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Efficient Enantioselective Synthesis of 3-Aminochroman Derivatives Through Ruthenium-Synphos Catalyzed Asymmetric Hydrogenation

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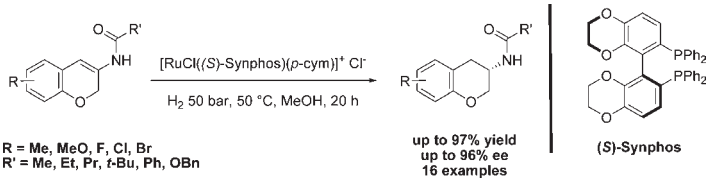
ABSTRACT



A highly enantioselective asymmetric hydrogenation of various trisubstituted enamides derived from chroman-3-ones promoted by cationic Ru-Synphos catalysts is reported. This atom-economical and clean method provides an efficient route to optically active 3-aminochroman derivatives, which are important pharmacophores found in numerous drug candidates, in high chemical yields and enantiomeric excesses up to 96%.

The 3-aminochroman moiety **I** (3,4-dihydro-3-amino-2*H*-1-benzopyrans) is an important structural unit that can be found in numerous pharmaceutical drug candidates used for the treatment and/or prevention of neuropsychiatric disorders, neurodegenerative disorders, pain, and sexual dysfunction.[1] Representative examples of this important class of compounds include Robalzotan (NAD-299)[2] and Alnespirone ((+)-S20499),[3] which display very high affinity and good selectivity for the 5-HT_{1A} serotonin receptor and are today under clinical development for the treatment of anxiety and depression (Figure 1). Compound **II** is a potent, nontoxic, and peripherally selective inhibitor of dopamine-β-hydroxylase, which can be used for the treatment of certain cardiovascular disorders such as hypertension and chronic heart failure.[4]

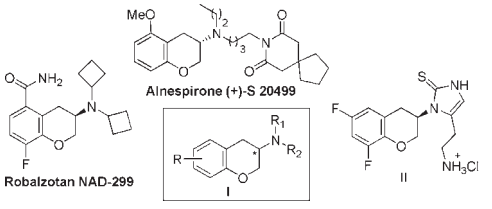


Figure 1. Structure of biologically active compounds containing the 3-aminochroman moiety **I**.

However, despite the obvious practical potential of aminochroman derivatives, only limited success has been achieved for the synthesis of the pharmaceutically interesting 3-aminochroman moiety **I**. To date, the most

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commonly used approach relies on the resolution of racemic mixtures of **I** through diastereomeric salt formation.[1,5] Viaud-Massuard and Guillaumet et al.[6] have described the preparation of 3-aminochroman derivatives by radical cyclization using L-serine derivatives as chiral starting materials. Although excellent enantioselectivity up to 99% was obtained, this route has some disadvantages that limit its practicality, such as the use of a large excess of highly toxic tin reagent combined with a long reaction sequence. In addition, this method remains essentially restricted to 5-substituted-3-aminochroman derivatives. In 2010, Sachetti et al.[7] reported a biocatalytic approach resulting in the synthesis of the (*R*)-5-methoxy-3-aminochroman, a key precursor to the antidepressant drug Robalzotan with a moderate ee of 51%. Consequently, the development of catalytic enantioselective methods that would allow practical access to the 3-aminochroman moiety, with high selectivity, is highly desirable. Asymmetric hydrogenation[8] of trisubstituted enamides derived from chromanone derivatives[9] would be the most atom-economical approach to these molecules. As far as asymmetric hydrogenation of enamides derived from 3-chromanone is concerned, and to the best of our knowledge, only rare examples of such an approach have been described in the literature. Bruneau, Dixneuf et al.[10] reported low to high ee values, ranging from 5 to 92%, for the asymmetric hydrogenation of some ene carbamate[10a] and enamide[10a,b] derivatives using Ru-based catalysts with a substrate scope mostly limited to the synthesis of 5-methoxy-3-aminochroman as a model substrate. Recently, one additional example concerning the enantioselective synthesis of (*R*)-6,8-difluorochroman-3-ylamine has been revealed in a patent using Ru- and Rh-complexes with enantioselectivities from 5 to 93% ee.[11] In connection with our ongoing research program toward the use of metal-catalyzed asymmetric hydrogenation for the synthesis of biologically relevant active compounds,[12] we report herein the efficient enantioselective synthesis of various 3-aminochroman derivatives **2** through ruthenium-Synphos catalyzed asymmetric hydrogenation of trisubstituted enamides **1** derived from chroman-3-ones.

We preliminarily screened a series of cationic ruthenium complexes in the asymmetric hydrogenation of the readily available *N*-acetyl enamide **1a**[10] as a model substrate. Four atropisomeric diphosphine ligands, including the milestone (*S*)-Binap **L1**,[13] and the (*S*)-MeO-Biphep **L2**[14] as well as the (*S*)-Synphos **L3**,[15] and the (*S*)-Difluorphos **L4**[16] developed in our group, were employed in this study. Initial hydrogenation experiments were conducted at 50 bar of hydrogen pressure and 50 °C in methanol with 1 mol % of Ru-catalyst for 20 h. The results depicted in Table 1 clearly showed that the stereochemical outcome of the reaction was strongly dependent on the nature of the complexes used. Indeed, the *in situ* generated $RuBr_2$ [diphosphine] catalysts were prepared according to our convenient procedure,[17] by mixing Ru(cod)(η^3-methylallyl)$_2$ with the required diphosphines in the presence of methanolic hydrobromic acid, which gave the 3-aminochroman derivative **2a** in moderate to good yields and selectivities ranging from 61 to 78% ee (Table 1, entries 1−4, 44−82% yields). Similar catalytic activity was achieved with the cationic monohydride ruthenium

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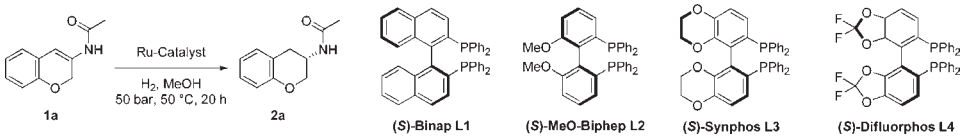
Table 1. Ruthenium Catalyzed Asymmetric Hydrogenation of Chromanone **1a**[a]



entry	Ru-catalyst	conversion (%)[b]	yield (%)[c]	ee (%)[d]
1	Ru(cod)(η^3-Methylallyl)$_2$ + (*S*)-Binap **L1** + HBr (2.2 equiv)	80	75	74
2	Ru(cod)(η^3-Methylallyl)$_2$ + (*S*)-MeO-Biphep **L2** + HBr (2.2 equiv)	82	78	78
3	Ru(cod)(η^3-Methylallyl)$_2$ + (*S*)-Synphos **L3** + HBr (2.2 equiv)	84	82	76
4	Ru(cod)(η^3-Methylallyl)$_2$ + (*S*)-Difluorphos **L4** + HBr (2.2 equiv)	54	44	61
5	Ru(cod)(η^3-Methylallyl)$_2$ + (*S*)-Binap **L1** + HBF_4 (1.1 equiv)	78	71	77
6	Ru(cod)(η^3-Methylallyl)$_2$ + (*S*)-MeO-Biphep **L2** + HBF_4 (1.1 equiv)	84	76	78
7	Ru(cod)(η^3-Methylallyl)$_2$ + (*S*)-Synphos **L3** + HBF_4 (1.1 equiv)	86	70	80
8	Ru(cod)(η^3-Methylallyl)$_2$ + (*S*)-Difluorphos **L4** + HBF_4 (1.1 equiv)	43	38	72
9	{[RuCl((*S*)-Binap **L1**)]$_2$(μ-Cl)$_3$}$^-$[NH_2Me_2]$^+$	98	86	79
10	{[RuCl((*S*)-MeO-Biphep **L2**)]$_2$(μ-Cl)$_3$}$^-$[NH_2Me_2]$^+$	>99	88	81
11	{[RuCl((*S*)-Synphos **L3**)]$_2$(μ-Cl)$_3$}$^-$[NH_2Me_2]$^+$	>99	93	83
12	{[RuCl((*S*)-Difluorphos **L4**)]$_2$(μ-Cl)$_3$}$^-$[NH_2Me_2]$^+$	92	86	78
13	[RuCl((*S*)-Binap **L1**)(*p*-cym)]$^+$Cl$^-$	94	90	72
14	[RuCl((*S*)-MeO-Biphep **L2**)(*p*-cym)]$^+$Cl$^-$	>99	88	74
15	[RuCl((*S*)-Synphos **L3**)(*p*-cym)]$^+$Cl$^-$	>99	96	84
16	[RuCl((*S*)-Difluorphos **L4**)(*p*-cym)]$^+$Cl$^-$	90	85	77

[a] All reactions were performed using 1 mmol of substrate **1** in methanol for 20 h, at 50 °C and 50 bar with 1 mol % of Ru-catalyst. [b] Determined by ^{1}H NMR of the crude product. [c] Isolated yield after flash chromatography. [d] Determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC). Absolute configuration was determined to be *S* by comparison of the specific rotation with reported data.

complex [Ru(H)(η^6-cot)Diphosphine]$^+BF_4^-$, which was previously successfully used for the industrial synthesis of (+)-*cis*-methyldihydrojasmonate[18] (entries 5−8, 38−76% yields, and 72−80% ee). When the reaction was carried out with the preformed dimeric [{RuCl((*S*)-Diphosphine)}$_2$(μ-Cl)$_3$]$^-$[NH_2Me_2]$^+$ complexes (entries 9−12) or the cationic [RuCl{(*p*-cym)(*S*)-Diphosphine}]$^+$Cl$^-$ catalysts (entries 13−16), a significant increase in terms of both conversions and yields was observed. With these catalytic systems, the selectivity of the reaction proved to be sensitive to the nature of the diphosphine used, since, among all the ligands tested, the electron-rich Synphos[15] ligand **L3** gave the higher enantioselectivity, with 83% and 84% ee, respectively (entries 11 and 15). Finally, from this initial screening, the cationic [RuCl{(*p*-cym(*S*)-Synphos}]$^+$Cl$^-$ complex emerged as the best catalyst, providing the 3-aminochroman product **2a** in more than 99% conversion and 96% isolated yield, with an encouraging enantiomeric excess of 84% (Table 1, entry 15).

With this encouraging result in hand, we next studied the effects of the solvent, temperature, and hydrogen pressure using 1 mol % of the [RuCl{(*p*-cym)(*S*)-Synphos}]$^+$Cl$^-$ catalyst. As outlined in Table 2, the reaction could be performed in all solvents examined, either protic or aprotic, providing the hydrogenated product **2a** in good to excellent yields, ranging from 83 to 96%. Polar solvents tend to give higher enantioselectivities (Table 2, entries 1−4, 79−84% ee) than nonpolar solvents (entries 5−8, 73−77% ee), the most efficient one being methanol, which allowed the isolation of the 3-aminochroman derivative **2a** in 96% yield and 84% ee (entry 1). The data in Table 2 also illustrated that a substantial change in hydrogen pressure and reaction temperature did not significantly affect the stereochemical outcome of the reaction, since excellent catalytic activity was still maintained (Table 2, entries 9−12, 94−96% yields, and 82−84% ee). Through these screenings, the best reaction conditions for asymmetric hydrogenation of **1a** were therefore set as the following: 1 mol % of [RuCl{(*p*-cym)(*S*)-Synphos}]$^+$Cl$^-$ as catalyst, methanol as solvent, under 50 bar of H_2 at 50 °C for 20 h.

Next, we evaluated the possibility of extending the scope of this transformation. Toward this end, several enamide derivatives were prepared according to known procedures[19] and subsequently hydrogenated under our optimized reaction conditions (Table 3). In most cases, substrates **1a**−**p** were fully converted to their corresponding 3-aminochroman derivatives **2a**−**p** in high isolated yields and good to excellent enantioselectivities up to 96%. As shown in Table 3, both reactivity and enantioselectivity were influenced by the nature of the amide moiety. Indeed, when comparing the results obtained with the *N*-acetyl enamide **1a**, the hydrogenation of enamides **1b**−**e** bearing an Et, Pr, *t*-Bu, and Ph group provides the hydrogenated products **2b**−**e** in lower enantioselectivities ranging from 76 to 80% (Table 3, compare entry 1 vs entries 2−5). A lower catalytic activity was observed for the hydrogenation of the

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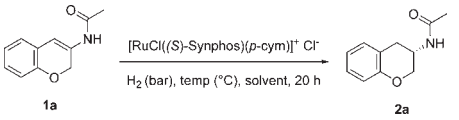
ene benzyl carbamate **1f**, probably as a result of electronic and steric factors (Table 3, entry 6).

Table 2. Optimization of the Reaction Conditions for Asymmetric Hydrogenation of **1a**[a]



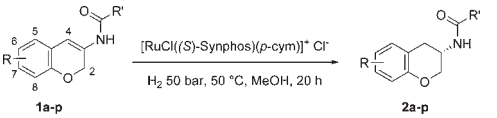
entry	solvent	temp (°C)	*P* (bar)	conv (%)[b]	yield (%)[c]	ee (%)[d]
1	MeOH	50	50	>99	96	84
2	EtOH	50	50	>99	96	80
3	*i*-PrOH	50	50	>99	93	79
4	EtOAc	50	50	>99	91	79
5	CH_2Cl_2	50	50	>88	83	73
6	THF	50	50	>93	89	77
7	1,4-dioxane	50	50	>99	93	76
8	toluene	50	50	>99	92	77
9	MeOH	70	50	>99	95	83
10	MeOH	30	50	>99	94	83
11	MeOH	50	70	>99	96	84
12	MeOH	50	20	>99	94	82

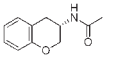
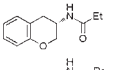
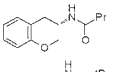
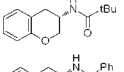
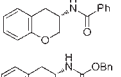
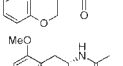
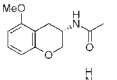
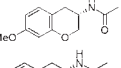
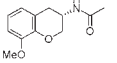
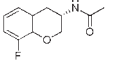
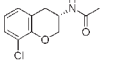
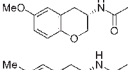
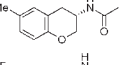
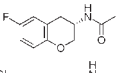
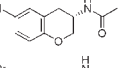
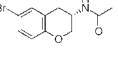
[a] All reactions were performed using 1 mmol of substrate **1a** with 1 mol % of Ru-catalyst. [b] Determined by ^{1}H NMR of the crude product. [c] Isolated yield after flash chromatography. [d] Determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC).

The data of Table 3 also revealed that the selectivity of the reaction was strongly dependent on the substitution pattern of the aromatic ring. A modest enantioselectivity of 34% was preliminarily obtained with the 5-methoxy substituted enamide **1g**, which was in agreement with the results of Bruneau, Dixneuf et al.[10] (Table 3, entry 7). This result could be attributed to the unfavorable steric hindrance between the *ortho*-substituted group of the substrate and the catalyst during the reaction. A better enantiofacial discrimination up to 74% was observed for the 7-methoxy substituted substrate **1h** (Table 3, entry 8). Pleasingly, for 8-substituted enamides **1i**–**k**, the desired products **2i**–**k** were obtained in excellent yields and selectivities, irrespective of the nature of the substituents, although electron-withdrawing groups tend to give slightly higher enantioselectivities compared to electron-donating groups (Table 3, entries 9–11, 92–97% yields, 91–93% ee). The same trend was observed for the reduction of enamides **1l**–**p**. Indeed, although the yields were essentially the same, the selectivity was influenced by the substituents of the phenyl ring, with higher enantioselectivities being obtained with an electron-withdrawing group (Table 3, entries 12–16, 92–95% yields, 91–96% ee).

In conclusion, we have successfully achieved the first general and efficient enantioselective Ru-Synphos catalyzed asymmetric hydrogenation of readily available trisubstituted enamides derived from 3-chromanones. This atom-economical protocol offers several advantages, including operational simplicity, high chemical yields, and enantioselectivities. This makes it a useful and attractive strategy for the preparation of the important 3-aminochroman moiety. Application to the synthesis of pharmaceutically active products is underway and will be reported in due course.

Table 3. Asymmetric Hydrogenation of Substrates **1a**–**p**[a]



entry		product	yield (%)[b]	ee (%)[c]
1	**2a**		96	84
2	**2b**		93	80
3	**2c**		92	77
4	**2d**		88	80
5	**2e**		91	76
6	**2f**		60	40
7	**2g**		85	34
8	**2h**		91	74
9	**2i**		93	91
10	**2j**		97	92
11	**2k**		92	93
12	**2l**		94	91
13	**2m**		95	91
14	**2n**		95	94
15	**2o**		93	95
16	**2p**		92	96

[a] All reactions were performed using 1 mmol of substrate **1** with 1 mol % of Ru-catalyst. In all cases, complete conversions were achieved. [b] Isolated yield after flash chromatography. [c] Determined by chiral stationary phase HPLC analysis or by chiral stationary phase-supercritical fluid chromatography (CSP-SFC) (see Supporting Information).

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via Internet at http://pubs.acs.org.