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# A highly efficient enantioselective synthesis of 2-methyl chromans via four sequential palladium-catalyzed reactions

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**Abstract**—An enantioselective synthesis of substituted 2-methyl chromans was accomplished in four steps using four sequential Pd-catalyzed reactions. A study of the key palladium-catalyzed regioselective aryl ether ring formation of two different substrates was also carried out to better understand the factors which affect the selectivity of the reaction.
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Chiral substituted 2-methyl chromans are found in numerous pharmaceutically active compounds including vitamin E (anti-oxidant),[1] clusifoliol (anti-tumor),[2] rhododaurichromanic acid A (anti-HIV),[3] siccanin (anti-fungal),[4] and troglitazone (diabetes).[5] Consequently, chiral 2-methyl chromans are considered high value targets in medicinal chemistry. Chiral 2-methyl chromans have also been used as chiral dopants for nematic liquid crystals.[6] Hence, the development of an efficient and reliable asymmetric synthesis of 2-methyl chromans would find significant application.

Recently, Trost et al. have developed an elegant asymmetric allylic alkylation (AAA) process for the preparation of chiral chromans.[7] The methodology involves an intramolecular Pd-catalyzed AAA reaction of a phenol onto a pendant allyl carbonate to form the chroman ring. The methodology was applied to the total synthesis of (+) clusifoliol, (−) siccanin, and the core of vitamin E.[8] Other recent methods for preparation of chiral chromans include the use of resolved chroman carboxylic acids,[9] intermolecular Mitsunobu reactions between 2-bromophenols and chiral halopropanols,[10] enzymatic desymmetrization of an achiral chroman derivative,[11] and the stereoselective intramolecular 1,3-dipolar nitrone cycloaddition[12] (Fig. 1).

In our approach to developing an asymmetric synthesis of 2-methyl chromans, we wanted to design the synthesis around a target molecule which contains a readily reactive functional group. This functional group could not only be easily transformed to other functional groups via traditional functional group manipulation, but could also serve as a point of connection for incorporation into the synthesis of biologically active molecules, thus substantially increasing the usefulness of this methodology. These traits along with our own drug development needs resulted in the identification of chiral chroman **1** as our initial target.

Our retrosynthetic approach is shown in Scheme 1. We envisioned that chiral chroman **1** can be made from its acyclic diol **2** via Pd-catalyzed ring closing aryl ether formation. Buchwald and co-workers recently described three examples of a Pd-catalyzed cyclization of aryl bromides containing a pendant diol.[13] These substrates contained a secondary alcohol that can cyclize to a six-membered heterocycle and a primary alcohol that can cyclize to a seven-membered heterocycle. In all three cases, the six-membered heterocycle was formed exclusively. In our case, however, the competition is between a congested tertiary alcohol to form a six-membered heterocycle and a primary alcohol to from a seven-membered heterocycle.

While it is clear that formation of the six-membered heterocycle should be more favorable relative to the seven-membered heterocycle, it is unclear whether the sterically congested tertiary alcohol would be more or less reactive than the primary alcohol. The acyclic diol **2** can be prepared from the hydrogenated Heck product of the Pd-catalyzed Heck reaction between 1-bromo-chlorobenzene and the chiral allylic diol **5**. The chiral

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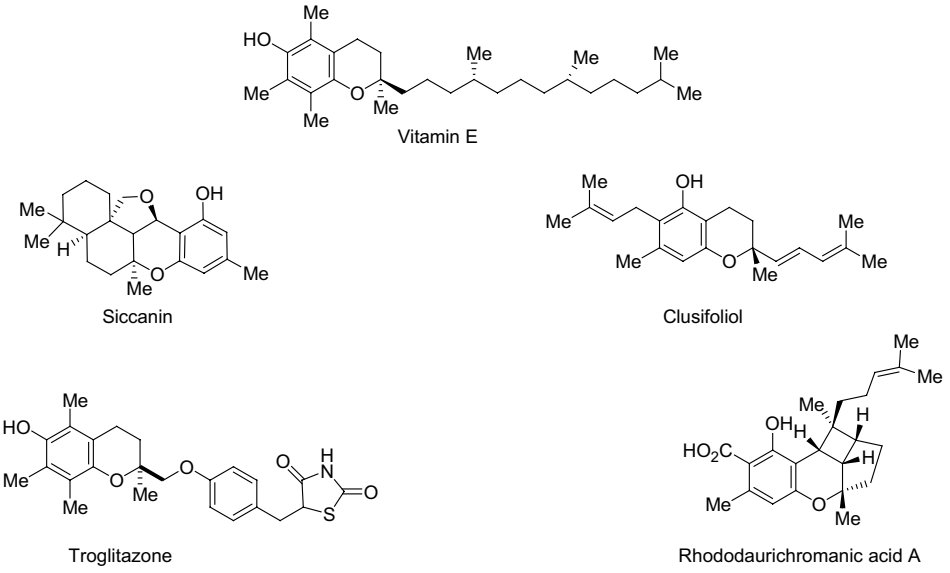



**Figure 1.** Vitamin E, siccanin, clusifoliol, troglitazone, and rhododaurichromanic acid A.

allylic diol **5** can be obtained from ring opening of racemic methyl vinyl oxirane using Trost's Pd-catalyzed dynamic kinetic asymmetric transformation.[14]

The synthesis of cyclization substrate **2** starts with the preparation of chiral butene diol **5** (Scheme 2). Following the procedure of Trost et al., racemic methyl vinyl oxirane was converted to **5** in 96% ee and in 60% isolated yield. The palladium-catalyzed procedure was carried out according to Trost's protocol without incident. The palladium-catalyzed Heck reaction with **4** using $Pd(OAc)_2/P(o\text{-tolyl})_3$ provided styrene derivative **3** in 84% isolated yield. Reduction of the double bond was accomplished using catalytic 5% Pd/C under a $H_2$ atmosphere to give **2** in 83% isolated yield (Fig. 2).

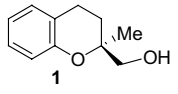
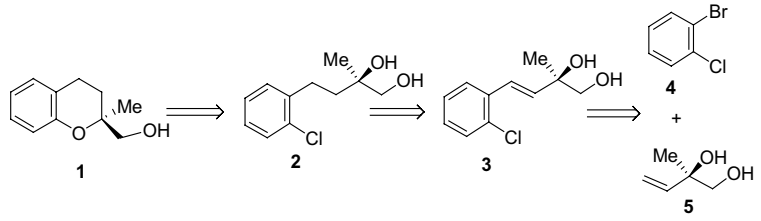
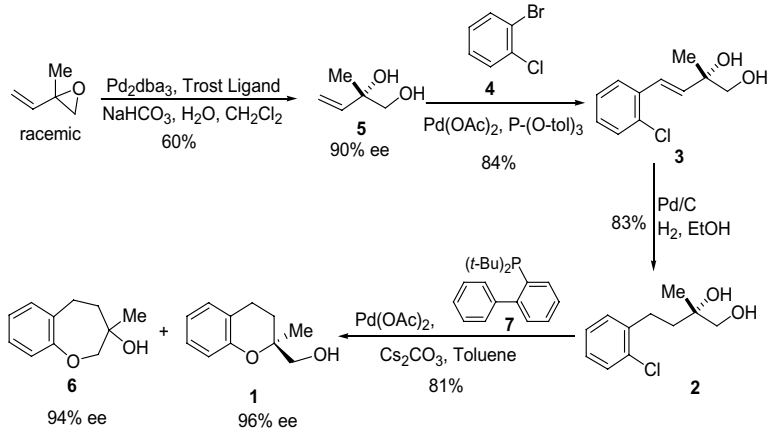


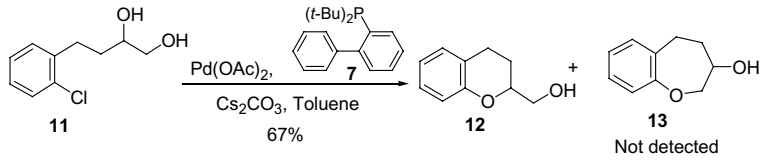
**Figure 2.** Chroman **1**.



**Scheme 1.** Retrosynthesis of **1**.



**Scheme 2.** Asymmetric preparation of **1**.




**Scheme 3.** Pd-catalyzed ring closing reaction of an analogous substrate.

Cyclization of **2** was carried out using the Buchwald procedure employing $Pd(OAc)_2$/ligand **7**.[15,16] Using $Cs_2CO_3$ as base and toluene as solvent, an 81% isolated yield of a 86:14 ratio of **1**:**6** was obtained at 90 °C.[17,18] Chiral HPLC analysis of the mixture showed **1** to be 96% ee and **6** to be 94% ee.[19] The regioisomeric products were not separable by silica gel chromatography, however, preparative HPLC separation gave a 64% overall isolated yield of chroman **1** (>99% ee) from substrate **2**, and a 13% overall isolated yield of heterocycle **6** (>99% ee). Reducing the reaction temperature to 70 °C resulted in an 88:12 ratio of **1**:**6**, whereas at 50 °C, <10% starting material conversion was observed.[20]

The observed 88:12 ratio of **1**:**6** can be rationalized in two ways.[21] First, formation of **1** over **6** is favored based on the propensity for forming a seven-membered intermediate palladacycle **9** versus an eight-membered palladacycle **10** (Fig. 3). The larger ground state population of **9** versus **10** results in formation of the six-membered ring product versus the seven-membered ring product. By contrast, one can also argue that the palladacycle resulting from coordination of a tertiary alcohol would reductively eliminate faster compared to a palladacycle resulting from coordination of a primary alcohol in order to minimize steric interactions in the coordination sphere of palladium.[22] It has been shown that increasing the steric environment in the Pd-coordination sphere of complexes of the type Pd(OR)(Ar)L facilitates reductive elimination to form the aryl ether bond.[23] Even though palladacycle **9** may be lower in ground state energy than **10**, if palladacycles **9** and **10** are in fast and reversible equilibrium, Curtin–Hammett dictates that the population of **9** and **10** are irrelevant and that the activation energy to product will be the controlling factor in the product distribution.

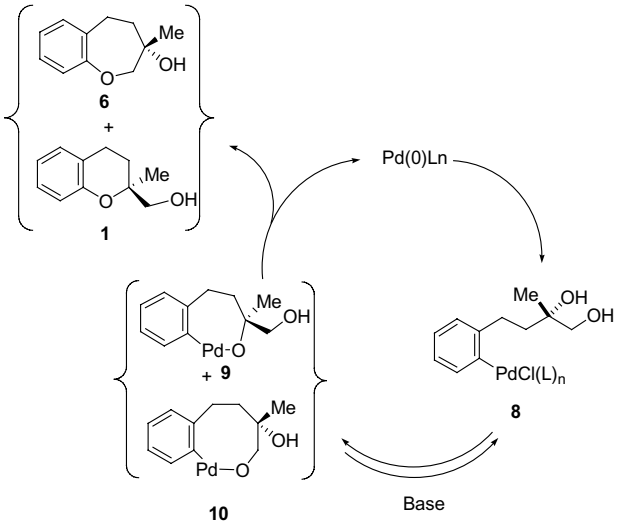



**Figure 3.** Catalytic cycle for the Pd-catalyzed aryl ether formation.

To further evaluate the factors that influence the selectivity of this cyclization reaction, substrate **11** was prepared and evaluated (Scheme 3). Substrate **11** was prepared via Heck reaction of 2-bromochlorobenzene with 3,4-butene diol, followed by hydrogenation. Using the exact conditions used for the cyclization of **2**, it was found that substrate **11** cyclized to provide **12** as the sole product. Secondary alcohol **13** was not detected by $^1H$ NMR or HPLCMS of the crude reaction mixture.[24] Primary alcohol **12** was independently prepared from chroman-2-carboxylic acid via formation of the ethyl ester followed by DIBAL reduction.[25]

The higher selectivity observed for the formation of the six-membered heterocycle with substrate **11** compared to substrate **2** suggest that steric factors influence product distribution. Cyclization of a tertiary alcohol to form a six-member ring is highly favored over cyclization of a primary alcohol to form a seven-member ring. By comparison, cyclization of a secondary alcohol to form six-member rings is exclusively favored over cyclization of a primary alcohol to form seven-member rings.

In summary, a novel, efficient, and highly selective method for the preparation of chiral 2-methyl chromans has been developed. The method involves four sequential palladium-catalyzed reactions. The palladium-catalyzed aryl ether synthesis of an aryl chloride with a pendant diol was carried out in good selectivity and yield. Investigation of a second substrate confirms that the steric environment adjacent to the alcohol can influence the selectivity in the ring closing reaction.

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17. The 81% yield corresponds to the average of three runs.
18. Chroman **1**: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.08–7.13 (m, 2H), 6.82–6.88 (m, 2H), 3.60–3.74 (m, 2H), 2.76–2.89 (br m, 2H), 2.01–2.09 (m, 2H), 1.72–1.77 (m, 2H), 1.29 (s, 3H). $^{13}$C NMR 153.5, 129.5, 127.4, 121.1, 120.1, 117.2, 76.5, 69.2, 27.2, 21.7, 20.1. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.14; H, 7.98.
19. SFC HPLC method: Chiralpak AD-H (250 × 4.6 mm), 4% MeOH/$CO_2$ for 4 min, ramp 2% per min to 40% MeOH/$CO_2$, hold 3 min, flow = 1.5 mL/min, 200 bar, 35 °C, 25 min, 210 nm. **6**, ret = 12.71 min; **6-ent**, ret = 13.41 min; **1**, ret = 14.07 min; **1-ent**, ret = 14.75 min.
20. Chroman **1** was independently prepared from chroman-2-carboxylic acid via esterification to the ethyl ester, α-alkylation with methyl iodide, and reduction of the ethyl ester to the corresponding alcohol using DIBAL.
21. One possible explanation for the observed selectivity is the potential for palladacycle **10** to β-hydrogen eliminate to provide an aldehyde product. NMR of the crude reaction mixture showed no aldehydic resonances and in fact showed clean reaction to the product heterocycles.
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24. Assuming 95% accuracy by $^1$H NMR, the selectivity of this cyclization step is at least 95:5.
25. Chroman **12**: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.06–7.13 (m, 2H), 6.842–6.89 (m, 2H), 4.12–4.16 (m, 1H), 3.86 (dd, 1H, $J$ = 11.7 and 3.4 Hz), 3.78 (dd, 1H, $J$ = 11.7 and 6.3 Hz), 2.91 (dd, 1H, $J$ = 16.4 and 6.3 Hz) 2.81 (dd, 1H, $J$ = 16.4 and 2.8 Hz), 2.14 (br s, 1H), 1.95–2.012 (m, 1H), 1.82–1.93 (m, 1H). $^{13}$C NMR 154.5, 129.6, 127.3, 121.9, 120.4, 116.7, 76.4, 65.6, 24.5, 23.1. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.23; H, 7.37.