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Practical Asymmetric Approach to Medium-Sized Carbocycles Based on the Combination of Two Ru-Catalyzed Transformations and a Lewis Acid-Induced Cyclization†

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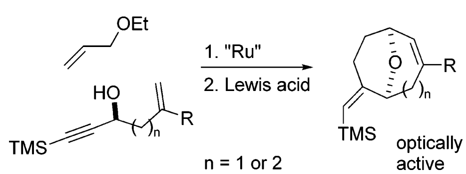
ABSTRACT



Ruthenium-catalyzed coupling of allyl ethyl ether to optically active 1-trimethylsilyl-1-alkyn-3-ols, followed by in situ ketalization and Lewis-acid-induced cyclization, affords enantiomerically pure 1,5-oxygen-bridged eight- and nine-membered carbocycles. Opening of the oxygen bridge under basic or electron transfer conditions provides optically pure medium-sized carbocycles, products that are difficult to construct using other currently available methodologies.

Medium-sized carbocycles, including eight- and nine-membered ones, form the structural core of numerous natural targets with promising biological activities,[1] and thus there is great interest in the development of practical routes for their rapid assembly. Unfortunately, rings of this size are difficult to construct using conventional cyclization routes due to unfavorable entropic and enthalpic factors.[2] Even the powerful ring-closing metathesis reaction (RCM) fails to give the desired carbocycles in good yields unless the substrates are conformationally biased toward the cyclization.[3] A number of alternative synthetic strategies[4] based upon cyclization−fragmentation reactions,[5] ring expansions,[6] rearrangements,[7] or cycloadditions[8] have been recently developed. A major drawback, however, with the majority of these strategies has been the lack of asymmetric versions that

† Dedicated to Prof. J. Elguero on the occasion of his 70th birthday.

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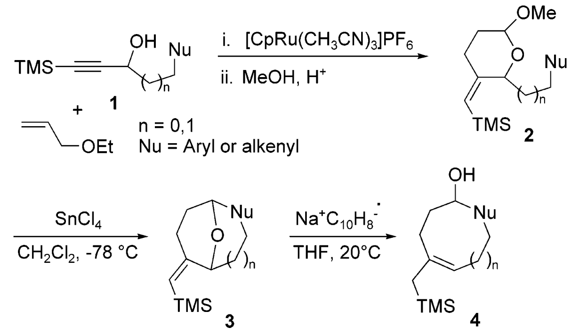
address the synthesis of the products in an enantioselective fashion. Although several interesting asymmetric approaches to seven-membered carbocycles have been reported,[9] in the case of eight- or nine-membered rings the progress has been much slower. Enantioselective access to rings of this size has primarily relied on the elaboration of naturally occurring chiral precursors, mainly carbohydrates,[10] albeit a few examples based on diastereoselective transformation of nonnatural, optically active precursors have also been reported.[11,12]

We have recently developed an atom-economical protocol for assembling oxygen-bridged medium-sized carbocycles from readily accessible precursors.[13] The route involves a ruthenium-catalyzed alkyne−alkene C−C bond-forming reaction between 1-trimethylsilyl-1-alkyn-3-ols and allyl ethers to yield a mixed acetal of type **2**, followed by a Lewis acid-promoted Prins-type cyclization (Scheme 1).

Scheme 1



Remarkably, the presence of the exocyclic double bond in the resulting oxabridged adducts, a functionality created in the Ru-catalyzed coupling reaction, allows for reductive opening of the oxygen bridge under electron-transfer conditions and hence for the unmasking of the embedded medium-sized carbocycle (**4**).[14]

Since the approach relies on the use of chiral alkynols as starting materials, it was reasoned that it might be feasible to develop an asymmetric alternative if such alcohols could be reliably prepared in an optically active form. Herein we show that this can be accomplished using a Ru-catalyzed asymmetric reduction of readily available ketones and demonstrate that the resulting alkynols can be rapidly homologated into a variety of enantiorich carbocyclic systems containing either eight- or nine-membered rings.

Our first efforts to obtain the chiral propargylic alcohols **1** focused on the use of the catalytic enantioselective alkynylation of aldehydes recently developed by Carreira and co-workers.[15,16] Unfortunately, addition of the required aldehydes to a toluene solution of trimethylsilylacetylene and Et_3N, in the presence of catalytic proportions of $Zn(OTf)_2$ and (+)-*N*-methylephedrine,[15a] did not produce the desired alkynols **1**. In these experiments, we could only isolate small proportions of aldol self-condensation products. This outcome is probably due to the absence of α-branching in the aldehydes, which favors the self-condensation reaction over the desired coupling.[17] At room temperature, in the presence of stoichiometric amounts of the reagents,[15b] we could get the desired products **1**, albeit in a low 20% yield, with the aldol byproducts again being predominant.[18]

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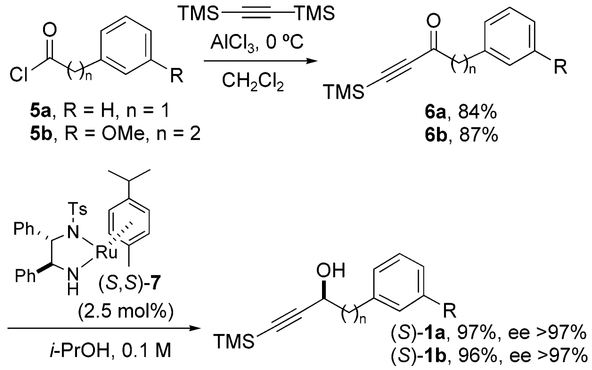
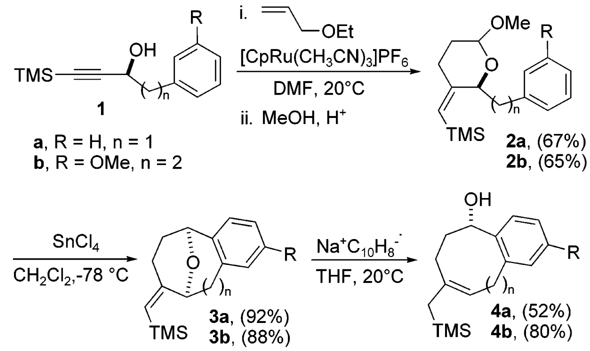
Scheme 2



The above results led us to turn our attention to an alternative method consisting of the asymmetric catalytic transfer hydrogenation of α,β-acetylenic ketones.[19] The required ketones **6a** and **6b** were prepared in one step according to the procedure described by Birkofer et al.[20] Addition of bis(trimethylsilylacetylene) to the solution of the corresponding acid chloride (**5a**,**b**) and $AlCl_3$ in CH_2Cl_2 gave the required ketones **6**, which could be isolated in good yields. Treatment of these ketones with catalytic amounts of Noyori's ruthenium complex **7** in ^{i}PrOH smoothly provided the desired alkynols **1a** and **1b** with excellent enantioselectivities and yields (Scheme 2).[21]

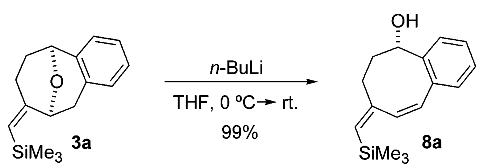
The transformation of the optically active alkynols **1a** and **1b** into the mixed acetals **2a** and **2b** was readily achieved in 67 and 65% yields by treatment with 1.5 equiv of allyl ethyl ether in the presence of $[CpRu(CH_3CN)_3]PF_6$ (10 mol %), followed by in situ ketalization.[22] Reaction of these compounds with 1 equiv of $SnCl_4$ promoted the desired Friedel−Crafts cyclization to give optically pure **3a** and **3b** in excellent yields (Scheme 3). The enantiomeric purity of tricycle **3a**, as well as that of the bicarbocyclic system **4b**, isolated after reductive opening of the oxygen bridge of **3b** under electron-transfer conditions, was higher than 98% (as determined by chiral HPLC comparison with a racemic standard). This analysis confirmed that no epimerization takes place during the carbocycle-assembling process.

Scheme 3



Complementary to the oxabridge ring openings shown in Scheme 3, we have also found that the presence of benzylic protons in **3a** allows cleavage of the oxygen bridge by means of a base-induced elimination reaction.[23] Thus, treatment of **3a** with *n*-BuLi in THF at 0 °C afforded the optically active cyclooctene **8a** in 99% yield (Scheme 4).

Scheme 4



The obtained results validate the methodology as a practical and rapid approach to enantiopure carbobicycles containing a cyclooctane or a cyclononane ring fused to an aromatic system. It remained to be proven whether the strategy could be extended to obtain synthetically appealing fused bicarbocyclic systems containing nonaromatic six-membered carbocycles. Toward this aim we prepared the ketone **6c**,[24] which contains a cyclohexene instead of a phenyl group as a latent nucleophile for the acid-induced cyclization. The ruthenium-catalyzed asymmetric transfer hydrogenation provided the desired optically active alkynol **1c** with excellent enantioselectivity and in 84% yield. Submission of **1c** to the required Ru-catalyzed alkyne−alkene coupling conditions afforded, after acidic workup in methanol, the mixed acetal **2c** in 43% yield (82% yield based on recovered starting alkynol). The Prins-like cyclization of **2c** to give the desired oxabridged bicarbocycle **3c** could be induced upon treatment with $SnCl_4$ at −78 °C (76% yield); however, we found that the reaction is slightly more efficient when carried out at room temperature in the presence of 1 equiv of $InCl_3$ (85% yield, Scheme 5).[25] The inherent stereochemical bias of **3c**, due to the presence of the oxygen bridge, bodes well for

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(21) **Procedure for the Preparation of Trimethylsilyl-1-alkyn-3-ols (1).** A mixture of (*S*,*S*)-**7** (7.7 mg, 0.013 mmol) and ketone **6** (100 mg, 0.52 mmol) in *i*-PrOH (5.2 mL) was stirred at room temperature for 20 h. The reaction mixture was then concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel to afford (*S*)-**1** as a colorless oil. Enantiomeric excess was determined by ^{19}F NMR via derivatization of the corresponding alkynols and their racemic analogues with (*R*)-(+)-α-(methoxy)-α-(trifluoromethyl)-phenylacetic acid. Only one diastereoisomer could be detected by ^{19}F NMR for the derivatized alkynol (*S*)-**1**, suggesting an enantiomeric excess > 97%.

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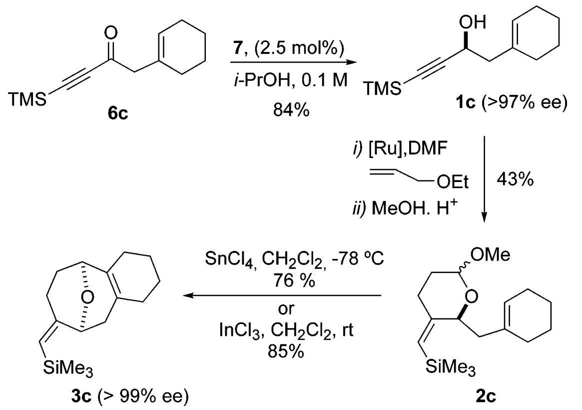
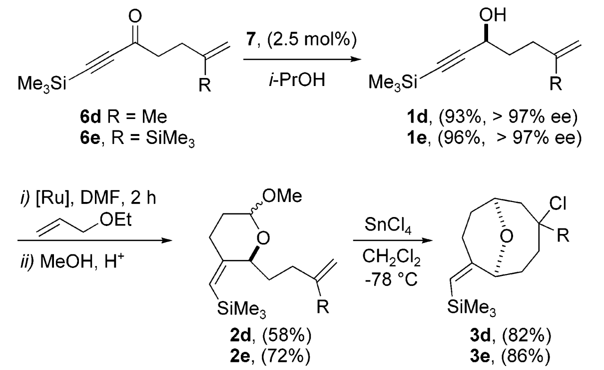
(24) Ketone **6c** was prepared from its corresponding acid chloride following the same procedure as for **6a**,**b**.

(25) Cho, Y. S.; Kim, H. Y.; Cha, J. H.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Chang, M. H. *Org. Lett*. **2002**, *4*, 2025−2028.

Scheme 5



Scheme 6



ensuing stereoselective manipulations of the system, in particular for the functionalization of the highly substituted double bond at the fusion position.

As a further demonstration of the versatility of the strategy, we have also completed the synthesis of enantiopure oxa-bridged cyclononanes. The required optically pure enynols were efficiently prepared by asymmetric hydrogenation of ynones **6d** and **6e**. The ruthenium-catalyzed coupling of alkynol **1d** or **1e** with allyl ethyl ether, followed by in situ ketalization, gave the expected mixed acetals **2d**,**e** in good yields. Reaction of these compounds with 1 equiv of $SnCl_4$ promoted the desired Prins-type cyclization, affording the optically active oxabridged cyclononanes **3d** and **3e** in excellent yield (Scheme 6).[26]

In summary, the sequential combination of an asymmetric catalytic hydrogen transfer reaction, a Ru-catalyzed coupling, and a Lewis acid-induced cyclization provides for one of the shortest routes so far described for the assembly of enantiopure, oxa-bridged, medium-sized carbocyclic systems. The route is rapid, versatile, and fairly ecological, as it relies on the use of catalytic reactions as key steps. Studies to further improve its practicality and to apply it to obtain target-relevant, more elaborated products are underway.

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

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(26) **3d** was obtained as an 8:2 mixture of isomers at the tertiary center and **3e** as a single diastereoisomer. This diastereoselectivity in the reaction confirms the stereodirecting role of the oxabicylic system.