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Catalytic Alkene Cyclization Reactions for the Stereoselective Synthesis of Complex “Terpenoid-like” Heterocycles

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Abstract

A new catalytic synthesis of densely-substituted tetrahydroquinolines is described. This reaction forms up to two rings, three bonds, and three stereogenic centers with excellent stereo- and regiocontrol in a single step. Although control experiments demonstrate that the active catalyst is protic acid, $\text{Sc}(\text{OTf})_3$ serves as an effective and practical pre-catalyst. The scope of this reaction is demonstrated with 21 monocyclizations and 14 bicyclization reactions.

Introduction

Cyclization reactions of carbocations are powerful methods for the synthesis of fused polycyclic organic molecules.¹ After the proposed biosynthesis of steroids was elucidated,² Johnson employed polycyclization reactions in the synthesis of steroids and related carbocyclic structures.³ The strategy involves an initiating electrophile that produces a cationic center and terminating nucleophile, usually an alkene, alkyne or an electron-rich aromatic ring.

Subsequent initiators have included epoxides,⁴ halonium ions,⁵ episulfonium ions,⁶ tertiary carbocations (from alkene protonation⁷ or addition to an oxonium ion⁸), and vinyl cations formed by the mercuration⁹ or auration¹⁰ of alkynes. Similar frameworks can also be assembled via radical cascade reactions.¹¹ In spite of the wide use of this type of reaction to prepare polycyclic hydrocarbons, catalytic alkene cyclization reactions that produce heterocycles are less common than their all-carbon counterparts.^{7c,10,12–16} To date, there is a single example of a polycyclization that forms a complex nitrogen-based heterocycle from a halonium-ion induced reaction.¹⁷ Herein we report broadly applicable mono- and bicyclization reactions that form densely-substituted tetrahydroquinolines and related tricyclic analogs of diterpenoids (Figure 1).

As part of our continuing interest in the exploration and modification of natural products that mediate biological processes, we sought to develop a cyclization reaction that produces nitrogen-containing heterocyclic analogs of terpenoids with high diastereoselectivity and in high yield. In addition to the assembly of complex core structures, we were specifically interested in reactions that would enable the products to be used in subsequent reactions on the ring where the cyclization is initiated. With this goal in mind, we chose *N*-geranyl anilines appended with various protecting groups as our initial substrates and examined reactions that installed heteroatoms.

Results and discussion

Cyclizations using an electrophilic sulfur reagent (PhSOCH₃) developed by Livinghouse were well-suited to our substrates. Initial studies focused on the use of PhSOCH₃ in the presence of a Lewis acid. Although, efficient bicyclization was initially observed with four equivalents of BF₃•OEt₂, a single equivalent of Sc(OTf)₃ was found to be superior (Table 1, entry 1).¹⁸ Tricyclic product **12** was formed in high yield as a single diastereomer. X-ray crystallographic analysis of a crystalline derivative revealed that the stereochemistry of the product is in direct analogy to carbocyclization reactions that proceed through “chair-chair” conformations and lead to trans-fused products. Although the cyclization of **9** was optimized to proceed with a single equivalent of Sc(OTf)₃, catalysis was not observed with this Lewis acid or any others examined. Replacement of acetyl (Ac) with the less basic methanesulfonyl (Ms) group enabled the reaction to proceed in the presence of catalytic quantities of Sc(OTf)₃ (Table 1, entries 5 and 6). A control experiment with DTBP suggests that the true catalyst is protic acid produced by adventitious moisture (Table 1, entry 7). A scan of protic acids revealed the necessity of strong acids such as TfOH. Given the practical advantage of handling Sc(OTf)₃, we settled on this reagent as the catalyst of choice.^{19,20} Finally, replacement of Ms with Ns (**11**, Table 1 entry 11) enabled a high yield of cyclization product with the added flexibility of facile cleavage of this group. Related reactions with epoxygeranyl starting materials failed to produce cyclization products.

Monocyclization reactions also proceed in high yield. Initial experiments using the optimized conditions for **11** with substrate **15** (Scheme 1) produced acyclic compound **17** resulting from addition of methoxide to the episulfonium ion. Although the analogous acyclic product **16** was also formed with PhSeCl, a significant quantity of the desired cyclization product **18a** was also observed. Changing from dichloromethane to more polar solvents resulted in complete cyclization to form **18a** in 73% and 87% yields from acetonitrile and nitromethane, respectively. High reactivity was also observed with phenylselenium chloride (PhSeCl), producing **18b** from **15** in 78% yield in dichloromethane. The yield of cyclized product **18b** was 83% with the addition of NaSbF₆ as a chloride scavenger and was increased to 95% by switching to nitromethane as solvent.

Optimized cyclization conditions were effective for a variety of prenylated aniline substrates (Table 2). Electron-rich anilines, i.e. those with at least one alkoxy group in the para position to the reacting carbon center were cyclized in 68-88% yield. In the case of **29**, **30**, and **32** in which two possible regioisomers could be formed, only one detectable isomer was observed. Although an interaction between the fused cyclohexyl ring of **27** reduced the efficiency of the formation of **36**, the *meta* methyl groups of **25** did not negatively impact the formation of **34**, in which a quaternary carbon is added to the *ortho* position. Substitution with a single *meta* methyl group (**26**) resulted in efficient cyclization with modest regioselectivity. The origin of higher regioselectivity resulting from a more electron rich aromatic ring is not immediately obvious, given that the reactions were conducted at similar temperatures.

We next investigated the monocyclization reactions using various substituted alkenes (Table 3). Allyl substituted sulfonamide **37** was inert to cyclization with PhSeCl and cyclized in good yield with PhSeCl. *N*-Cinnamyl substrate **38** reacted smoothly to provide a single detectable diastereomer of **42** and the expected *anti*-configuration was confirmed by X-ray crystallography. Alkyl-substituted internal alkenes *E*- and *Z*-**39** exhibited lower overall reactivity when compared to phenyl-substituted **38**. Cyclization of *E*-**39** gave exclusively *anti*-products with both PhSeCl and PhSeCl. The analogous reaction of *Z*-**39** produced a mixture when treated with PhSeCl, suggesting that the intermediate selenonium ion undergoes isomerization faster than cyclization. The same cyclization mediated by PhSeCl proceeded with high diastereoselectivity to give *syn*-**44a**. Finally, installation of an allylic

stereogenic center completely controlled the formation of the two new stereogenic centers formed on cyclization of **40** to **45**.

The cyclization reaction exclusively forms 6-membered rings. Methallyl substrate **46**, which can conceivably form either 5- or 6-membered ring products, was subjected to the standard conditions (Scheme 2). Only starting material and small amounts of seleno-halogenation of the double bond were observed. In contrast, homoallylic substrate **47** resulted in exo-cyclization and produced tetrahydroquinoline **48** in high yield.

Optimized conditions for the monocyclization were employed in the bicyclization of geranylated aniline sulfonamides (Table 4). Overall, narrower substrate scope was observed and in nearly every case. PhSeCl as a mediator resulted in higher yields than PhSCl. Electron-rich substrates **49-51**, produced tricyclic compounds **57-59** in excellent yields. The less activated **52-54** were cyclized in 32-51% yield. In several cases (**60-63**), purification was complicated by co-elution of starting material and product, which was avoided by purifying after removing the nitrobenzenesulfonyl (Ns) group. A notable difference between the mono- and bicyclization reactions is the lack of regioselectivity in the latter relative to the former. Substrates **55** and **56** produce **63** and **64**, respectively, with little preference for attack at the *ortho* or *para* positions relative to the alkoxy groups.

Conclusions

In conclusion, we have developed the first catalytic alkene cyclization reaction mediated by sulfur- and selenium-based electrophiles that produces heterocycles. Monocyclization reactions proceed with high levels of diastereo- and regioselectivity. Excellent substrate control was observed when a substrate with an allylic stereogenic center was employed. Although bicyclization reactions also proceeded in high yield in many cases, the regioselectivity for attack of the aromatic ring was lower than that observed for monocyclization. This new method provides a superb platform for the synthesis of densely-substituted tetrahydroquinolines that should prove useful for the synthesis of natural products and nitrogen analogs of diterpenoids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1. (A) Densely-substituted tetrahydroquinolines in the core structures of natural products (**1** and **3**) and a synthetic analog of THC (**2**). (B) Electrophile-induced mono- and bicyclization reactions.

Scheme 1.

Optimization of Monocyclization Reactions Mediated by Sulfur and Selenium Electrophiles

Scheme 2.

Monocyclization reactions of methallyl- and homomethallyl-substrates

Table 1

Optimization of Sulfur-mediated Bicyclization

Entry	Substrate (R^1)	Conditions ^a	Yield
1	9 (Ac)	1.0 equiv $\text{Sc}(\text{OTf})_3$	90%
2	9 (Ac)	0.5 equiv $\text{Sc}(\text{OTf})_3$	44%
3	10 (Ms)	1.0 equiv $\text{Sc}(\text{OTf})_3$	0% ^b
4	10 (Ms)	0.3 equiv $\text{Sc}(\text{OTf})_3$	32% ^b
5	10 (Ms)	0.1 equiv $\text{Sc}(\text{OTf})_3$	52% ^b
6	10 (Ms)	0.1 equiv $\text{Sc}(\text{OTf})_3$ (0.02 M 10)	86% ^b
7	10 (Ms)	0.1 equiv $\text{Sc}(\text{OTf})_3$, 0.1 equiv DTBP, (0.02 M 10) ^c	0% ^b
8	10 (Ms)	0.05 equiv TfOH (0.02 M 10)	57% ^b
9	10 (Ms)	0.2 equiv $p\text{TSA}$ (0.02 M 10)	18% ^b
10	10 (Ms)	0.1 equiv Tf_2NH (0.02 M 10)	44% ^b
11	11 (Ns)	0.1 equiv $\text{Sc}(\text{OTf})_3$ (0.02 M 11)	89%

^aSubstrate concentration at 0.1 M unless otherwise noted

^bYield 20 calculated by HPLC with an internal standard curve

^cDTBP (di-*tert*-butyl-4-methylpyridine) was added as a Brønsted acid scavenger.

Table 2

Cyclization Reactions of Prenylated Anilines

<p>28a, 88% (X=S) 28b, 71% (X = Se)^a</p>	<p>29, 75% >95:5 regioselectivity</p>	<p>30, 84% >95:5 regioselectivity</p>
<p>31, 68%</p>	<p>32, 71% >95:5 regioselectivity</p>	<p>33 (X=S); 76%</p>
<p>34, 86%</p>	<p>35, 88% 77:23 regioselectivity</p>	<p>36, 60%^b</p>

^a Solvent was acetonitrile with 1.2 equivalent of NaSbF₆ added, ^b Yield over two steps after removal of Ns group with K₂CO₃/PhSH.

Table 3

Variation of Substitution in Cyclization Substrates

	R ¹	R ²	R ³
37, 41	H	H	H
38, 42	Ph	H	H
<i>E</i> -39, 43	<i>n</i> -Pr	H	H
<i>Z</i> -39, 44	H	<i>n</i> -Pr	H
40, 45	Ph	H	<i>n</i> -Bu

41-45a (X=S)
41,43-45b (X=Se)

41a, <10% (X=S)
41b, 69% (X = Se)

42, 98%; >95:5 dr

43a, (X=S); 50%, >95:5 dr
43b, (X=Se); 87%, >95:5 dr

44a, (X=S); 10%, >95:5 dr
44b, (X=Se); 50%, 65:35 dr

45a, 68%, (X=S) 80:20 dr^a
45b, 70%, (X=Se) >95:5 dr^a

^a Temperature was -20 °C.

^a Temperature was -20 °C.

Table 4

Bicyclization Reactions of Geranylated Anilines

11, 49-56

PhXCl (1.2 equiv)
 Sc(OTf)₃ (10 mol%)
 CH₃NO₂, -20 °C

14, 57-64

57a, 92% (X=S);
 57b, 94% (X=Se)

14a, 85% (X=S)
 14b, 84% (X=Se)

58, 80% (X=S)^a

59a, 53%^b (X=S)
 59b, 55%^b (X=Se)

60, 49%^b (X=S)

61, 32%^b (X=Se)

62, 51%^b (X=Se)

63a, 22%^b (X=S);
 76:24 regioselectivity
 63b, 70%^b (X=Se)
 61:39 regioselectivity

64a, 61% (X=S);
 52:48 regioselectivity
 64b, 72% (X=Se);
 55:45 regioselectivity

^a Mediator was PhSOCH₃ and loading of Sc(OTf)₃ was 25%, ^b Yield over two steps after removal of Ns group with K₂CO₃/PhSH.