Pergamon

Tetrahedron Letters 41 (2000) 10167–10170

TETRAHEDRON LETTERS

The synthesis of highly functionalized seven-membered allyl ethers using palladium-catalyzed alkoxyallylation of activated olefins and ring-closing olefin metathesis

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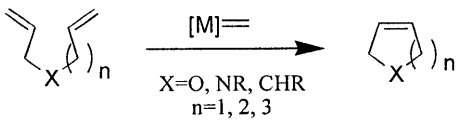
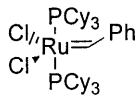
Received 7 September 2000; revised 16 October 2000; accepted 17 October 2000

Abstract

The investigation of palladium-catalyzed alkoxyallylation of activated olefins, followed by ring-closing metathesis to synthesize functionalized seven-membered ring allyl ethers is described. The influence of the olefin substituents on the diastereoselectivity of the alkoxyallylation has also been examined. © 2000 Elsevier Science Ltd. All rights reserved.

Oxygen-containing medium-ring heterocycles are important structural units commonly found within frameworks of a variety of natural or synthetic biologically active materials.[1] For instance, the polycyclic skeleton of marine neurotoxin bravetoxin B[2] comprises a δ-lactone ring, seven tetrahydropyran rings, two oxepane rings, and a didehydrooxocane ring. As part of our ongoing drug discovery program, we were interested in the construction of compound libraries containing functionalized medium-sized ether rings. In recent years, ring-closing metathesis (RCM) has established itself as a valuable method for the synthesis of medium-sized rings, including heterocyclic variants.[3] With their pioneering efforts, Grubbs and others have demonstrated that well-defined transition metal alkylidenes, such as **1**, could effect the ring-closing metathesis of diolefins to provide five-, six- and seven-membered rings with diverse functionality[4] (Scheme 1).





1

Scheme 1.

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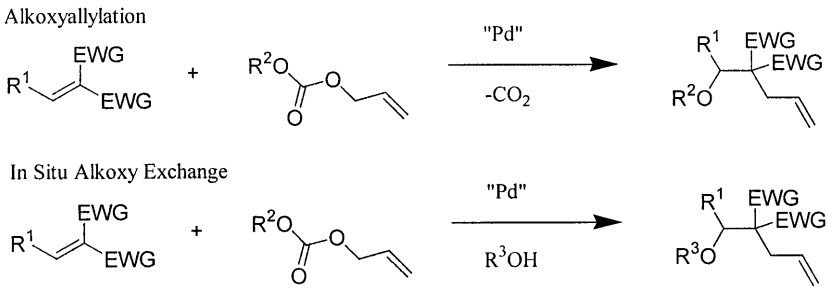
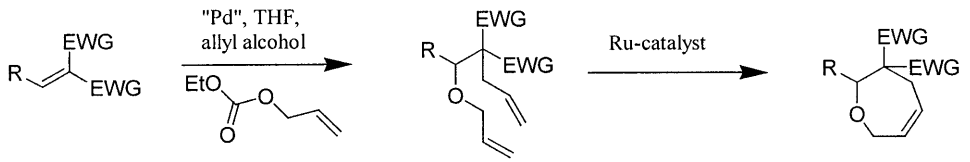
PII: S0040-4039(00)01834-7

In 1998, Yamamoto et al.[5] (Scheme 2) reported that ethylidenemalononitriles undergo a facile palladium-catalyzed alkoxyallylation in the presence of allylic ethyl carbonate to give the corresponding alkoxyallylation products. Also, by introducing a second alcohol to the reaction (R^3OH), the authors reported that alcohol R^3OH would exchange in situ with ethoxy anion and proceed via Michael addition to ethylidenemalononitriles. We envisioned using an allyl alcohol that would provide oxygen-tethered dienes serving as substrates for RCM. In this context, we wish to report the first tandem example using the palladium-catalyzed alkoxyallylation of activated olefins, followed by the ring-closing metathesis for the syntheses of highly functionalized seven-membered ring allyl ethers (Scheme 3).



Scheme 2.

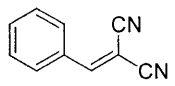
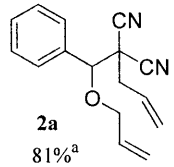
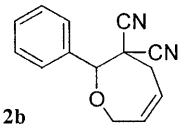
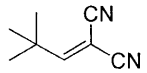
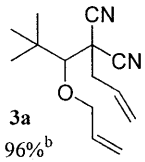
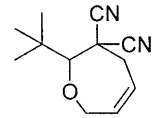
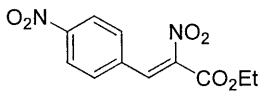
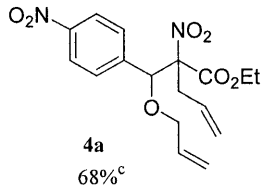
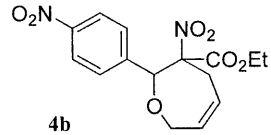
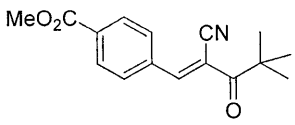
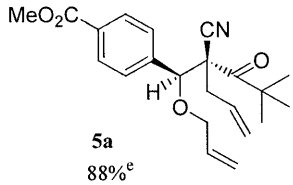
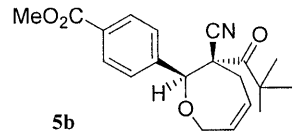


Scheme 3.

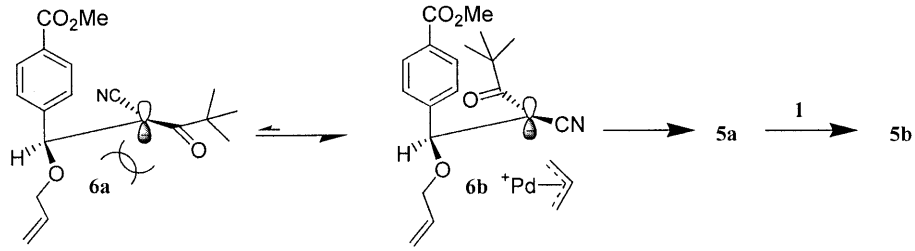
We first evaluated the utility of olefin sources containing the same electron withdrawing groups. For example, $Pd(PPh_3)_4$ (5 mol%) catalyzed alkoxyallylation[6] of aryl-substituted ethylidenemalononitrile **2**[7] (Table 1, entry 1) and *tert*-butyl-substituted alkene **3**[8] in the presence of allyl alcohol (10 equiv.) provided the dienes **2a** and **3a** as the only observed products. Treating dienes **2a** and **3a** under standard ring-closing metathesis conditions[9] supplied the seven-membered allyl ethers **2b** and **3b**. Next, we examined the alkoxyallylation on the unsymmetrical olefin ethyl 2-nitro-3-(4-nitrophenyl) acrylate **4**. Two diastereomers of **4a** were formed in approximate 1:1 ratio, which upon RCM provided allyl ether products **4b**. Interestingly, a diastereoselective alkoxyallylation was found with substrate **5**, which upon RCM yielded a single cyclic allyl ether diastereomer **5b**.[10]

We believe the diastereoselective formation of **5a** is controlled by the conformational stability of the planar anion intermediate **6a** and **6b** after the Michael addition step. A plausible mechanism consistent with the observed diastereoselectivity is shown in Scheme 4. In **6b** the *t*-Bu ketone group is pointing away from the allyloxy group, which reduces the conformational strain (conformational energy) of the transition-state. Therefore, during the alkoxyallylation, **6b** is the favored conformer and it attacks the π-allylpalladium species to generate **5a**. On the other hand, when substrate **4** is allowed to react, NO_2 and CO_2Et have a more similar steric influence and the two conformers in the transition-state are essentially degenerate. Therefore, the *trans*/*cis* diastereomers of **4a** resulted in an approximate 1:1 ratio.

Table 1
Alkoxyallylation of activated olefins and ring-closing metathesis of alkoxydienes

entry	olefin	product of alkoxyallylation	product of ring closing metathesis
1	 **2**	 **2a** 81%[a]	 **2b** 94%[a]
2	 **3**	 **3a** 96%[b]	 **3b** 71%[b]
3	 **4**	 **4a** 68%[c]	 **4b** 66%[d]
4	 **5**	 **5a** 88%[e]	 **5b** 63%[e]

[a] yield based on recovered SM. [b] isolated yield. [c] yield based on recovered SM; **4a** isolated as mixture of diastereomers (~1:1). [d] isolated yield; **4b** seperated by silica gel column chromatography (~1:1). [e] isolated yield, single diastereomer.



Scheme 4.

In summary, we have demonstrated a synthetic protocol utilizing palladium-catalyzed alkoxyallylation of activated olefins followed by ring-closing metathesis, which affords convenient access to highly functionalized seven-membered ring allyl ethers. In addition, the diastereoselective synthesis is influenced by the steric factors of the substituents on the olefin starting material. Efforts to expand the scope of substrates, control of the diastereoselectivity and elaboration of the scaffolds into small molecule libraries are currently being pursued.

References

1. For leading references, see: (a) In *Comprehensive Heterocyclic Chemistry*; Meth-Cohn, O., Ed.; Pergamon: New York, 1984. (b) In *Carbocycle Construction in Terpene Synthesis*; Ho, T.-L., Ed.; VCH: New York, 1988.
2. *Classics in Total Synthesis*; Nicolaou, K. C.; Sorensen, E. J.; VCH, 1996; p. 731, and references cited therein.
3. Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446, and references cited therein.
4. (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800. (c) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324. (d) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426.
5. Nakamura, H.; Sekido, M.; Ito, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6838.
6. Typical procedure for alkoxyallylation: Anhydrous THF solution of olefin (1 equiv.), ethyl allylcarbonate (1 equiv.), allyl alcohol (10 equiv.) and $Pd(PPh_3)_4$ (5 mol%) was stirred at room temperature under nitrogen for 24 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 5/1).
7. Bϕgesϕ, K. P. *J. Med. Chem.* **1983**, *26*, 935.
8. Shim, J.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 8470. As previously described in reference 5, the alkoxyallylation does not proceed well with alkyl-substituted olefin substrates that have γ-protons; however, the alkoxyallylation proceeds reasonably well on ethylidenes with electron rich or electron deficient aromatic ring substituted at the β-carbon.
9. Typical procedure for ring-closing metathesis: At room temperature under ethylene atmosphere, diene (0.005 M in dry CH_2Cl_2, 1 equiv.) was added drop-wise to **1** (5 mol%) in dry CH_2Cl_2 via an addition funnel over 2 h; the resulting mixture was stirred for 24 h. The solvent was then evaporated and the product(s) was purified by silica gel column chromatography (hexanes/ethyl acetate = 5/1).
10. Dr. Richard Staple at the Department of Chemistry and Chemical Biology of Harvard University has kindly deposited the crystallographic data for the structural analysis of **5b** (Fig. 1). Copies of this information may be obtained free of charge by written request to the senior author.

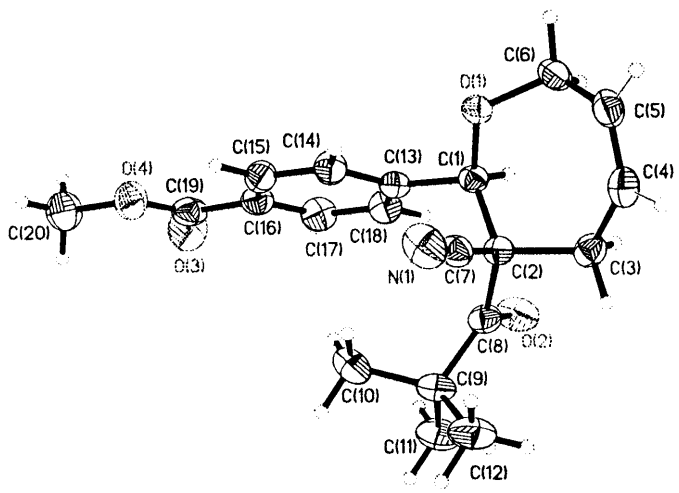


Figure 1.