H), 2.33 (t, J=7.3 Hz, 2H), 1.64 (s, 3H), 1.34 (t, J=6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 136.6, 136.0, 130.6, 130.5, 129.21, 129.16, 123.8, 123.1, 113.7, 77.2, 72.5, 69.8, 68.8, 68.6, 55.2, 35.7, 31.1, 28.6, 13.6; IR (thin film, NaCl) 3433, 2907, 2857, 1613, 1513, 1464, 1360, 1302, 1173, 1093, 1035, 802 cm^{-1}; LRMS (EI, Na) calcd for $C_{27}H_{36}O_5Na$, 463.26 *m/z* (M+Na); observed, 463.3 *m/z* (M+Na)$^+$.

4.3. Representative procedure for the stereoselective synthesis of cross-conjugated trienes

*4.3.1. Synthesis of (3E,5E)-1-(4-methoxybenzyloxy)-(4-(2-methoxybenzyloxy)ethyl)-5-vinyl-7-methyl-3,5-octadiene, **37***

To a −78 °C solution of alkyne **13** (200 mg, 0.56 mmol) in 3.7 mL of PhMe was added 850 μL of $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in hexanes, 0.85 mmol) and 860 μL of *c*-C_5H_9MgCl (1.96 M in Et_2O, 1.68 mmol) dropwise via a gas-tight syringe. The resulting clear, yellow solution turned dark reddish brown while warming slowly to −30 °C over 1 h. The reaction mixture was stirred at −30 °C for 1 h and then cooled to −78 °C. To a separate −78 °C solution of allene **36** (44 mg, 0.39 mmol) in 1.0 mL PhMe was added 160 μL of *n*BuLi (2.45 M in hexanes, 0.39 mmol) dropwise via gas-tight syringe. The resulting solution was stirred for 15 min, removed from the cold bath, and added to the −78 °C titanium solution dropwise via cannula. After warming slowly to −30 °C over 1 h, the reaction was quenched with 5 mL of satd NH_4Cl solution. The mixture was warmed to room temperature before extracting with EtOAc (3×15 mL). The combined organic layer was washed with satd $NaHCO_3$ solution (1×30 mL), brine (1×30 mL) and dried over anhydrous Na_2SO_4. Flash column chromatography of the crude material (5% EtOAc/hexanes, then 7.5% EtOAc/hexanes) provided 121 mg (69%) of triene **37** as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.21 (m, 4H), 6.88–6.83 (m, 4H), 6.53 (dd, J=17.4, 10.6 Hz, 1H), 5.36 (t, J=7.3 Hz, 1H), 5.15 (d, J=10.1 Hz, 1H), 5.13–5.06 (m, 2H), 4.42 (s, 2H), 4.37 (s, 2H), 3.78 (s, 3H), 3.78 (s, 3H), 3.46 (t, J=7.1 Hz, 2H), 3.36 (t, J=7.3 Hz, 2H), 2.74–2.65 (m, 1H), 2.51 (t, J=7.6 Hz, 2H), 2.42 (dt, J=14.1, 7.3 Hz, 2H), 0.95 (d, J=6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 159.0, 138.7, 138.5, 138.1, 132.6, 130.7, 130.6, 129.2, 129.1, 126.6, 116.4, 113.69, 113.65, 72.44, 72.39, 69.7, 68.7, 55.21, 55.20, 30.2, 28.8, 26.9, 23.1; IR (thin film, NaCl) 2957, 2864, 1613, 1513, 1464, 1360, 1302, 1248, 1173, 1097, 1037, 820 cm^{-1}; LRMS (EI, Na) calcd for $C_{29}H_{38}O_4Na$, 473.28 *m/z* (M+Na); observed, 473.5 *m/z* (M+Na)$^+$.

Acknowledgements

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Supplementary data

Complete experimental details for all preparative procedures along with spectral data for all products are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.015.

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