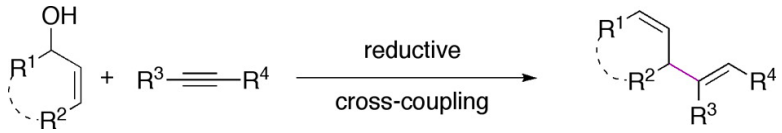
Communication

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

Filip Kolundzic, and Glenn C. Micalizio

J. Am. Chem. Soc., **2007**, 129 (49), 15112-15113 • DOI: 10.1021/ja075678u



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 11/16/2007

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

Received July 30, 2007; E-mail: glenn.micalizio@yale.edu

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(O*i*-Pr)$_4$ or ClTi(O*i*-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. Entries 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 on the basis of 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 monosubstituted olefins (**34** and **36**) can be coupled to internal alkynes in an efficient manner, these processes proceed without 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).

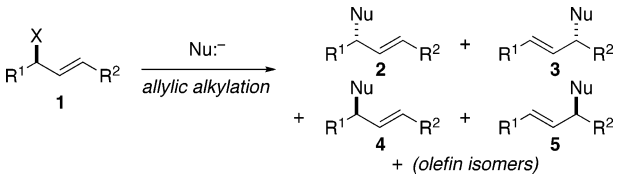
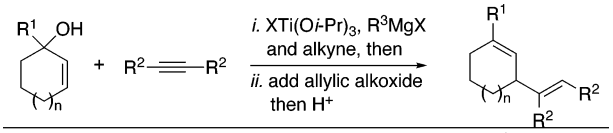


Figure 1. Issues of selectivity in modern allylic alkylation.

Table 1



entry	allylic alcohol	alkyne	yield (%)	1,4-diene[a]
1	**6**; R = H, n=1	**7**	65	**8**; n=1
2	**9**; R = H, n=2		68	**10**; n=2
3	**11**; R = Me, n=1		61	**12**; R = Me, n=1
4	**13**; R = Ph, n=1		79	**14**; R = Ph, n=1
5	**15**; R = *c*-C$_5$H$_9$, n=1		40	**16**; R = *c*-C$_5$H$_9$, n=1
6	**17**	**7**	57	**18**
7[b]	**19** (er = 97:3)	**7**	54	**20**[c] (er = 96:4)
8	**21**	**7**	50	**22** (dr ≥ 20:1)

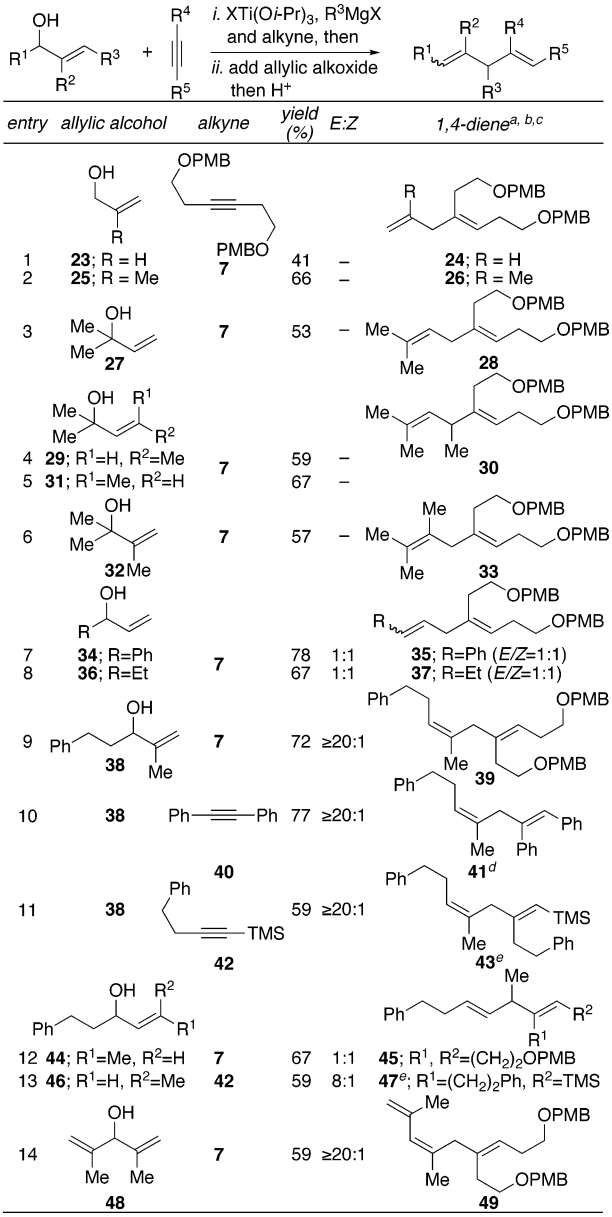
[a] Reaction conditions for cross coupling: alkyne (1.0 equiv), ClTi(O*i*-Pr)$_3$, PhMe, C$_5$H$_9$MgCl, −78 to −35 °C, then recool to −78 °C, add Li-alkoxide of allylic alcohol (1.0 equiv) (−78 to 0 °C). [b] ClTi(O*i*-Pr)$_3$ was replaced with Ti(Oi-Pr)$_4$ in this experiment. [c] Absolute stereochemistry not determined.

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

10.1021/ja075678u CCC: $37.00

Table 2



entry	allylic alcohol	alkyne	yield (%)	E:Z	1,4-diene[a, b,c]
1	**23**; R = H	**7**	41	–	**24**; R = H
2	**25**; R = Me	**7**	66	–	**26**; R = Me
3	**27**	**7**	53	–	**28**
4	**29**; R^1=H, R^2=Me	**7**	59	–	**30**
5	**31**; R^1=Me, R^2=H	**7**	67	–	**30**
6	**32**Me	**7**	57	–	**33**
7	**34**; R=Ph	**7**	78	1:1	**35**; R=Ph (*E*/*Z*=1:1)
8	**36**; R=Et	**7**	67	1:1	**37**; R=Et (*E*/*Z*=1:1)
9	**38**	**7**	72	≥20:1	**39**
10	**38**	**40**	77	≥20:1	**41**[d]
11	**38**	**42**	59	≥20:1	**43**[e]
12	**44**; R^1=Me, R^2=H	**7**	67	1:1	**45**; R^1, R^2=$(CH_2)_2$OPMB
13	**46**; R^1=H, R^2=Me	**42**	59	8:1	**47**[e]; R^1=$(CH_2)_2$Ph, R^2=TMS
14	**48**	**7**	59	≥20:1	**49**

[a] Reaction conditions for cross coupling: alkyne (1.0 equiv), ClTi(O*i*-Pr)$_3$, PhMe, C_5H_9-MgCl, −78 to −35 °C, then recool to −78 °C, add Li-alkoxide of allylic alcohol (1.0 equiv) (−78 to 0 °C). [b] All 1,4 diene products were isolated as a single olefin isomers. [c] No evidence was found for the production of regioisomeric products. [d] In the formation of the titanium−alkyne complex, the temperature was kept under −55 °C (see Supporting Information for details). [e] rr ≥ 20:1.

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.

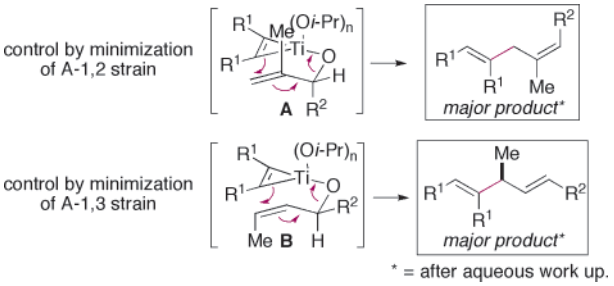


Figure 2. Empirical model for this direct allylic alkylation reaction.

Overall, we have described a new stereoselective cross-coupling reaction between allylic alcohols and alkynes for the synthesis of 1,4-dienes. While occurring 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 boatlike 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.

Acknowledgment. We gratefully acknowledge financial support of this work by the American Cancer Society (Grant RSG-06-117-01), the American Chemical Society (Grant PRF-45334-G1), the Arnold and Mabel Beckman Foundation, Boehringer Ingelheim, Eli Lilly & Co., and the National Institutes of Health−NIGMS (Grant GM80266). The authors also thank Dr. Gorka Peris for the determination of er in entry 7 of Table 1.

Supporting Information Available: Experimental procedures and tabulated spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a review of nucleophilic addition reactions to allylic electrophiles, see: (a) Magid, R. M. *Tetrahedron*, **1980**, *36*, 1901−1930. For a review cross-coupling reactions via π-allyl intermediates, see: (b) Kazmaier, U.; Pohlman, M. In *Metal Catalyzed Cross-Coupling Reactions*; De Meijere, A., Ed.; Wiley-VCH: Weinheim, Germany, 2004; pp 531−583. 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. For recent examples, see: (d) Zheng, W.; Zheng, B.; Zhang, Y.; Hou, X. *J. Am. Chem. Soc.* **2007**, *129*, 7718−7719. (e) Weix, D. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7720−7721.

(2) For examples of metal-mediated coupling reactions of allylic alcohols with alkynes, see: (a) Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 5579−5584. (b) Trost, B. M.; Martinez, J. A.; Kulawiec, R. J.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 10402−10403. (c) Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615−623. (d) Dérien, S.; Jan, D.; Dixneuf, P. H. *Tetrahedron* **1996**, *52*, 5511−5524.

(3) For copper-mediated alkylation of allylic alcohols, see: (a) Tanigawa, Y.; Ohta, H.; Sonoda, A;, Murahashi, S.-I. *J. Am. Chem. Soc.* **1978**, *100*, 4610−4612. (b) Yamamoto, Y.; Maruyama, K. *J. Organomet. Chem.* **1978**, *156*, C9−C11. (c) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1981**, *46*, 2144−2148.

(4) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203−3206.

(5) Sato, F.; Urabe, H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002, pp 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, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 2764−2765. (b) Reichard, H. A.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 1440−1443. (c) McLaughlin, M.; Takahashi, M.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3912−3914. (d) Takahashi, M.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 7514−7516. An analysis of these mechanistic hypotheses is the subject of ongoing studies in our laboratory.

JA075678U