ORGANIC LETTERS

2009
Vol. 11, No. 5
1071−1074

A Regioselective Ru-Catalyzed Alkene−Alkyne Coupling To Form (*Z*,*Z*)-1,3-Dienes

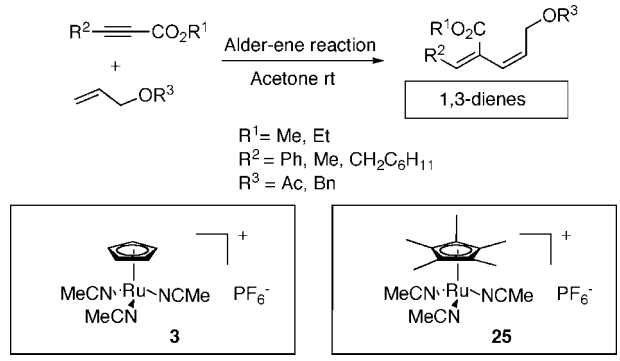
Barry M. Trost* and Alicia Martos-Redruejo

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

bmtrost@leland.stanford.edu

Received December 8, 2008

ABSTRACT



Generally, Ru-catalyzed alkene−alkyne coupling forms 1,4-dienes. A version of this process which generates a 1,3-diene as the *Z*,*Z*-isomer preferentially has now been observed. The scope of this new atom-economic process is described herein.

The development of atom-economic reactions[1] constitutes a major theme of our program. The Ru-catalyzed alkene-alkyne coupling reaction to form 1,4-dienes has been one of the most exciting of these methods and has found utility in simplifying synthetic strategies to complex bioactive targets.[2] As shown in Figure 1, path a, the proposed mechanism involves formation of a ruthenacyclopentene[3,4] which then undergoes a β-hydrogen insertion followed by a reductive elimination to give diene products. The geometrical constraints imposed by the ruthenacycle would be expected to favor insertion into the external C−H_a bond (path a) since the C−H and Ru−C bonds can best become *syn*-coplanar, which is optimum.

In accordance with this expectation, up to the present, only 1,4-dienes were observed.[5] Nevertheless, endocyclic β-hydrogen insertions within the ruthenacycle (i.e., of C−H_b, path b) have been reported as feasible.[6]

In the course of our continuing studies, we have now observed that this latter path may dominate for certain

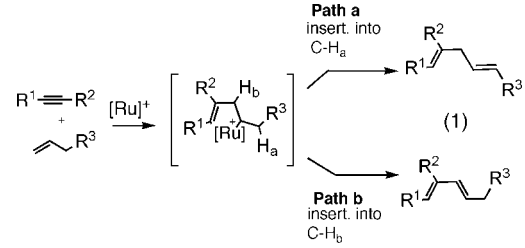


Figure 1. Proposed mechanism.

(1) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
(2) (a) Wender, P. A.; Miller, B. L. *Org. Synth.: Theory Appl.* **1993**, *2*, 27. (b) Bertz, S. H.; Sommer, T. J. *Org. Synth.: Theory Appl.* **1993**, *2*, 67.
(3) Trost, B. M.; Indolese, A. *J. Am. Chem. Soc.* **1993**, *115*, 4361.
(4) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, F. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977.

10.1021/ol8028324 CCC: $40.75
Published on Web 02/04/2009

substrates even when path a is still feasible. The fact that 1,3-dienes, important building blocks for subsequent atom-economic cycloadditions, are the products of this pathway attaches particular importance to this new observation. In our study of the effect of substituents at the allylic position of the alkene partner, we examined the reaction of allyl acetate with ethyl 2-butynoate (Figure 2). Such a study was also motivated by the prospect of the Ru catalyst initiating ionization of the allyl ester in competition with the alkene−alkyne coupling.[7]

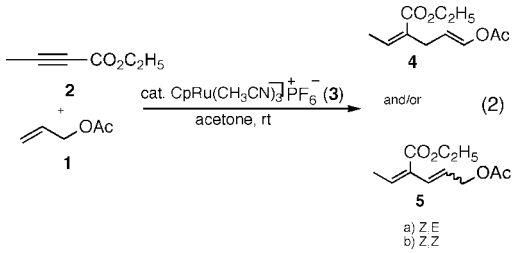


Figure 2. Effect of substituents at the allylic position.

Subjecting a 1:2 alkene−alkyne mixture to 10 mol % of a Ru cationic complex **3**[8] gave an 82% yield of **5a** and **5b**. Surprisingly, the spectral data indicated the structure of the major product to be the *Z*,*Z*-isomer of the conjugated diene **5b**. The chemical shifts and coupling constants in the proton NMR clearly reveal the 1,3-diene. The 11.7 Hz coupling constant for the disubstituted double bond of the major isomer confirms it is *Z*, whereas the 16 Hz coupling for the minor one establishes it as *E*. Table 1 summarizes our efforts to optimize the result. Lowering the alkene/alkyne ratio at 0.8 M to 1:1 (entry 2) and catalyst loading to 5% led to incomplete reaction even after 24 h (entry 7). Raising the temperature at these lower loadings does not help. On the other hand, raising the concentration to 1.6 M allows lowering the catalyst load (entry 9) or lowering both the ratio of substrates to 1:1 and catalyst load (entry 10) while maintaining complete conversion and no loss in yield albeit with a longer reaction time (12 h instead of 2 h).

For convenience, we chose to explore the scope by using the conditions of entry 1 as summarized in Table 2. Using ethyl 2-butynoate (**2**), we established that placing a branch at the allylic position (entry 2) or changing the allylic ester to an ether (entry 3) has no effect on the outcome. Additional allyl substituents were also explored. For example, entry 6 examines an aryl ether in contrast to an alkyl ether and entries 8 and 9 the use of a Boc carbonate. Entry 11 tests the chemoselectivity wherein reaction occurs exclusively at the monosubstituted allyl double bond, an observation reinforcing the extraordinary chemoselectivity observed in these Ru catalyzed reactions. No formation of 1,4-dienes was observed in any of the crude product mixtures.

Table 1. Optimization of Coupling of Ally Acetate **1** and Ethyl 2-Butynoate **2**

entry	[**2**]	**1**:**2** ratio	**3** (mol %)	*T* (°C)	time[a] (h)	% yield
1	0.8	1:2	10	rt	2	82
2	0.8	1:1	10	rt	24	(41)[b]
3	0.8	1:2	5	rt	24	(36)[b]
4	0.8	1:2	10	40	24	(18)[b]
5	0.8	1:2	5	40	24	(35)[b]
6	0.8	1:1	5	40	24	(32)[b]
7	0.4	1:1	5	rt	24	(34)[b]
8	0.4	1:1	5	40	12	(20)[b]
9	1.6	1:2	5	rt	12	84
10	1.6	1:1	5	rt	12	80

[a] Time monitored by NMR after 2, 8, and 12 h. [b] Starting alkyne (>50%) remains after reaction time.

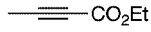
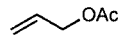
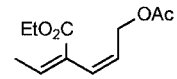
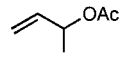
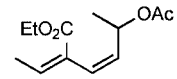
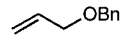
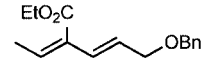
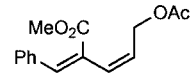
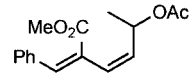
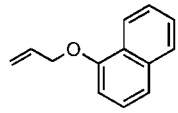
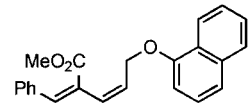
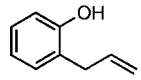
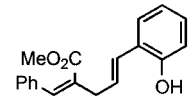
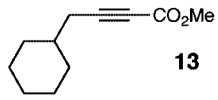
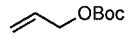
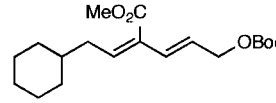
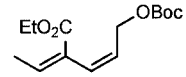
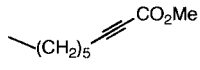
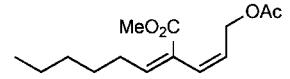
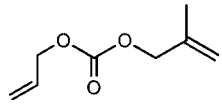
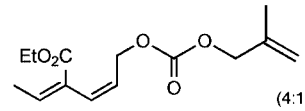
It is to be noted that the degree of selectivity for formation of the *Z*-disubstituted double bond depends upon the nature of the allylic oxygen substituent. In all of the examples, the use of acetoxy gave very high to exclusive formation of the *Z*-alkene as did benzyloxy. However, in all others, varying amounts of *Z*,*E*-dienes along with the *Z*,*Z*-dienes were observed, and in one case (entry 8), the *Z*,*E*-isomer was the major one; in the four cases that gave the poorest *Z* vs *E* selectivity (entries 6, 8, 9, and 11), the effect of the steric demands of the catalyst was explored (Table 3).

Using the Cp*Ru(+) complex **25**[9] under the same conditions did enhance the selectivity in all cases, save one; that of the reaction of alkynoate **7** with allyl carbonate **13** (see Table 3, entry 2) wherein no reaction occurred. In two of the examples (entries 3 and 4), the *Z*,*Z* product became the sole isomer formed. The source of the regio- and geometric selectivities is not obvious nor simple.

With respect to the regioselectivity of addition to the alkynoate, preference for formation of the new C−C bond α to the ester was previously noted.[10] For the reactions of these alkene partners, this preference is exclusive in all cases. With respect to the regioselectivity of the *β*-H insertion, this heretofore unprecedented selectivity to form the 1,3-diene exclusively is more difficult to rationalize. The reaction of *o*-allylphenol was performed to show the chemoselectivity with a phenolic OH (Table 2, entry 7). This substrate, being unfunctionalized at the allylic position, gave 1,4-diene product as expected.[11] We previously noted that but-3-en-2-ol behaved normally.[12] As reported herein, its acetate

(5) Trost, B. M.; Frederiksen, U.; Rudd, M. *T Angew. Chem., Int. Ed.* **2005**, *44*, 6630.
(6) Mitsudo, T.; Zhang, S. M.; Nagao, M.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 598.
(7) Trost, B. M.; Fraisse, P.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059.
(8) Trost, B. M.; Older, C. M. *Organometallics* **2002**, *21*, 2544.
(9) Steinmetz, B.; Schenk, W. A. *Organometallics* **1999**, *18*, 943.
(10) (a) Trost, B. M.; Muller, T. J. J. *J. Am. Chem. Soc.* **1994**, *116*, 4985. (b) Trost, B. M.; Muller, T. J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888. (c) Trost, B. M.; Calkins, T. L. *Tetrahedron Lett.* **1995**, *36*, 6021.
(11) That reporting *o*-allylphenol as a substrate is irrelevant, this substrate, being unfunctionalized at the allylic position, gave what it should have.
(12) Trost, B. M.; Toste, D. *Tetrahedron Lett.* **1999**, *40*, 7739.

Table 2. Alkynoate−Alkene Coupling Catalyzed by $CpRu(CH_3CN)_3^+PF_6^-$ (**3**)

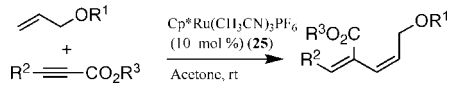
entry	alkyne	alkene	time	product	isolated
1	**2** 	**1** 	1 h	**5** 	(82%)[a]
2	**2**	**9** 	1 h	**15** 	91%
3	**2**	**10** 	3 h	**16** 	68%
4	**6**	**1**	4 h	**17** 	75%
5	**6**	**9**	2 h	**18** 	83.5%
6	**6**	**11** 	4 h	**19** 	(2.5:1)[b] 64.3%
7	**6**	**12** 	2 h	**20** 	(76%)[c]
8	**7** 	**13** 	4 h	**21** 	(1:3)[b] 74.3%
9	**2**	**13**	4 h	**22** 	(2.5:1)[b] 62.2%
10	**8** 	**1**	2 h	**23** 	68%
11	**2**	**14** 	4 h	**24** 	(4:1)[b] 65%

[a] The (*Z*/*E*) geometric isomer 2.5%. [b] Ratio (*Z*,*Z*)/(*Z*,*E*). All reactions were run using a 1:2 alkyne/alkene in acetone at room tempererature with 10% of **3**. [c] The *o*-allylphenol, unfunctionalized at the allylic position, gave 1,4-diene product as expected.

completely changes this regioselectivity. We did note in our Pd-catalyzed alkene−alkyne coupling that the presence of an allylic electronegative oxygen substituent did favor 1,3- over 1,4-diene formation.[13] This work indicates that trend also applies to the Ru-catalyzed alkene−alkyne coupling, at least for certain types of oxygen substituents such as those bearing acyl groups. While it has been previously noted that an endocyclic β-H insertion can occur in a ruthenacyclopentene[6] even though it looks to be geometrically challenged, why it would favor formation of a *Z* alkene is certainly obtuse

(13) Trost, B. M.; Chung, J. I. L. *J. Am. Chem. Soc.* **1985**, *107*, 4586.

Table 3. Cross-Coupling of Alkynoates and Alkenes by $Cp^*Ru(CH_3CN)_3^+PF_6^-$ (**25**)

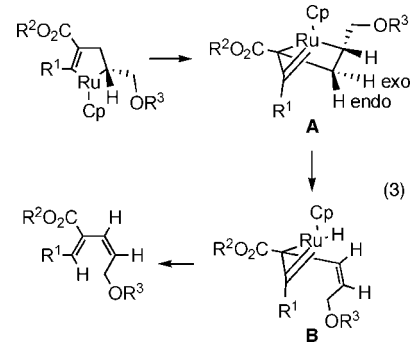


entry	alkyne	time (h)	alkene	product	isolated yield (%)
1	**6**	8	**11**	**19**	(6:1)[b] 5
2	**7**	8[c]	**13**	**21**	s.m.
3	**2**	8	**13**	**22**	60[a]
4	**2**	8	**14**	**24**	56[a]

[a] Only the 2*Z*,4*Z*-isomer was observed in this case. [b] Recovered starting material was recovered in 24% yield. [c] Starting alkyne (>70%) remains after 8 and 12 h reaction time.

at best. A possible explanation invoking the involvement of a bicycloruthenacyclopentene as depicted in **A** (eq 3) may account for it.[14] By slowing the exo β-H insertion process due to the presence of the OR^3 group, conversion of the monocycle to the bicycle **A** now creates a more geometrically favorable endocyclic β-hydrogen insertion. Placing the R^3OCH_2 group exocyclic as in **A** then favors the *Z*-alkene as depicted in eq 3. At present, this rationalization is tenuous at best. The lack of any detectable amount of 1,4-diene products combined with the preferential formation of the *Z*,*Z*-isomer makes a pathway invoking isomerization of an initially formed 1,4-diene highly unlikely.

(14) The isomerization of vinylmetal complexes to metallacyclopropenes has been previously proposed. See: Tanke, R. S.; Crabtree, R. H *J. Am. Chem. Soc.* **1990**, *112*, 7984. D'Alliessi, D. G.; Faller, J. W *Organometallics* **2002**, *21*, 1743.



In summary, we report a most unusual regio- and geometrical selective Ru catalyzed alkene-alkyne coupling. These observations clearly suggest that the mechanism of the alkene−alkyne coupling is more complex than previously realized. As such, it promises to provide new and unexpected pathways as the scope of this reactivity mode continues to be explored.

Acknowledgment. We thank the National Science Foundation for generous support of our programs and the University of Granada for a fellowship to A.M.R. We thank the generosity of Umicore for a gift of the ruthenium salts that are used to form the Ru complexes.

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

OL8028324