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Cobalt-catalyzed oxidative cyclization of *gem*-disubstituted conjugated alkenols

Tânia M. F. Alves, Mateus O. Costa, Beatriz A. D. Bispo, Fabiana L. Pedrosa, Marco A. B. Ferreira *

Department of Chemistry, Laboratório de Química Bio-Orgânica, Federal University of São Carlos—UFSCar, Rod. Washington Luis, km 235, C.P. 676 São Carlos, SP, Brazil

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ABSTRACT

Aryl *gem*-disubstituted conjugated alkenols underwent oxidative cyclization affording 2,5,5-trisubstituted tetrahydrofurans in reasonable yields and good diastereoselectivities using the reductive termination variation of the Mukaiyama aerobic oxidative reaction. Under oxidative termination, the same alkenols produced diols and ketonic by-products via the double hydration and beta-scission competing pathways. Furthermore, the differences in alkenol reactivity under the reductive and oxidative termination conditions were investigated.

Introduction

Substituted tetrahydrofurans (THFs) are common structural elements of natural products and other biologically active molecules.[1] Therefore, significant efforts have been dedicated to the development of new stereoselective methods for the construction of such moieties.[2] In particular, synthetic approaches for the formation of 2,5-disubstituted-THFs have received considerable attention.[2] However there is a lack of stereoselective methodologies for 2,5,5-trisubstituted-THFs possessing aromatic motifs in tertiary carbinol centers, presented in some biologically active compounds (Fig. 1).[3]

A powerful strategy to achieve 2,5-*trans*-THFs in a stereoselective manner involves the Mukaiyama aerobic oxidative cyclization reaction of bis-homoallylic alcohols under a catalytic amount of Co(II) complexes in the presence of O_2 (Scheme 1).[4] The low cost and non-toxic metal, open reaction conditions, lack of moisture sensitivity, and use of green solvents make this approach appealing. Therefore, the reaction mechanism has been investigated by Hartung, showing evidences of the formation of carbon free radical intermediates.[5] Additionally, with slight variations on reaction conditions, these radical intermediates can be transformed into synthetically useful functional groups such as alcohols,[4–6,9] bromides,[6b] alkyls,[6b,7] and alkylsulfanyls.[8] They are also able to perform a nucleophilic radical addition to electron-withdrawing conjugated double/triple bonds.[7] This methodology has proven to be an extremely powerful tool in asymmetric synthesis of natural products and biologically active compounds.[9]

A critical issue for the application of this methodology has been the degree of substitution of the double bond. Previous work has explored tertiary pentenol derivatives forming 2,5,5-trisubstituted-THFs in moderate yields and selectivities (Scheme 2).[3c] Moreover, excellent selectivities and yields for terminal unsubstituted and *gem*-alkyl olefins have been achieved.[4–9] Alkyl or aryl substituents attached at the terminal position provide excellent 2,5-*trans* diastereoselectivity independent of the double bond geometry.[5a,6b] However, the newly formed stereocenter in the side chain is obtained in a ratio of 1:1 from the radical symmetric intermediate under the traditional oxidative termination.[5a,6b] Harsh reaction conditions were also necessary to cyclize trialkyl-trisubstituted terminal olefins, affording the products with low yield and diastereoselectivity.[5]

We envisioned whether this transformation could be performed employing aryl *gem*-disubstituted conjugated double bonds (Scheme 2). We hypothesized that this reaction would stereoselectively form a 2,5,5-trisubstituted THF, thus creating a tertiary carbinol center with an aromatic group. Herein we report our contribution toward extending the scope of this methodology and in understanding the reactivity of these systems.

Results and discussion

Reductive termination

Initially, we focused on the feasibility of the Mukaiyama cyclization of simple model substrates **1a**, under reductive

* Corresponding author.
E-mail address: marco.ferreira@ufscar.br (M.A.B. Ferreira).

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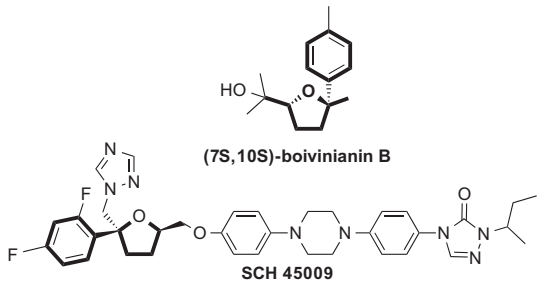


Figure 1. Examples of biologically active compound containing 2,2,5-trisubstituted THF structural motifs.

termination version for construction of the **2a** core (Table 1). In this initial screening, we used 1,4-cyclohexadiene (1,4-CHD) as a reducing agent (Table 1). The combination of CoL_2 (**3**, **5**, or **6**) (Fig. 2), 1,4-CHD (20 equiv) in toluene and open flask conditions (atmospheric air), catalyzed the reaction to afford the expected THFs (**2a**–**c**) and complete conversion of alkenol **1a** after 4 h (entries 1–3). The mass balance was a critical issue leading us to suspect that under these conditions we had decomposition of the starting material and/or product. A more sterically bulky alkenol could also be associated with the lower selectivity due to repulsive interaction in catalyst coordination.[3c] Aiming to improve the reaction conditions, we systematically varied the concentration. At lower and higher concentrations (entries 4 and 5, respectively), we experienced difficulties in achieving acceptable yields. It is noteworthy that when only 1,4-CHD is used as solvent, as described by Hartung,[5,7] decomposition of the starting material was observed (entry 6). The best yield was achieved with 0.06 M employing catalyst **5** at 15 mol % (entry 7). We were not able to reduce the catalyst loading, as 7.5 mol % of **5** lead to a reduced reaction yield, producing **2a** in only 13% (entry 8). No substrate consumption occurred in the absence of O_2 and 1,4-CHD (entry 9). Finally, the alkenol **1b** (entry 10) lead to similar results to **1a**, revealing a minor influence of an electron withdrawing group on aromatic ring on this reaction. However, it was noted a higher yield for the alkenol **1c** (entry 11) possessing an electron donating group.

The alkenol **1a**′ possessing a trisubstituted double bond also generated the cyclic product **2a**′ in 31% yield (Scheme 3). However, attempts to lengthen the alkyl chain proved to be unfruitful as no products were observed with the alkenol **1a**″ even after 24 h, with partial recovery of the starting material.

With the best reaction condition in hand, we next investigated the diastereoselectivity of the Mukaiyama cyclization with alkenols **7a**–**h** (Scheme 4). The reaction gave a separable mixture by silica gel chromatography of 2,5-*trans* (**8a**–**h**) and 2,5-*cis* (**9a**–**h**) THFs in moderate to poor yields and good diastereoselectivities in favor of **8a**–**h** (2,5-*trans*). The relative stereochemistry was confirmed by NOE experiments of both **8b**/**9b** diastereoisomers.[10] Better diastereoselectivities were obtained at 60 °C, but a reduction in the yield also occurred. When comparing the reaction involving the compounds **7a** and **7h**, erosion of diastereoselectivity was observed for electron-donating aromatic substituents.

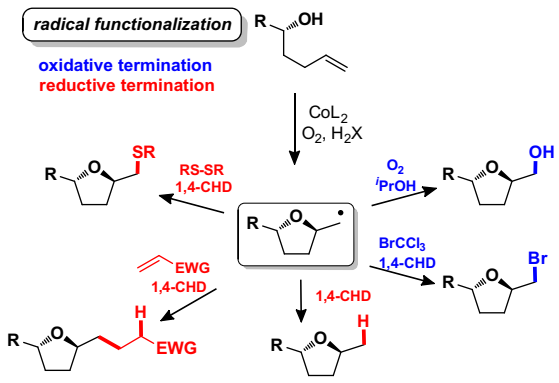
Despite the quantitative consumptions of starting materials the isolated yields after flash chromatography were lower than expected. We were not able to assess the yields from NMR using an internal standard of the crude material due to paramagnetic character of the cobalt catalyst, which produced broad signals in most cases. To examine these results further, we collected kinetic information by monitoring the cyclization of alkenols **7b** and **7h** at 60 °C via quantitative GC–MS analysis. The consumption of starting material and formation of cyclized products were monitored and the changes in concentration are plotted as a function of time in Figure 3. After approximately 2 and 3 h, respectively, the starting material was completely consumed for the reactions of **7b** and **7h**. The amount of products remains unchanged after this point, with yields of 49% for **7b** and 54% for **7h**. The achieved diastereoselectivity ratios were 5.7:1 for **8b**:**9b** and 1.2:1 for **8h**:**9h**. Additionally, the diastereomeric ratios of the products are nearly constant with respect to conversion.

While the diastereoselectivities obtained from the kinetic progress were very similar to those obtained from isolated products after silica gel chromatography, the yields decrease by approx. 30–40%. Pagenkopf obtained similar results for 2,5,5-trisubstituted THF.[3c] We hypothesize in our case a product decomposition by a ring opening due to exposure to silica gel through the formation of a stable tertiary carbocation.

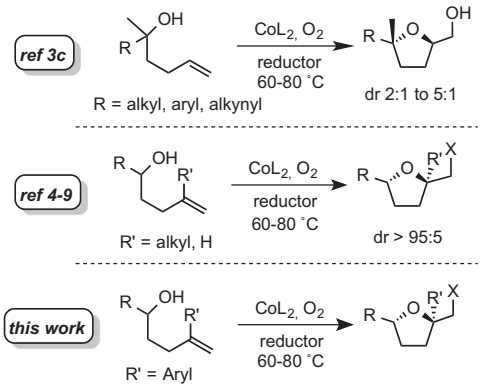
Finally, a control experiment was performed in order to verify if the presence of the catalyst was critical to induction of selectivity. The alkenol **7g** was cyclized in the presence of *p*-TSA (1 equiv) and CH_2Cl_2 (0.06 M), at room temperature affording a separable mixture by silica gel chromatography of **8g**:**9g** in 58% yield with no diastereoselectivity (dr = 1:1), proving the importance of the catalyst in this reaction.

Oxidative termination

In a second stage of this study, we explored the oxidative termination version of the Mukaiyama cyclization. In this screening, we used catalysts **3**–**6** (Fig. 2), *t*-BuOOH as additive, and *i*-PrOH as solvent under O_2 (1 atm) atmosphere. Surprisingly, as shown in Table 2, we were unable to obtain the cyclized product **10** under oxidative termination for alkenols **1a**–**c**. Depending on the cobalt



Scheme 1. Synthetic variations of Mukaiyama oxidative cyclization.



Scheme 2. Scope of the Mukaiyama oxidative cyclization.