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Synthesis of Substituted 1,4-Dienes by Direct Alkylation of Allylic Alcohols

Filip Kolundzic and **Glenn C. Micalizio**[*]
Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107

Convergent C–C bond formation is a central theme in modern synthetic organic chemistry. Among the many strategies to accomplish this type of bond construction, allylic alkylation represents an emerging and powerful reaction class. Generally, the chemistry of allyl electrophiles dominates this area, and major challenges within the field reside in the control of regio- and stereoselection in the bimolecular C–C bond forming event (i.e. **1** → **2**–**5**; Figure 1).[1] Here, we describe a metal-mediated alkylation of unactivated allylic alcohols with internal alkynes[2] that proceeds with net allylic transposition and delivers stereodefined 1,4-dienes in a regioselective manner.[3]

Treatment of substituted allylic alkoxides with preformed titanium–*π* complexes, generated in situ from the corresponding alkyne and $Ti(Oi\text{-}Pr)_4$ or $ClTi(Oi\text{-}Pr)_3$,[4] results in efficient allylic alkylation (Table 1). As depicted in entries 1 and 2, cross-coupling of the cyclic allylic alcohol **6** or **9** with the symmetric alkyne **7** provides stereodefined 1,4-dienes **8** or **10** in 65 and 68% yields respectively. Entris 3–6 demonstrate that this convergent C–C bond forming reaction occurs with allylic transposition, providing the stereodefined 1,4-diene products **12**, **14**, **16** and **18** as single isomers.

In addition to being regioselective, this cross-coupling reaction proceeds with a high degree of stereochemical control. As depicted in entry 7, coupling of a stereodefined allylic alcohol **19** (er = 97:3) with alkyne **7** provides the functionalized 1,4-diene **20** with negligible erosion of stereochemistry (er = 96:4). The absolute stereochemistry of **20** was assigned based on the stereoselection observed in the coupling of **21** with alkyne **7** (entry 8). This process provides the *trans*-trisubstituted cyclohexene **22** in 50% yield (dr ≥20:1), demonstrating that C–C bond formation occurs in a suprafacial manner across the allyl system.

Whereas simple primay allylic alcohols can be employed in coupling reactions with internal alkynes (Table 2, entry 1), increased efficiency is observed with more substituted coupling partners (entry 2). Tertiary acyclic allylic alcohols are also effective in this reaction, and provide highly substituted 1,4-dienes when coupled with internal alkynes. For example, coupling of 2-methyl-3-buten-2-ol (**27**) with alkyne **7** furnishes the prenylated product **28** in 53% yield (entry 3). Similarly, both (*E*)- and (*Z*)-2-methyl-3-penten-2-ol (**29** and **31**) can be coupled to an internal alkyne to furnish a 3-alkyl-1,4-diene-containing product (**30**) (entries 4 and 5). As depicted in entry 6, even tetrasubstituted olefins can be preparred with this cross coupling reaction.

Coupling of acyclic secondary allylic alcohols with internal alkynes is also possible, yet these processes are more complex due to the generation of an additional stereodefined double bond. Whereas secondary allylic alcohols containing mono-substituted olefins (**34** and **36**) can be coupled to internal alkynes in an efficient manner, these processes proceed without

E-mail: glenn.micalizio@yale.edu.

stereoselection (*E*/*Z* ca. 1:1) (entries 7 and 8). In contrast, secondary allylic alcohols bearing 1,1-disubstituted olefins can be coupled with internal alkynes in a highly stereoselective manner. In these cases, 1,4-dienes bearing a stereodefined (*Z*)-trisubstituted olefin are produced with high selectivity (entries 9 and 10).

As depicted in entry 11, this stereoselective cross-coupling reaction can be employed with unsymmetrical alkynes. In this case, cross coupling of allylic alcohol **38** with the TMS-substituted alkyne **42** provides the stereodefined 1,4-diene **43** in 59% yield. In accord with known preferences for titanium alkoxide-mediated functionalization of silyl-substituted alkynes, C–C bond formation occurs selectively at the site distal to the TMS-substituent of alkyne **42**.[5]

As depicted in entries 12 and 13, allylic alcohols bearing (*Z*)-disubstituted olefins provide 1,4-diene products with superior selectivity in comparison to the (*E*)-disubstituted olefin isomers. Whereas cross-coupling of (*E*)-**44** with alkyne **7** affords the 1,4-diene **45** as a 1:1 mixture of olefin isomers (entry 12), the corresponding cross-coupling of (*Z*)-**46** with **42** provides 1,4-diene **47** as an 8:1 mixture favoring the formation of a product containing an (*E*)-disubstituted olefin (entry 13).

Finally, this new C–C bond forming reaction is tolerant of neighboring π-unsaturation in the allylic alcohol coupling partner. As illustrated in entry 14, cross-coupling of allylic alcohol **48** with alkyne **7** provides the stereodefined triene **49** in 59% yield.

Overall, we have described a new stereoselective cross-coupling reaction between allylic alcohols and alkynes for the synthesis of 1,4-dienes. While occuring with allylic transposition, high stereoselectivity in the generation of substituted olefins is observed in coupling reactions with cyclic, as well as acyclic allylic alcohols. In general, the stereochemical results from this cross-coupling are consistent with an empirical model whereby C–C bond formation occurs through a boat-like geometry of a transient mixed titanate ester (i.e. **A** and **B**; Figure 2).[6] Further study of the mechanism and scope of this, and related coupling reactions is underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. For a review of nucleophilic addition reactions to allylic electrophiles, see: a)Magid RM. Tetrahedron 1980;36:1901–1930.1930 For a review cross-coupling reactions via π-allyl intermediates, see: b) Kazmaier U, Pohlman M. De Meijere A. Metal Catalyzed Cross-Coupling Reactions Wiley-VCHWeinheim2004:531–583.583 For a recent review of asymmetric allylic substitution catalyzed by copper complexes, see: c)Yorimitsu H, Oshima K. Angew Chem Int Ed 2005;44:4435–4439.4439 For recent examples, see: d)Zheng W, Zheng B, Zhang Y, Hou X. J Am Chem Soc 2007;129:7718–7719.7719 [PubMed: 17539637]e)Weix DJ, Hartwig JF. J Am Chem Soc 2007;129:7720–7721.7721 [PubMed: 17542586]
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Treptow B. J Am Chem Soc 1995;117:615–623.623d)Dérien S, Jan D, Dixneuf PH. Tetrahedron 1996;52:5511–5524.5524

3. For copper-mediated alkylation of allylic alcohols, see: a)Tanigawa Y, Ohta H, Sonoda A, Murahashi SI. J Am Chem Soc 1978;100:4610–4612.4612b)Yamamoto Y, Maruyama K. J Organomet Chem 1978;156:C9–C11.C11c)Goering HL, Kantner SS. J Org Chem 1981;46:2144–2148.2148
4. Harada K, Urabe H, Sato F. Tetrahedron Lett 1995;36:3203–3206.
5. Sato, F.; Urabe, H. Titanium and Zirconium in Organic Synthesis. Marek, I., editor. Wiley-VCH; Weinheim: 2002. p. 319-354.
6. The empirical model presented for understanding selectivity in these cross-coupling reactions invokes a formal metallo-[3,3]-rearrangement; we are aware that a plausible mechanistic proposal for these reactions can be based on directed formation of intermediate bicyclic metallacyclopentenes, followed by syn-elimination: a)Ryan J, Micalizio GC. J Am Chem Soc 2006;128:2764–2765.2765 [PubMed: 16506731]b)Reichard HA, Micalizio GC. Angew Chem Int Ed 2007;46:1440–1443.1443c) McLaughlin M, Takahashi M, Micalizio GC. Angew Chem Int Ed 2007;46:3912–3914.3914d) Takahashi M, Micalizio GC. J Am Chem Soc 2007;129:7514–7516.7516 An analysis of these mechanistic hypotheses is the subject of ongoing studies in our laboratory. [PubMed: 17530760]

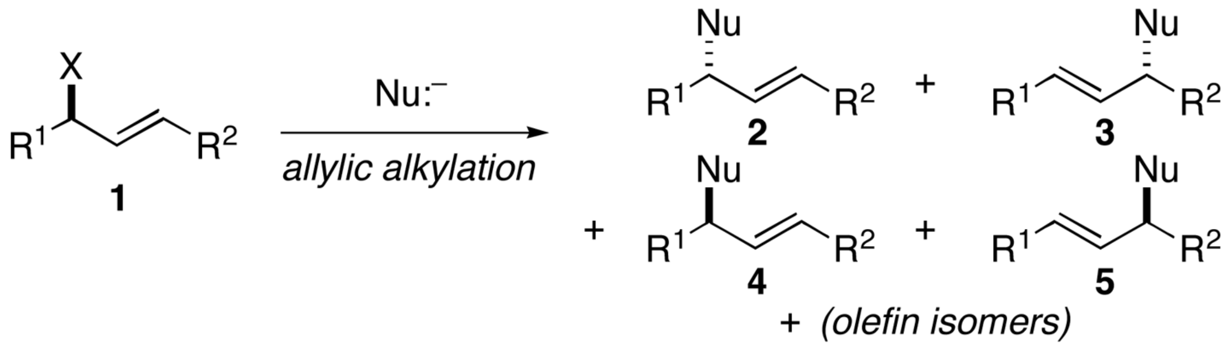


Figure 1.
Issues of selectivity in modern allylic alkylation.

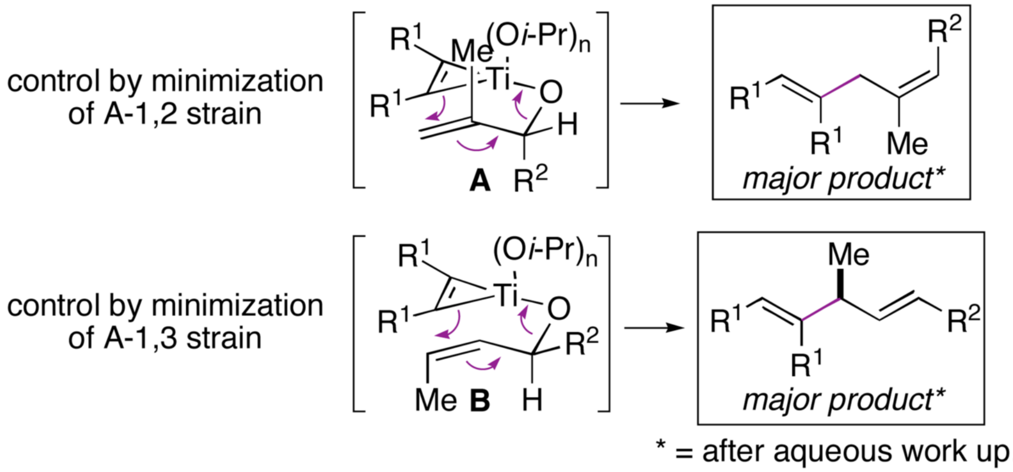
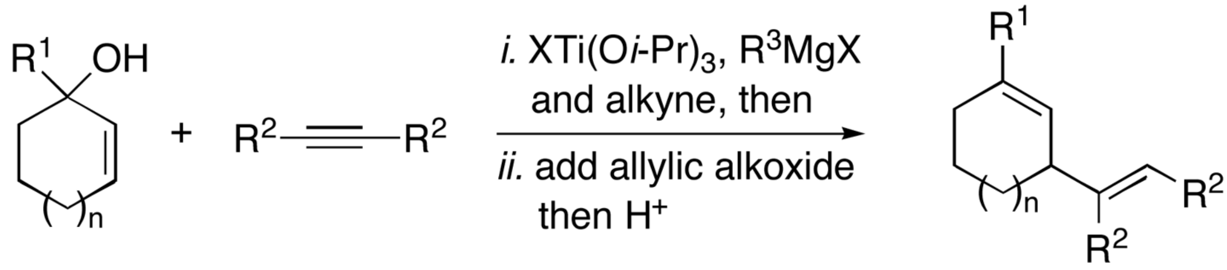
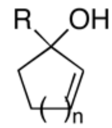


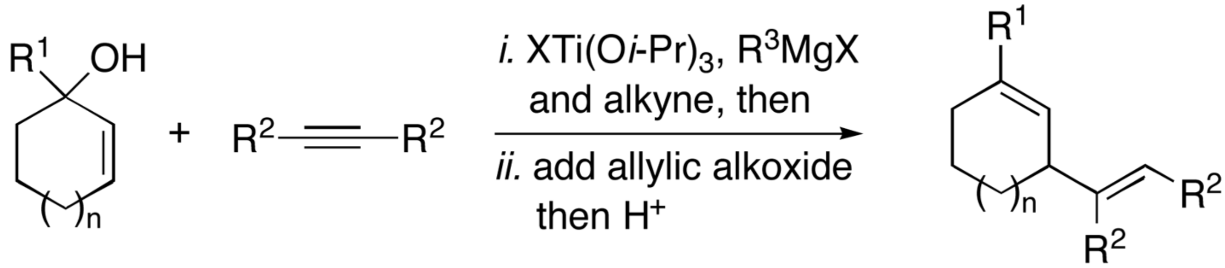
Figure 2.

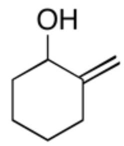
Empirical model for this direct allylic alkylation reaction.

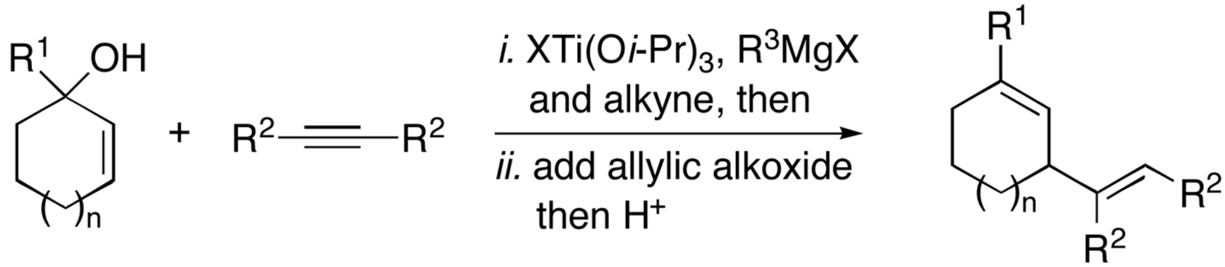
Table 1

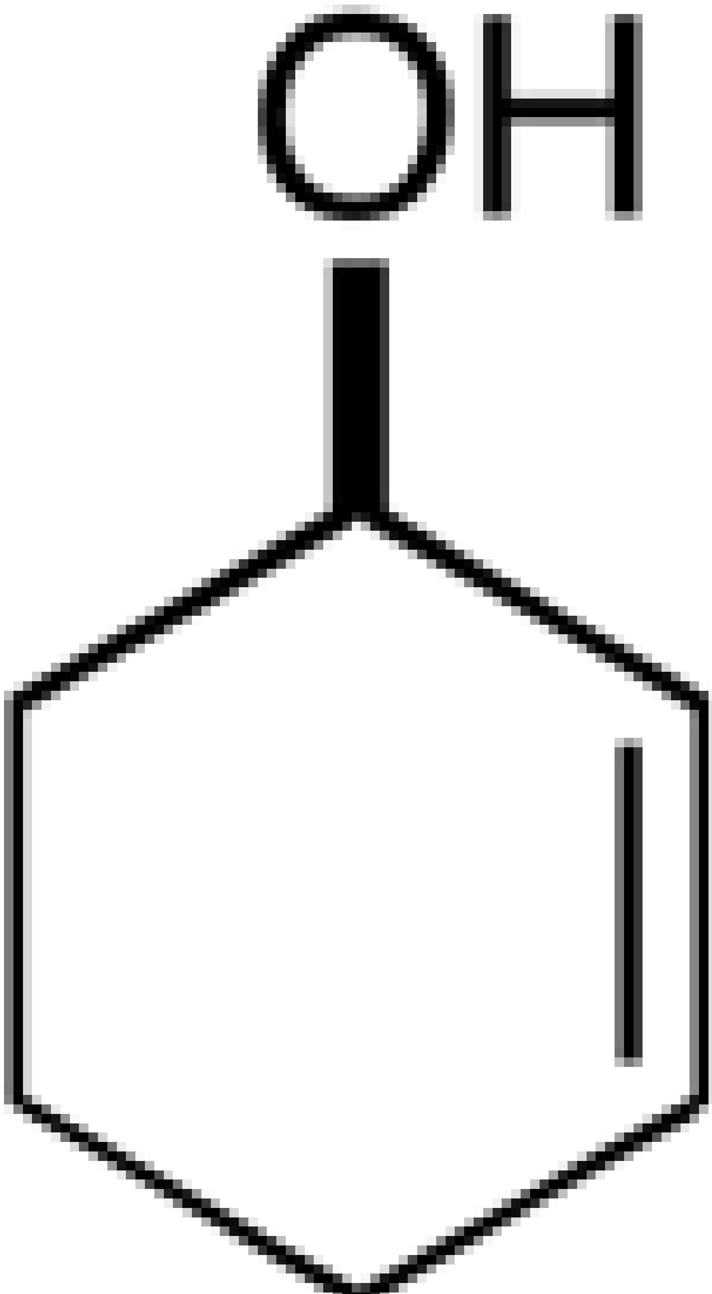


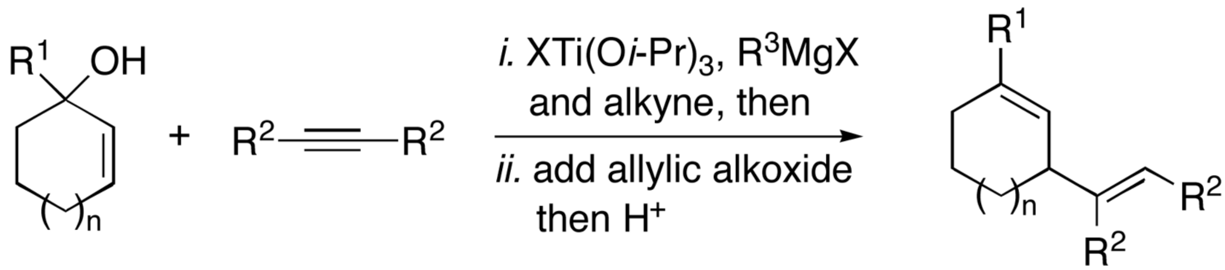
entry	allylic alcohol
1	 **6**; R = H, n=1

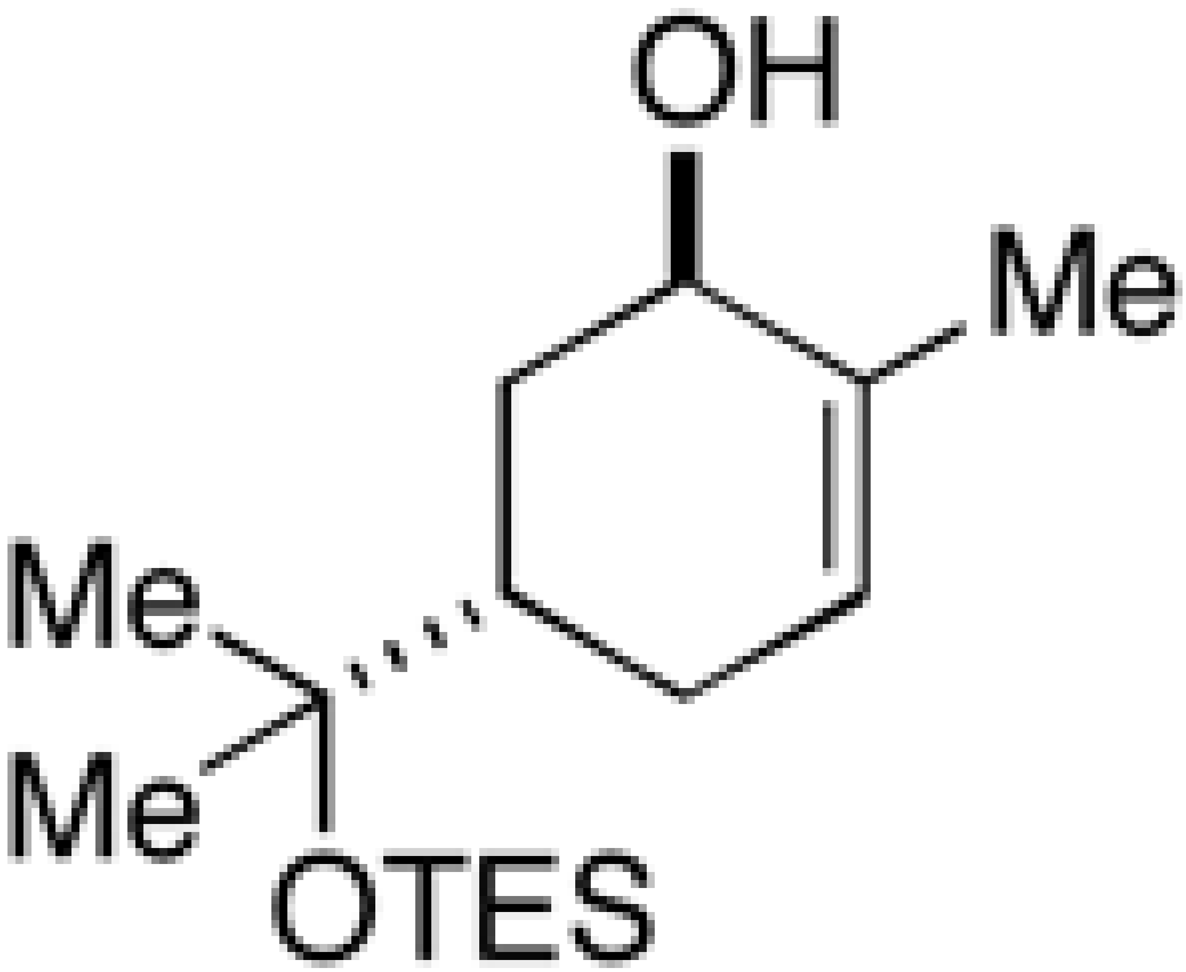


entry	allylic alcohol
2	**9**; R = H, n=2
3	**11**; R = Me, n=1
4	**13**; R = Ph, n=1
5	**15**; R = *c*-C_5H_9, n=1
6	 **17**



entry	allylic alcohol
7[b]	 **19**(er = 97:3)



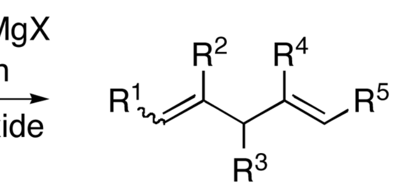
entry	allylic alcohol
8	 **21**

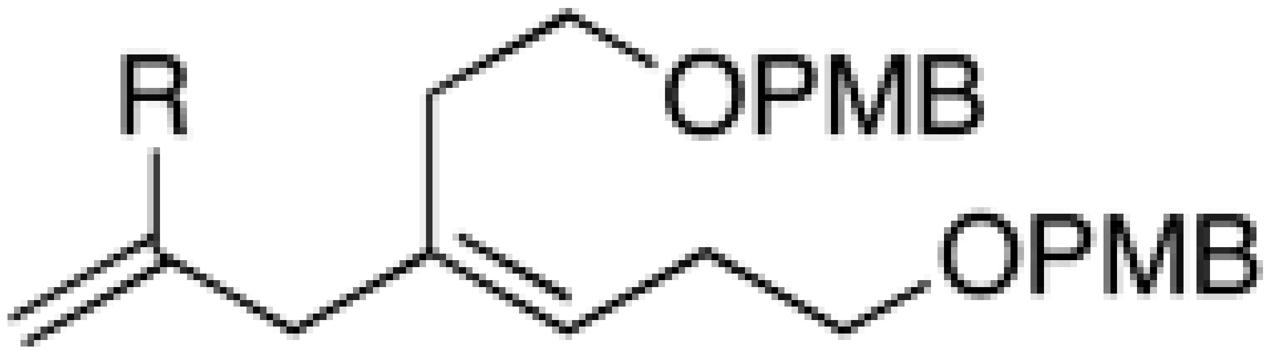
[a]Reaction conditions for cross coupling: alkyne (1.0 eq), ClTi(O*i*-Pr)$_3$, PhMe, C_5H_9MgCl, −78 to −35 °C, then recool to −78 °C, add Li-alkoxide of allylic alcohol (1.0 eq) (−78 to 0 °C).

[b]ClTi(O*i*-Pr)$_3$ was replaced with Ti(O*i*-Pr)$_4$ in this experiment.

[c]Absolute stereochemistry not determined.

Table 2

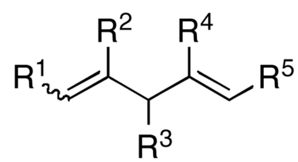


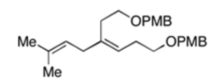
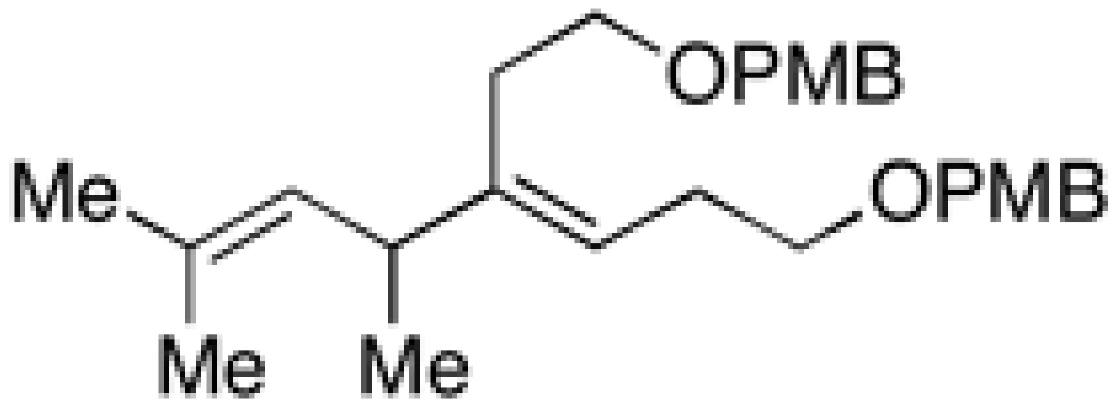
1,4-diene[a, b, c]	E:Z	yield (%)
		

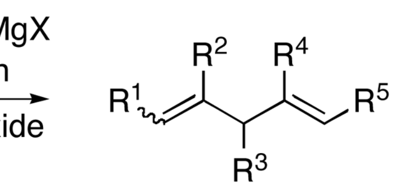
MgX

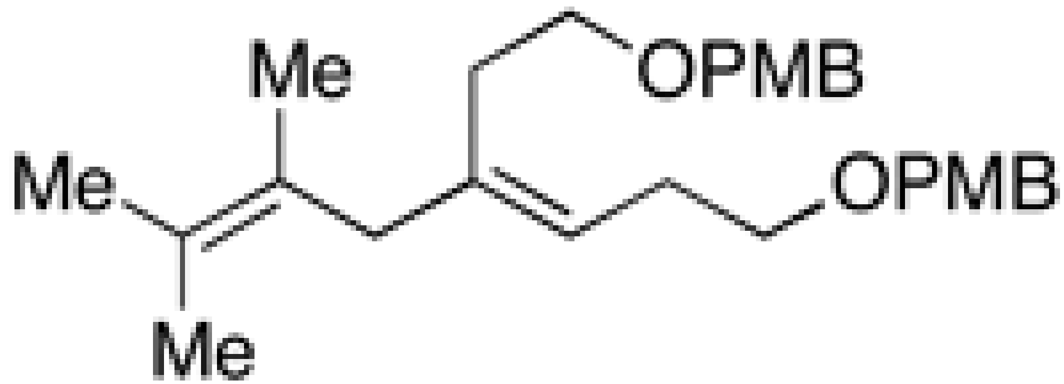
n

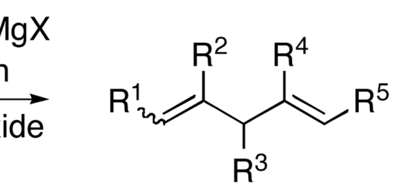
ide

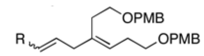


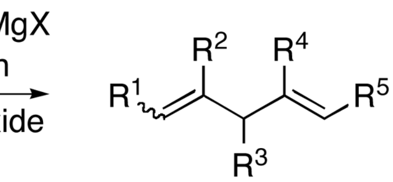
yield (%)	E:Z	1,4-diene[a, b, c]
41	—	**24**; R = H
66	—	**26**; R = Me
53	—	 **28**
59	—	 **30**
67	—	

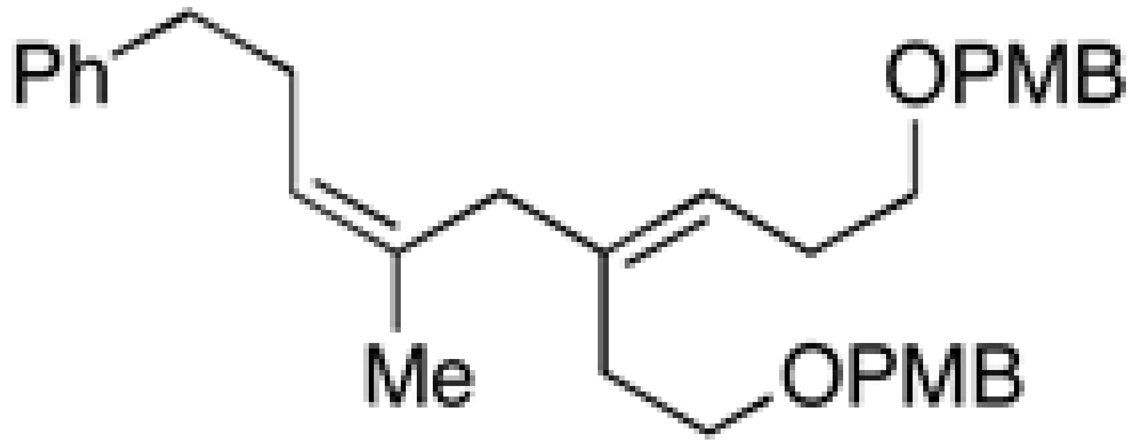


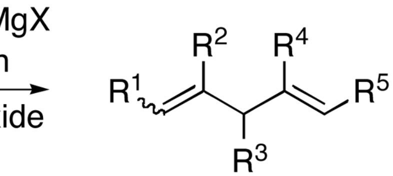
yield (%)	E:Z	1,4-diene[a, b, c]
57	—	 **33**

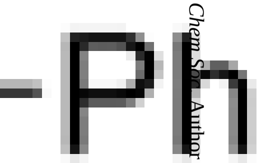
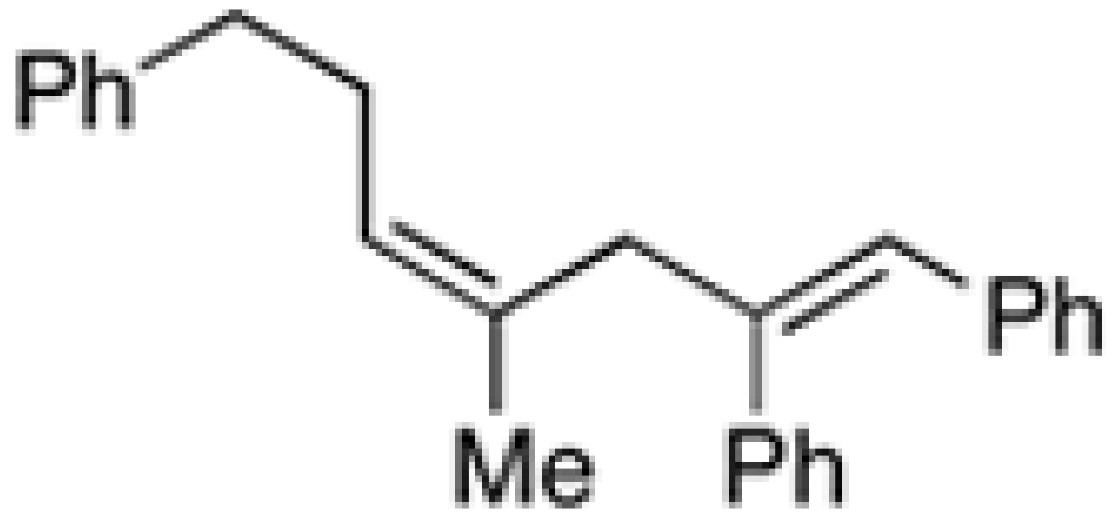


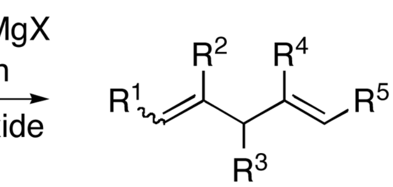
yield (%)	E:Z	1,4-diene[a, b, c]
		
78	1:1	**35**; R=Ph (E/Z=1:1)
67	1:1	**37**; R=Et (E/Z=1:1)

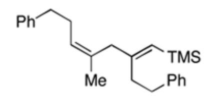


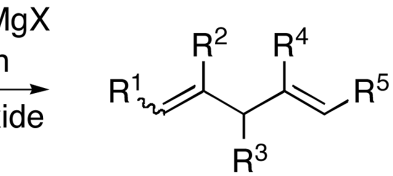
yield (%)	E:Z	1,4-diene[a, b, c]
72	≥20:1	 **39**

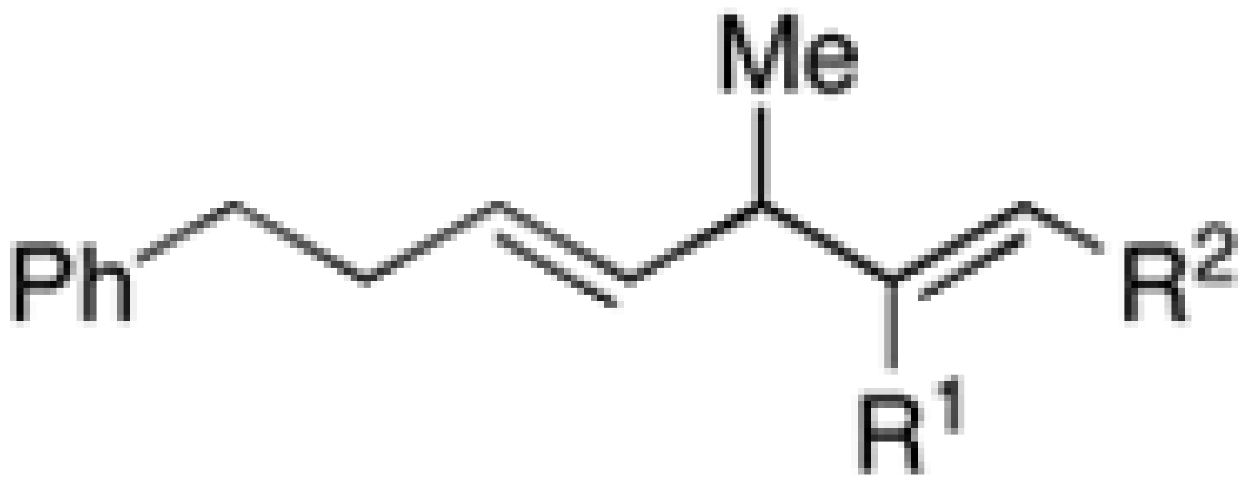


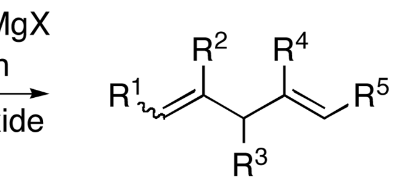
	yield (%)	E:Z	1,4-diene[a, b, c]
	77	≥20:1	 **41**[d]

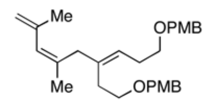


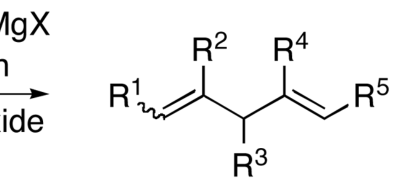
yield (%)	E:Z	1,4-diene[a, b, c]
59	≥20:1	 43[e]



yield (%)	E:Z	1,4-diene[a, b, c]
		
67	1:1	**45**; R^1, R^2=$(CH_2)_2$OPMB
59	8:1	**47**[e]; R^1=$(CH_2)_2$Ph, R^2=TMS



yield (%)	E:Z	1,4-diene[a, b, c]
59	≥20:1	 **49**



yield (%)	E:Z	1,4-diene[a, b, c]