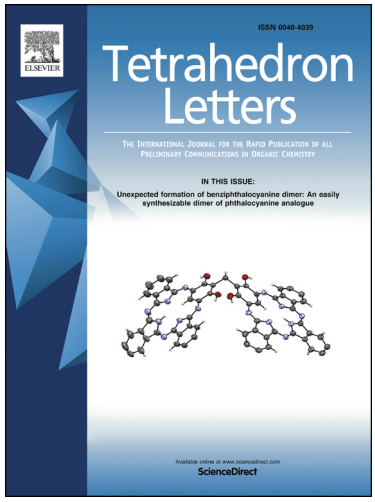

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PII: S0040-4039(17)30855-9
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.07.022
Reference: TETL 49104

To appear in: *Tetrahedron Letters*

Received Date: 27 June 2017
Accepted Date: 3 July 2017

Please cite this article as: Shockley, S.E., Hethcox, J.C., Stoltz, B.M., Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via a Catalytic Enantioselective Allylic Alkylation Strategy, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.07.022

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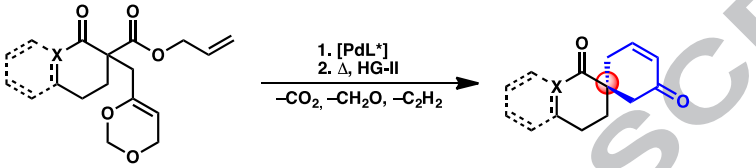

Enantioenriched All-Carbon Quaternary Spirocycles

Tetrahedron Letters
journal homepage: www.elsevier.com

Asymmetric Synthesis of All-Carbon Quaternary Spirocycles via a Catalytic Enantioselective Allylic Alkylation Strategy

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Allylic alkylation
Spirocycle
Asymmetric catalysis
Palladium catalysis
Masked bromomethyl vinyl ketone

ABSTRACT

Rapid access to enantioenriched spirocycles possessing a 1,4-dicarbonyl moiety spanning an all-carbon quaternary stereogenic spirocenter was achieved using a masked bromomethyl vinyl ketone reagent. The developed protocol entails an enantioselective palladium-catalyzed allylic alkylation reaction followed by a one-pot unmasking/RCM sequence that provides access to the spirocyclic compounds in good yields and selectivities.

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The widespread prevalence of spirocycles in biologically active molecules has inspired the development of many methods for the synthesis[1] and, more recently, the enantioselective synthesis[2] of this motif. During the course of our ongoing efforts in natural product synthesis, the preparation of an enantioenriched spirocyclic cyclohexenone derivative bearing both an all-carbon quaternary stereogenic spirocenter as well as a 1,4-dicarbonyl moiety spanning the spirocenter was required. This goal was challenging not only due to the difficulties in constructing 1,4-dicarbonyls,[3] but also due to the inherent challenges of enantioselectively synthesizing an all-carbon quaternary stereocenter.[4] As the enantioselective synthesis of all-carbon quaternary stereocenters via palladium-catalyzed allylic alkylation has been developed extensively by our group,[5] we envisioned that rapid entry to the spirocyclic cyclohexenone framework could be achieved if the olefin was disconnected via a ring-closing metathesis reaction (RCM) and the resultant α-quaternary carbonyl derivative could be synthesized asymmetrically via our allylic alkylation methodology (Figure 1a). In addition to the application to our own synthetic endeavor, we imagined that this strategy would be amenable to the synthesis of a wide array of all-carbon quaternary spirocyclic compounds, such as acorenone, laurencenone B, and α-chamigrene (Figure 1b).[6] However, this plan hinged on the challenging use of bromomethyl vinyl ketone as an alkylating reagent.

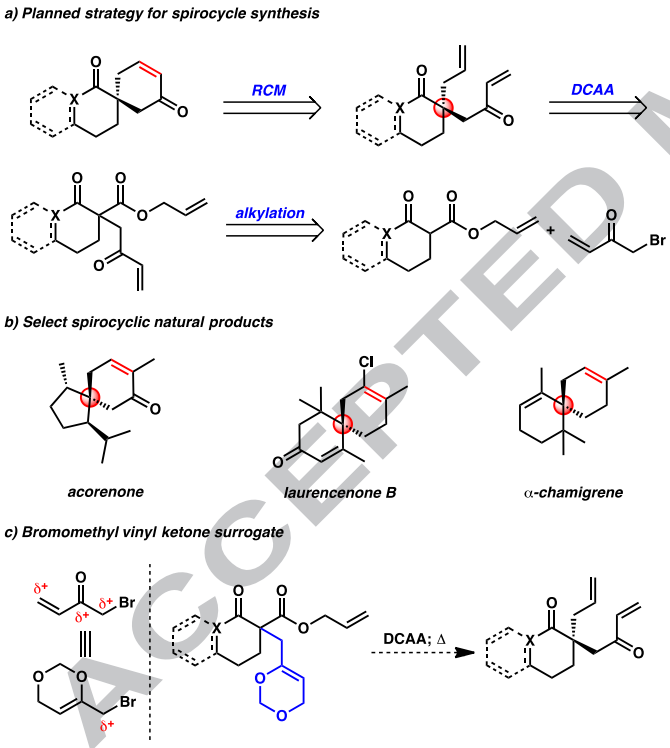
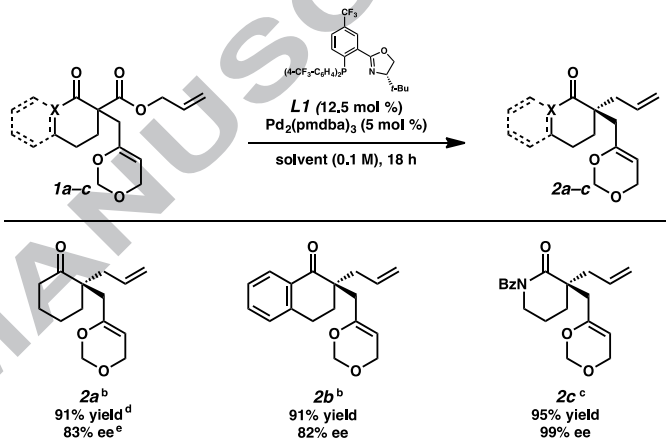


Figure 1. Strategy and inspiration for the catalytic enantioselective synthesis of all-carbon quaternary spirocycles.

Nucleophilic addition to bromomethyl vinyl ketone can be problematic due to the three electrophilic positions on the molecule, which include positions for Michael addition, 1,2-addition, and S_N2 displacement (Figure 1c, left). As a solution to this issue, Funk has developed the use of 6-(bromomethyl)-4*H*-1,3-dioxin as a bromomethyl vinyl ketone surrogate (Figure 1c, left).[7] Following alkylation, the dioxin functionality of this reagent can be unmasked under thermal conditions to release formaldehyde and reveal the latent enone. Therefore, we envisioned that we could obviate the challenges of using bromomethyl vinyl ketone by utilizing Funk's dioxin reagent in our planned strategy (Figure 1c, right). However, the use of a substrate bearing such a bulky substituent with Lewis basic oxygens had not yet been explored in our palladium-catalyzed allylic alkylation chemistry.

Fortuitously, we rapidly discovered that the standard conditions developed by our group for palladium-catalyzed allylic alkylation reactions were adaptable to this new substrate class (Table 1). The use of a catalyst prepared from $Pd_2(pmdba)_3$ and (*S*)-$(CF_3)_3$-*t*-Bu-PHOX (**L1**) provided access to a variety of dioxin-substituted allylic alkylation products in consistently high yields and enantioselectivities. Cyclohexanone **2a** was obtained in 91% yield and 83% ee. Moreover, tetralone **2b** was afforded in similarly high yield and selectivity, and we were pleased to find that lactam **2c** could be accessed in an excellent 95% yield and 99% ee. Based on these results in combination with the previously established trends in our palladium-catalyzed allylic alkylation methodology,[5] we infer that the masked methyl vinyl ketone substituent should be broadly applicable to all of the ring systems tolerated in this chemistry.

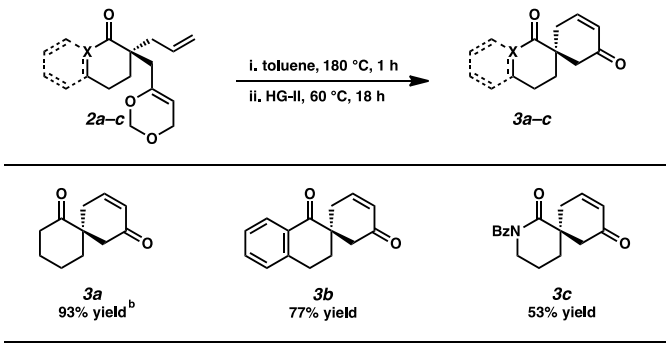
Table 1. Enantioselective Palladium-Catalyzed Allylic Alkylations with Substrates Bearing a Masked Methyl Vinyl Ketone.[a]



[a] Reactions performed on 0.2 mmol scale. [b] Performed using THF at 23 °C. [c] Performed using toluene at 40 °C. [d] Isolated yield. [e] Determined by chiral HPLC or SFC.

With the feasibility of utilizing substrates bearing a masked methyl vinyl ketone functionality in our allylic alkylation chemistry established, we moved to demonstrate the ease with which this strategy can provide access to the desired spirocyclic compounds. Though the masked methyl vinyl ketone synthon has been shown to provide access to bridged and fused bicycle systems,[7] to the best of our knowledge, the utility of this reagent for the synthesis of spirocycles has yet to be demonstrated. We were pleased to find that the planned thermal unmasking/RCM sequence proceeded smoothly in a single reaction vessel. In this procedure, dioxin **2** is unmasked via heating in toluene at 180 °C for one hour, whereupon the reaction is cooled to 60 °C and a solution of Hoveyda-Grubbs second-generation catalyst is introduced to complete the annulation. Using this newly developed protocol, spirocyclic cyclohexenones **3a**, **3b**, and **3c** were obtained in good to excellent yields, thus demonstrating the viability of this strategy for the synthesis of enantioenriched spirocycles.

Table 2. One-Pot Synthesis of Spirocyclic Compounds.[a]



[a] Reactions performed on 0.1 mmol scale. [b] Isolated yield.

In summary, we have demonstrated that substrates bearing a bulky, highly oxygenated methyl vinyl ketone surrogate can be utilized in an enantioselective palladium-catalyzed allylic alkylation reaction. The resulting allylic alkylation products are obtained in high yields and selectivities with neither the increased sterics nor the added Lewis basic oxygen atoms adversely affecting reactivity. Furthermore, we developed a one-pot unmasking/RCM procedure showcasing that these allylic alkylation products can be easily advanced to enantioenriched spirocycles bearing both an all-carbon quaternary stereogenic spirocenter as well as a 1,4-dicarbonyl functionality spanning the spirocenter. This simple two-step strategy is amenable to the synthesis of a range of enantioenriched spirocyclic natural products; further results in this area will be reported in due course.

Acknowledgments

The NIH-NIGMS (R01GM080269) and Caltech are thanked for support of our research program. J.C.H. thanks the Camille and Henry Dreyfus postdoctoral program, and S.E.S. thanks the NIH-NIGMS for a predoctoral fellowship (F31GM120804). Dr. Mona Shahgholi and Naseem Torian (Caltech) are thanked for mass spectrometry assistance. Dr. Scott Virgil (Caltech) is thanked for assistance with instrumentation.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

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Highlights

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