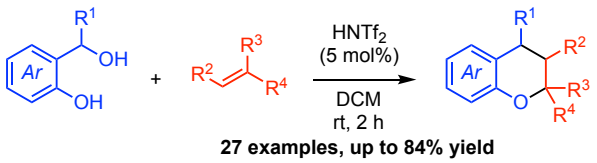
Synthesis of Chromanes by Triflimide-catalyzed Annulations of Benzylic Alcohols and Alkenes.

Jingyi Luo, Kayla G. Eichmann, Maria D. Guerrero, Kalli G. Koukounas, Weiwei Wang, Rebekah G. Reynolds, Monica Jones and Regan J. Thomson*

[1]Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208, USA.

Supporting Information Placeholder



ABSTRACT: The convergent synthesis of a series of chromane derivatives by a triflimide-catalyzed annulation of *o*-hydroxy benzylic alcohols with alkenes is reported. The reaction proceeds from simple starting materials under mild conditions and provides chromane products of varying substitution patterns.

The heterocyclic chromane motif, characterized by a benzene ring fused with a dihydropyran ring, is a substructure present in many natural products and bioactive molecules.[1-4] Notable examples of pharmaceuticals on the current market containing this substructure include the oral contraceptive ormeloxifene (**1**),[5] anti-diabetic and anti-inflammatory drug troglitazone (**2**),[6] anti-hypertension agent cromakalim (**3**),[7] and the beta-blocker nebivolol (**4**) (**Figure 1**).[8]

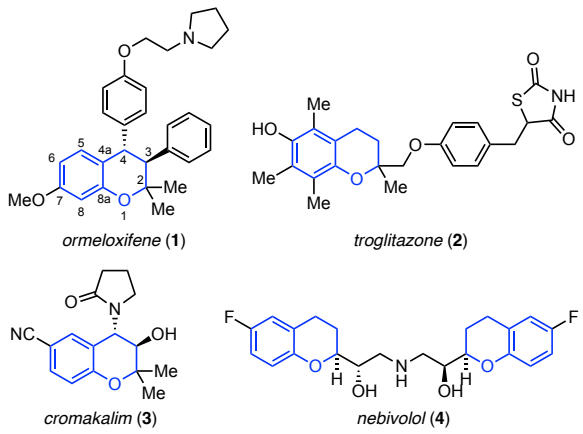


Figure 1. Representative examples of chromane-containing pharmaceuticals.

Synthetic approaches toward the synthesis of chromanes have exploited different disconnections of the benzopyran ring system.[9] Friedel-Crafts alkylation of a phenol is commonly used to form the C4a–C4 sp^2–sp^3 bond, and nucleophilic or electrophilic addition of the phenolic oxygen is utilized to close the dihydropyran ring (i.e., O1–C2).[10-12] Several studies have been published on the Lewis-acid catalyzed annulation of phenols and 1,3-dienes, which builds both the C4a–C4 and O1–C2 connections in tandem.[13-16] While many strategies utilize substrates derived from phenols, formation of the aryl C8a–O1 bond has been commonly achieved via metal-catalyzed C–O cross coupling.[17-18] Alternative strategies target the O1–C2 and C3–C4 bonds for disconnection, such as the hetero-Diels–Alder reaction of *o*-quinone methides[19-22] and the Baylis–Hillman reaction of salicyladehyde derivatives.[23] Generally speaking, approaches that allow for the convergent assembly of the core ring system from simple, readily available precursors are of the highest utility. Within this context, our lab had previously reported a method for the synthesis of indanes and tetralins from benzylic alcohol building blocks through a triflimide-catalyzed allyl silane annulation (**Figure 2a**).[24] These reactions proceeded by initial benzylic carbocation formation followed by allylsilane addition and subsequent ring closure by Friedel–Crafts alkylation, with the nature of the allylsilane controlling which product was formed.[24] In an effort to expand and further generalize this methodology, we reasoned that the same strategy could be applied to the synthesis of chromane derivatives by analogous reactions with *o*-hydroxy benzylic alcohol substrates (**Figure 2b**). In our envisioned cascade sequence, triflimide-catalyzed formation of the delocalized carbocation **10** (shown also as its quinone methide resonance structure **11**) would facilitate allylsilane addition to form the C3–C4 bond with a subsequent triflimide-catalyzed intramolecular cycloetherification of phenol **12** delivering the desired chromane structure (i.e., **13**). In 2015, Aoyama and coworkers reported the annulation of *o*-hydroxybenzhydrol substrates with alkenes generated from in situ dehydration of tertiary alcohols to synthesize a series of chromane derivatives, providing precedent for our proposed reaction pathway.[25]

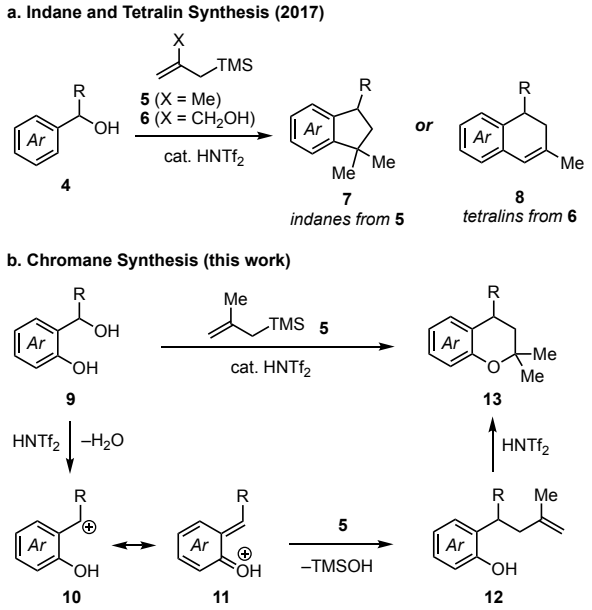


Figure 2. (a) Previously reported triflimide-catalyzed annulations for the synthesis of indanes and tetralins. (b) Analogous approach to chromanes reported herein.

We commenced our investigation by exploring the reaction of 2-(hydroxy(phenyl)methyl)phenol (**9**, R = Ph) with methallyltrimethylsilane (**5**) to deliver chromane **13a** (**Figure 3**). While nitromethane was used as the solvent in our prior method for the synthesis of indanes, we found that use of dichloromethane as the solvent afforded chromanes in comparable yields and with increased ease of workup. Thus, we were pleased to observe that 5 mol% triflimide successfully catalyzed the reaction of 2-(hydroxy(phenyl)methyl)phenol (**9**, R = Ph) with methallyltrimethylsilane (**5**) in dichloromethane at room temperature to form 2,2-dimethyl-4-phenylchroman (**4**) in 73% yield after two hours (**Figure 3**). We next proceeded to apply these conditions to the synthesis of a variety of 4-substituted chromanes (**Figure 3**). The aryl ring of the chromane substructure was able to tolerate various modifications to afford products in good yield, including those with electron-withdrawing or electron-donating properties (i.e., compounds **13a**–**13h**). We also experimented with the identity of the 4-substituent of the chromane nucleus (i.e., compounds **13i**–**13p**). Substrates with 4-aryl substituents bearing various functional groups (**13a**–**13k**) yielded the desired products in fair to good yield, whereas substrates with alkyl groups or no substituent at the 4-position (**13l**–**13o**) delivered the chromane product with a significant reduction in yield. This diminished efficiency is most likely due to the comparative instability of the benzyl cation intermediates and elimination side reactions. Supporting this hypothesis is the observation that alkynyl product **13p** is produced in high yield (81%).

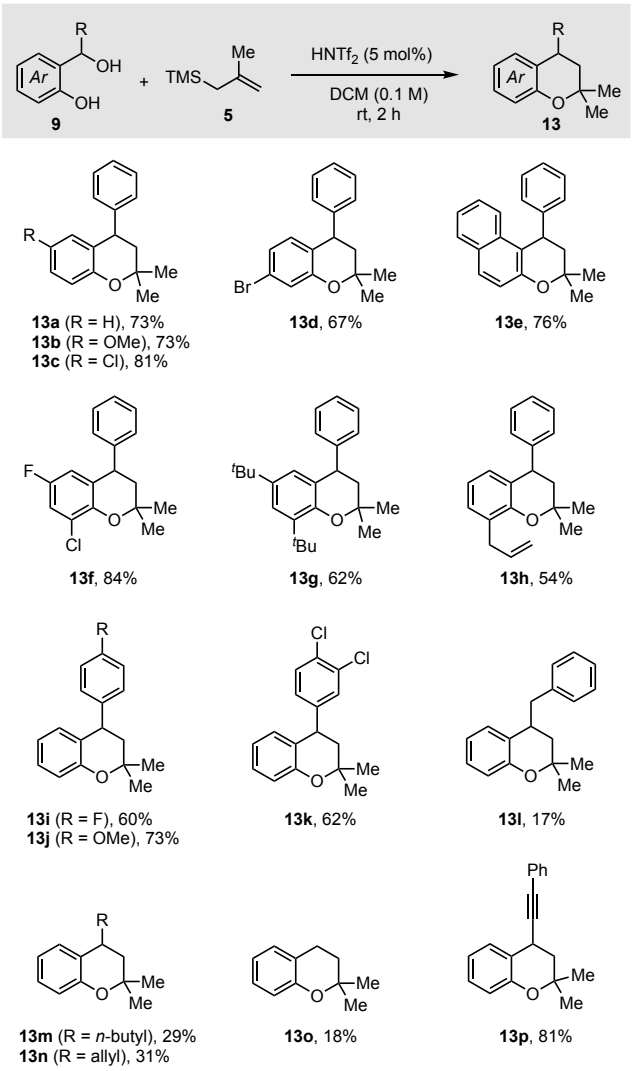


Figure 3. Chromane synthesis from methyallylsilane. Reported yields are of isolated product after flash chromatography.

We next attempted varying substituents of the allylsilane component (**Figure 4**). Chromane **15** was obtained from benzyl alcohol **9b** and 2-phenyl substituted silane (**14**) in fair yield, albeit as a 1.5:1 mixture of diastereomers (**Figure 4a**). Use of allylsilane **16**, however, resulted in the formation of isomeric chromane **20** as the unexpected major product. We suspected this product resulted from the addition of 2-methyl-1-butene (**18**), generated by *in situ* proteodesilylation of silane **16** (**Figure 4b**).[26] While it was disappointing that our initial silane-based approach did not lead to appreciable amounts of our desired product (i.e., **19**), the presumed productive addition of 2-methyl-1-butene (**24**) led us to attempt directly reacting 2-hydroxylbenzyl alcohol substrates with alkenes (**Figure 5**). Specifically, the use of 1-methylstyrene (**21**, R^2 = H, R^3 = Me, R^4 = Ph) gave rise to chromane products **22a**–**22d** in good yields, but again with expected low levels of relative stereocontrol. Of note, however, is the 80% yield obtained for aliphatic bearing products **22c** and **22d**, which stands in contrast to the lower yields obtained for related aliphatic products derived from methallylsilane **5** (i.e., compounds **13l** and **13m** in **Figure 3**). A reasonable explanation for this difference in efficiency might be that 1-methylsyrene is inherently more nucleophilic than silane **5** and adds to the initially formed

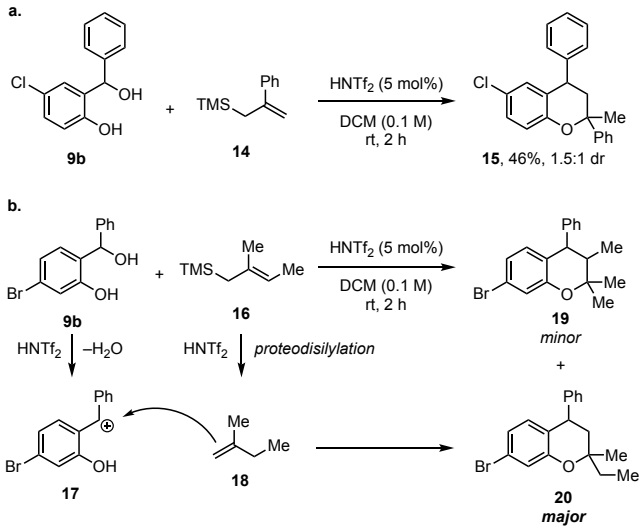


Figure 4. Reactions of different silane nucleophiles.

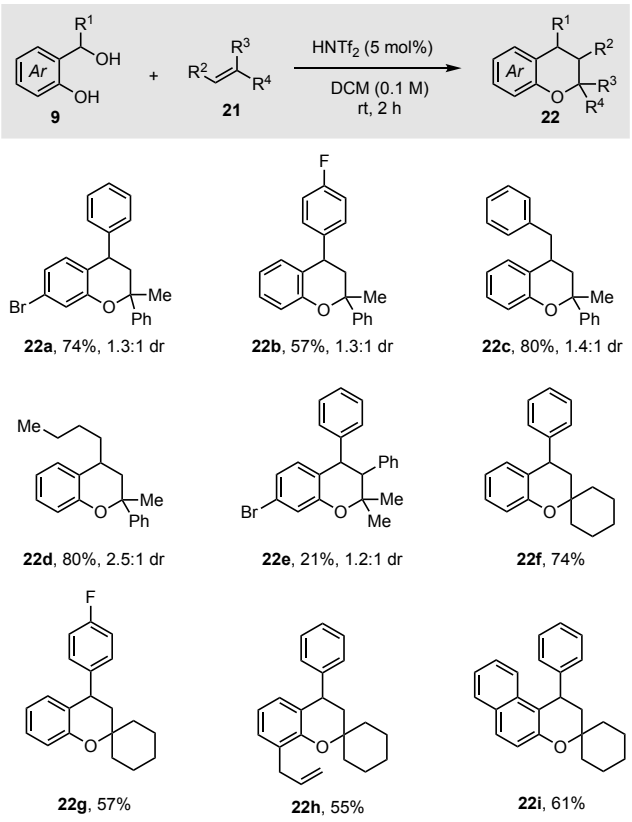


Figure 5. Chromane synthesis using alkenes. Reported yields are of isolated product after flash chromatography. Diastereomeric ratios determined by ^{1}H NMR spectroscopy.

unstable carbocation intermediate before it can decompose. Supporting this notion of reactivity impacting yields, we observed a low 21% yield of chromane **22e** derived from 2,2-dimethylstyrene (**21**, R^2 = Ph, $R^3 + R^4$ = Me) , whose addition is likely slowed by steric congestion leading to nonproductive decomposition pathways. In contrast, methylenecyclohexane (**21**, R^2 = H, R^3,R^4 = $-(CH_2)_5-$) proved to be an effective reaction partner, producing interesting spirocyclic chromanes **22f**–**22i** with good yields.

In summary, we have expanded our previous work on triflimide-catalyzed annulations of benzylic alcohols to access a variety of chromanes from simple starting materials. Reaction conditions are mild, require 5 mol% of a Bronsted acid and proceed at room temperature, and the substrates are easily accessible from the corresponding salicylaldehyde derivatives. We found that this method could be utilized with both allylsilanes, as in our previous work, and with widely available, inexpensive alkenes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Synthetic procedures and characterization data for new compounds (PDF)

Corresponding Author

* r-thomson@northwestern.edu.

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