ORGANIC LETTERS

2000
Vol. 2, No. 12
1761−1764

A Regioselective Ru-Catalyzed Alkene−Alkyne Coupling

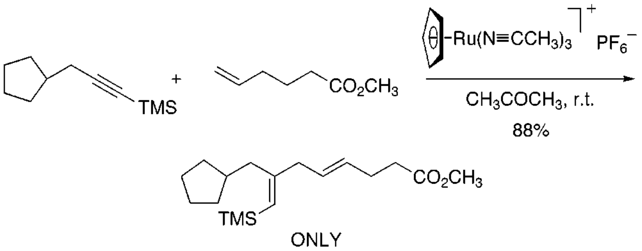
Barry M. Trost,* Michelle Machacek, and Matthew J. Schnaderbeck

Department of Chemistry, Stanford University, Stanford, California 94305-5080

bmtrost@leland.stanford.edu

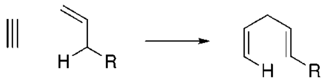
Received April 13, 2000

ABSTRACT



The reaction of silylalkynes and terminal alkenes proceeds with complete control of regioselectivity by the silyl substituent to give geometrically defined vinylsilanes. Since terminal alkynes normally give mixtures, protodesilylation of these adducts then constitutes a regioselective addition of terminal alkynes to terminal alkenes.

Simple addition reactions are attractive because they represent atom-economical processes[1] that quickly build molecular complexity.[2] The intermolecular cross-coupling of an alkene and alkyne (a type of Alder ene reaction) as shown in eq 1



(1)

requires metal catalysis if the alkyne does not bear a strong electron-withdrawing group,[3] and even in the latter cases, Lewis acids are typically employed.[4] The ability to utilize a Ru complex as shown in Scheme 1 expands the scope considerably to even unactivated systems, provides unusual selectivities, and allows the reaction to proceed under rather mild conditions.[3] A major consideration of the synthetic utility of any new reaction deals with selectivity. While chemoselectivity and stereoselectivity, in terms of alkene geometry of the product, are excellent, regioselectivity remains an issue. Consideration of the proposed mechanism reveals the origin of the regioselectivity problems. The orientation of the terminal alkene is not a factor, since only one will lead to a productive intermediate. On the other hand, the alkyne can and will coordinate and undergo cyclization in either orientation. In essence, the competition between interactions of the substituents on the carbons forming the new C−C bond of the ruthenacycle and the substituents on

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[1] Trost, B. M. *Science* **1991**, *254*, 1471. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

[2] Wender, P. A.; Miller, B. L. *Org. Synth.: Theory Appl.* **1993**, *2*, 27. Bertz, S. H.; Sommer, T. J. *Org. Synth.: Theory Appl.* **1993**, *2*, 67.

[3] Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615.

[4] Cf. Dauben, W. G.; Brookhart, T. *J. Am. Chem. Soc.* **1981**, *103*, 237. Snider, B. B. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 1−28.

[5] Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983.

[6] Greene, T. W.; Wutz, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1999; pp 68−86.

[7] Fleming, I.; Dunoques, J.; Smithers, R. H. *Org. React.* **1989**, *37*, 57.

[8] For a related study in cobalt catalyzed reactions, see: Earl, R. A.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6991. Also see: Baxter, J. B.; Knox, G. R.; Pauson, P. L.; Spicer, M. O. *Organometallics* **1999**, *18*, 197, 215.

[9] Albers, M. O.; Robinson, D. J.; Shaver, A.; Singleton, E. *Organometallics* **1986**, *5*, 2199. Ashworth, T. V.; Singleton, E.; Hough, J. J. *J. Chem. Soc., Dalton Trans.* **1977**, 1089. Bennett, M. A.; Wilkenson, G. *Chem. Ind. (London)* **1959**, 1516.

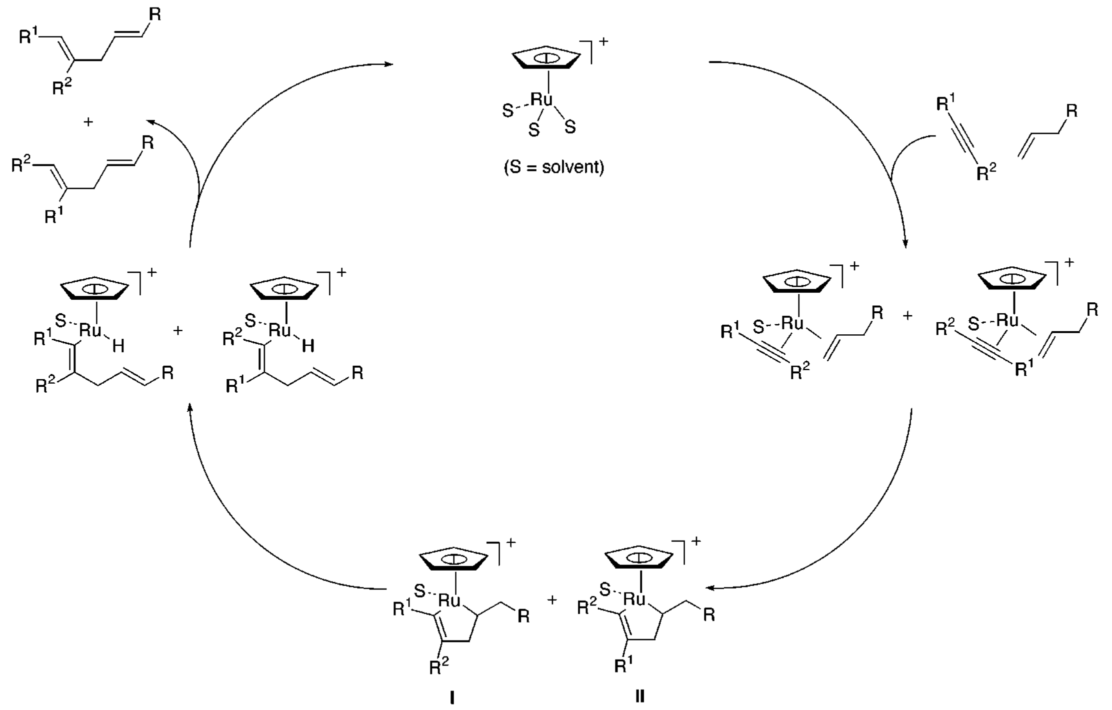
[10] All new compounds have been satisfactorily characterized spectrally, and elemental compositions have been confirmed by combustion analysis and/or high-resolution mass spectrometry.

[11] Gill, T. P.; Mann, K. R. *Organometallics* **1982**, *1*, 485.

[12] Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739. Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 9728.

10.1021/ol0059504 CCC: $19.00

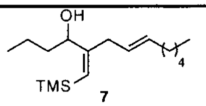
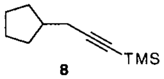
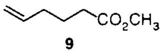
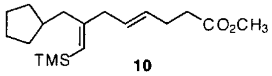
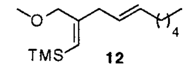
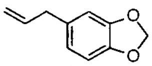
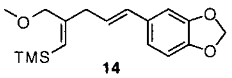
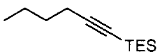
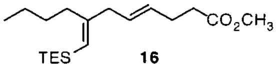
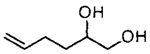
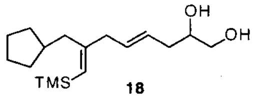
Scheme 1. Mechanistic Proposal for Ru-Catalyzed Alkene−Alkyne Addition



the alkyne and the ruthenium would then dictate the regioselectivity. The latter can be repulsive, if they simply derive from nonbonded steric interactions, or attractive, if a substituent could possibly coordinate to ruthenium. To illustrate, while the branched to linear ratios for the reactions of terminal alkynes typically range from 4:1 to 5:1, it can fall to nearly 1:1 or even reverse as in the case of the propargyl alcohol **1** with 1-octene (**2**) as shown in eq 2.

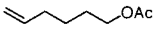
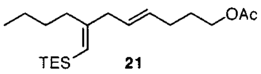
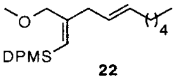
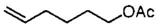
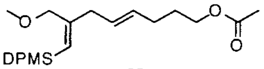
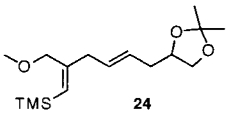
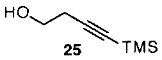
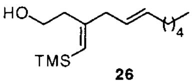
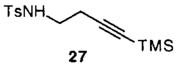
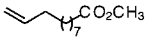
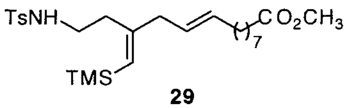
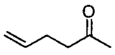
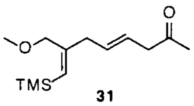
A silyl substituent has proven to be an effective regiochemical control element for both steric and electronic reasons in a number of reactions.[5] In the present instance, it is difficult to conjecture in which direction the selectivity

Table 1. Cross-Coupling of Silylalkynes and Alkenes Catalyzed by CpRu(COD)Cl (**5**)[a]

					yields	
entry	alkyne	alkene	time	product[d]	isolated[b]	brsm[c]
1	**6**	**2**	24 h	 **7**	18%	78%
2	 **8**	 **9**	2 h	 **10**	10%	84%
3	$CH_3OCH_2C{\equiv}CTMS$ **11**	**2**	8 h	 **12**	31%	N.D.
4	**11**	 **13**	8 h	 **14**	13%	86%
5	 **15**	**9**	4 h	 **16**	46%	88%
6	**8**	 **17**	2 h	 **18**	20%	74%

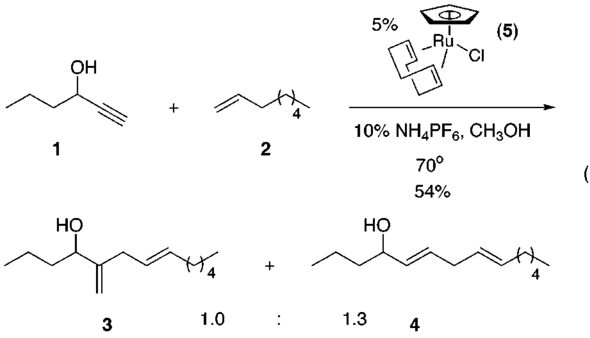
a) Typically the reactions were performed by reacting a 1:1 mixture of the alkyne and alkene at 0.5 M in methanol as in eq. 2. b) Isolated yield of pure adduct and actually best described as conversion. c) Isolated yield corrected for the amount of unreacted starting material (i.e. based upon recovered starting material). d) See ref. 10.

Table 2. Cross-Coupling of Silylalkynes and Alkenes Catalyzed by $CpRu(NCCH_3)_3{}^+PF_6{}^-$ (**20**)[a]

entry	alkyne	alkene	product[c]	isolated yield
1	**6**	**2**	**7**	52% (55%)[b]
2	**8**	**9**	**10**	88
3	**11**	**2**	**12**	81%
4	**11**	**13**	**14**	80% (83%)[b]
5	**15**	**9**	**16**	88%
6	**15**		 **21**	76%
7	$CH_3OCH_2C{\equiv}C$-DPMS **19**	**2**	 **22**	72% (82%)[b]
8	**19**		 **23**	69% (71%)[b]
9	**11**	**17**	 **24**	85%
10		**2**	 **26**	79%
11		 **28**	 **29**	78%
12	**11**	 **30**	 **31**	61%

a) All reactions were run using a 1:1 ratio of alkyne:alkene in acetone at room temperature with 10% **20** for 2 h. b) Yield corrected for recovered starting material. c) See ref. 10.

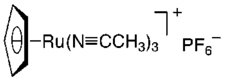
might change. If, in Scheme 1, R^2 = a silyl group, steric interactions between the silicon substituent and the alkene would disfavor I; however, such interactions between the silicon substituent and the ruthenium center could disfavor II. Despite this ambiguity, the attractiveness of the silicon group, because of its ease of introduction onto the terminal alkyne, the ease by which vinylsilanes can undergo protodesilylation,[5,6] and perhaps most significantly, the utility of vinylsilanes for further elaboration,[5,7] led us to explore its protential.[8]



(2)

Initial studies as outlined in Table 1 were quite promising. For example, the silyl version of the propargyl alcohol **1** (i.e., **6**) reacts with 1-octene, utilizing the ruthenium complex **5**[9] as catalyst to form a single product **7**[10] that corresponds to the branched product **3** after protodesilylation (Table 1, entry1). Gratifyingly, in each and every case, only one regio- and geometric isomer was obtained. Disappointingly, the conversions were unacceptably low, as revealed by the fact that the yields of product based upon recovered starting material are actually quite good. Since increasing reaction times normally did not improve the yields, the source of the problem appeared to be a limitation on the catalyst turnover number. Indeed, doubling the catalyst did double the isolated yield but led to no increased turnover number.

In a search for a way to increase our turnover number, we examined a second generation ruthenium catalyst **20**[11] whose higher intrinsic activity in other reactions under study[12] suggested its exploration. Its higher reactivity presumably stems from the absence of chloride as a “ligand”. Whereas methanol is an unsatisfactory solvent for complex **20**, acetone proved to be excellent. Indeed, subjecting a 1:1 ratio of alkyne and alkene to 10 mol % of **20** in acetone at room temperature allowed reaction to go to completion within 2 h in most cases. Comparison of entries 1−5 of both tables reveals the efficacy of the second generation catalyst. Only in the case of the propargyl alcohol was the yield modest; however, the reaction still did proceed nearly to completion in 2 h. Increasing the bulk of the silyl group from TMS to TES (Table 2, entries 5 and 6) has no discernible effect. On the other hand, increasing it to diphenylmethylsilyl (Table 2, entries 7 and 8) led to some recovered starting material in the 2 h reaction time frame. The excellent chemoselectivity as illustrated by the compatibility with alcohols, esters, amides, ketones, and internal alkenes is noteworthy considering the high reactivity of this cationic complex. It is interesting to note that the vicinal diol undergoes simultaneous acetonide formation (Table 2, entry 9) and suggests the effectiveness of this complex as a catalyst for such ketalizations.



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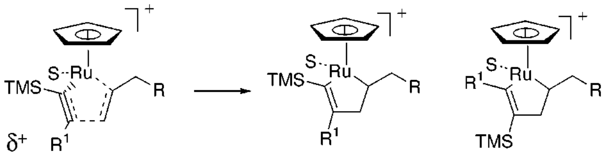
The dramatic influence on regioselectivity of the silyl group is particularly noteworthy with alkynes **1**, **11**, **25**, and **27**. The parent alkynes related to these substrates have a strong tendency to increase the amount of the linear products. For example, 3-butyn-1-ol gave a 1:1 ratio of branched and linear product with safrole (**13**). Only **26**, which would form the branched adduct after protodesilylation, is generated with the silyl substrate. These results indicate that **33** rather than **34** is the product-determining intermediate. If steric factors alone dictated the regioselectivity, these observations require that the steric hindrance afforded to the C−C bond forming reaction to generate **34** would be worth at least 2.5 kcal/mol in the transition state. On the other hand, it is possible that an electronic effect may also be involved. The simplest notion invokes the silicon stabilizing the forming C−Ru bond. However, another aspect should be considered. In the electrocyclic process leading to the ruthenacycle, the ability of silicon to stabilize a positive charge β to itself may induce a polarization of the alkyne−ruthenium cationic π-complex and thus subsequent nucleophilic attack by the alkene as depicted in **32** which then generates the observed product. Further work to verify the mechanistic scheme is clearly needed before any definitive conclusions can be drawn. The ability to effect ipso substitution of the silyl group with electrophiles with complete control of regio- and geometric selectivity[5] imparts special significance to this highly selective synthesis of vinylsilanes.



32 **33** **34**

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for the generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California-San Francisco supported by the NIH Division of Research Resources.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0059504