Organic Letters
Letter
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Diversity-Oriented Asymmetric Catalysis (DOAC): Stereochemically Divergent Synthesis of Thiochromanes Using an Imidazoline–Aminophenol–Nickel-Catalyzed Michael/Henry Reaction

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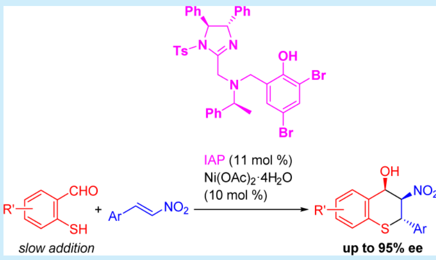
Supporting Information

ABSTRACT: The (*S*,*S*)-diphenylethylenediamine-derived imidazoline–aminophenol–Ni complex catalyzed tandem asymmetric Michael/Henry reaction of 2-mercaptobenzaldehydes with β-nitrostyrenes to give the corresponding (2*S*,3*R*,4*R*)-2-aryl-3-nitrothiochroman-4-ols in up to 99% diastereoselectivity with 95% ee was demonstrated in diversity-oriented asymmetric catalysis. Reduction of the nitro group of the chiral thiochromanes gave a new series of (2*S*,3*R*,4*R*)-3-amino-2-arylthiochroman-4-ols with retention of the stereoselectivity.



Chromane moieties are often found in various biologically significant compounds isolated from nature. The biological activity of these compounds following the replacement of the oxygen atom in the chromane group with sulfur to form thiochromanes has been studied with regard to research and development of pharmaceuticals.[1] As an example, the thiochromane derivative **1** is the sulfur analogue of benzopyranoxazine (PD 128907) and was developed as a dopamine D_3 receptor-selective agonist (Figure 1).[2] In addition, the anti-AIDS agent 7-thia-DCK (**2**) represents an advanced analogue of the compound suksdorfin, which is isolated from *Lomantium suksdorfii*.[3] Finally, the conformationally restricted rivastigmine analogue **3** was designed and synthesized as an acetylcholinesterase (AChE) inhibitor for the treatment of Alzheimer's disease.[4] Because the biological activities of such compounds are greatly affected by the spatial conformations of the thiochromane group, significant effort has been devoted to synthesizing specific thiochromane enantiomers. Both resolution chemistry[5] and enantioselective reduction[6] have been applied during the catalytic asymmetric synthesis of thiochromanes with the aim of generating products having a monostereogenic center.[7] Considering the significance of the molecular structure of pharmaceutical compounds, it is vital to control the isomerism of multiple stereogenic centers when synthesizing thiochromanes. For this reason, the use of a tandem, one-pot reaction process that generates multiple σ-bond represents a promising means of achieving the desired structural tuning.[8]

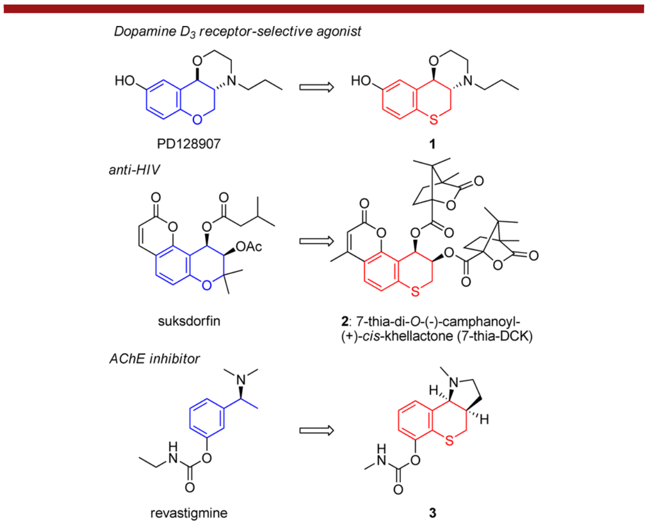


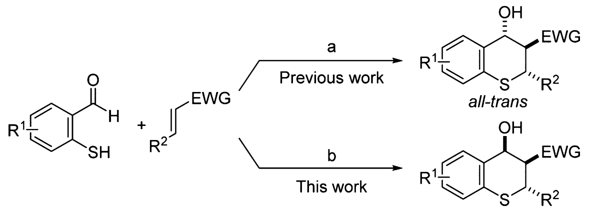
Figure 1. Examples of thiochromane groups in pharmaceutical compounds.

After reporting the first-ever Michael/aldol/dehydration cascade reaction of 2-mercaptobenzaldehydes with α,β-unsaturated aldehydes using a pyrrolidine silyl ether catalyst,[9] Wang et al. succeeded in the Michael/aldol reaction of 2-mercaptobenzaldehydes with α,β-unsaturated oxazolidinones to give the corresponding 2,3,4-trisubstituted thiochromanes with *all-trans* configurations.[10] In 2008, Zhao et al. reported the tandem asymmetric Michael/Henry reaction of 2-mercaptobenzaldehydes with β-nitrostyrenes. This reaction sequence was catalyzed by cupreine and generated *all-trans* 2,3,4-trisubstituted thiochromanes (Scheme 1a).[11−13]

With the aim of constructing molecules with contiguous multiple stereogenic centers in diversity-oriented asymmetric catalysis (DOAC),[14] we initially developed an imidazoline–aminophenol (IAP)–metal catalyst capable of promoting tandem reactions.[15] The IAP–Cu and IAP–Ni catalyst enabled the first-ever tandem Friedel–Crafts/Henry reaction[15b] and Michael/Mannich reaction[15d,e] using nitroalkenes, respectively.

Received: February 5, 2014
Published: March 6, 2014

Scheme 1. Stereochemically Divergent Synthesis of Substituted Thiochromanes



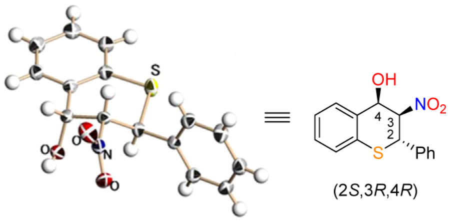


Figure 2. Molecular structure of **6a** as determined by X-ray crystallographic analysis.

Based on this IAP–metal catalyst system, we now report the Michael/Henry reaction of 2-mercaptobenzaldehydes with *β*-nitrostyrenes to give products containing three stereogenic centers (Scheme 1b).

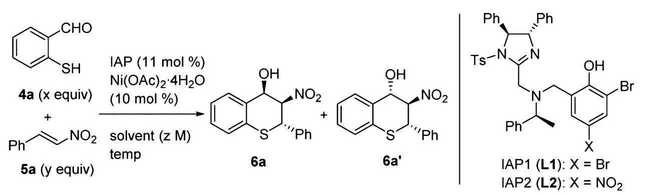
Our study of the catalytic asymmetric synthesis of thiochromanes began with the development of an appropriate catalyst system for the reaction of 2-mercaptobenzaldehyde (**4a**) with *trans*-nitrostyrene (**5a**).

When an almost 1:1 mixture of **4a** with **5a** was treated with the IAP1 (**L1**)–Ni catalyst in Et_2O, the new thiochromane diastereomer **6a** was obtained in 51% ee as the major diastereomer (dr = 71/29) along with the known *all-trans* isomer **6a′** in 4% ee (Table 1, entry 1). The absolute configuration of (2*S*,3*R*,4*R*)-**6a** was determined by a single-crystal X-ray analysis as shown in Figure 2.

At −20 °C, the ee of **6a** was improved to 72% with 92/8 diastereoselectivity, although it was necessary to extend the reaction time to 15 h to obtain the same 70% yield. Attempts to improve the chemical yield by increasing the relative amount of **4a** led to reductions in both the diastereo- and enantioselectivity values (entries 2–4). These results indicated that **4a**, when added in excess, tends to coordinate strongly to the nickel center and thus poisons the catalyst. This was avoided through the slow addition of **4a** using a syringe pump, which gave the thiochromane in quantitative yield while maintaining high levels of the diastereoselectiviy (91/9) and enantioselectivity (78% ee) for **6a** (entry 5). Among the solvents we tested, toluene gave the highest diastereoselectivity (97/3) for **6a**, along with 90% ee (entries 5–10). Finally, when the reaction was performed under highly dilute conditions (0.025 M) at −40 °C, the thiochromane **6a** was obtained in quantitative yield as a pure diastereomer with up to 95% ee (entry 12). Increasing the mole ratio of **L1** to $Ni(OAc)_2$ to 2:1 did not lead to any further improvements (entry 13),[15f] and similarly, the use of the IAP2 (**L2**)[15c] catalyst in place of **L1** did not result in any appreciable changes in the product output (compare entries 12 and 14). The results obtained using other metal salts in the catalytic system are provided in the Supporting Information.

When the optimized reaction conditions were applied, the scope and limitations of the **L1**–Ni-catalyzed thiochromane synthesis were examined, with the results presented in Scheme 2. Various electron-withdrawing and -donating substituents were appended to the benzene ring of the *β*-nitrostyrene, and it was found that the **L1**–Ni-catalyzed Michael/Henry reaction continued to proceed efficiently to give the associated thiochromanes (**6**) with high diastereoselectivities and enantioselectivities ranging from 84 to 95% ee (**6a–l**). In addition, when (*E*)-2-(2-nitrovinyl)thiophene was utilized, **6m** was obtained in a highly diastereoselective manner with 94% ee. Two substituted 2-mercaptobenzaldehydes were also examined, and these produced the products **6n** and **6o** with 80 and 87% ee, respectively. Unfortunately, the use of an aliphatic

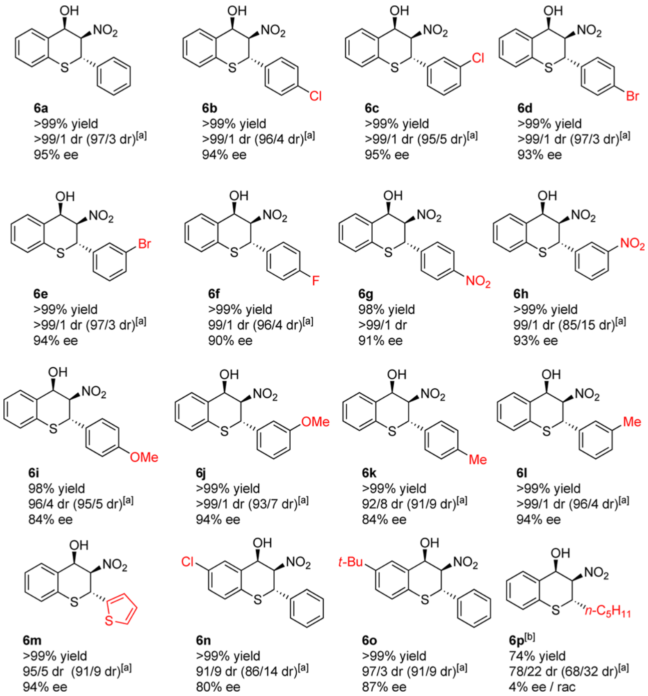
Table 1. Development of the Catalytic Synthesis of Tri-Substituted Thiochromanes Using the IAP–Ni Catalyst



entry	x/y	temp (°C)	solvent	z (M)	time (h)	yield (%)	dr[b] 6a/6a′	ee 6a/6a′
1	1/1.1	rt	Et_2O	0.1	1	70	71/29	51/4
2	1/1.1	−20	Et_2O	0.1	15	70	92/8	72/24
3	1.5/1	−20	Et_2O	0.1	23	93	71/29	62/14
4	2/1	−20	Et_2O	0.1	23	89	53/47	37/0
5[a]	1.5/1	−20	Et_2O	0.1	17	>99	91/9	78/50
6[a]	1.5/1	−20	CH_2Cl_2	0.1	21	>99	96/4	69/43
7[a]	1.5/1	−20	$CHCl_3$	0.1	18	>99	96/4	86/59
8[a]	1.5/1	−20	THF	0.1	40	<66	63/37	68/47
9[a]	1.5/1	−20	CH_3CN	0.1	21	>99	69/31	30/17
10[a]	1.5/1	−20	PhMe	0.1	18	92	97/3	90/83
11[a]	1.5/1	−20	PhMe	0.025	15	>99	99/1	94/ND
12[a]	1.5/1	−40	PhMe	0.025	16	>99	>99/1	95/ND
13[a,c]	1.5/1	−40	PhMe	0.025	17	>99	>99/1	95/ND
14[a,d]	1.5/1	−40	PhMe	0.025	20	>99	>99/1	95/ND

[a]**4a** was slowly added over 15 h. [b]Determined by ^1H NMR of the crude product. [c]Using 21 mol % of **L1**. [d]Using **L2** (11 mol %) instead of **L1**.

Scheme 2. L1−Ni-Catalyzed Thiochromane Synthesis



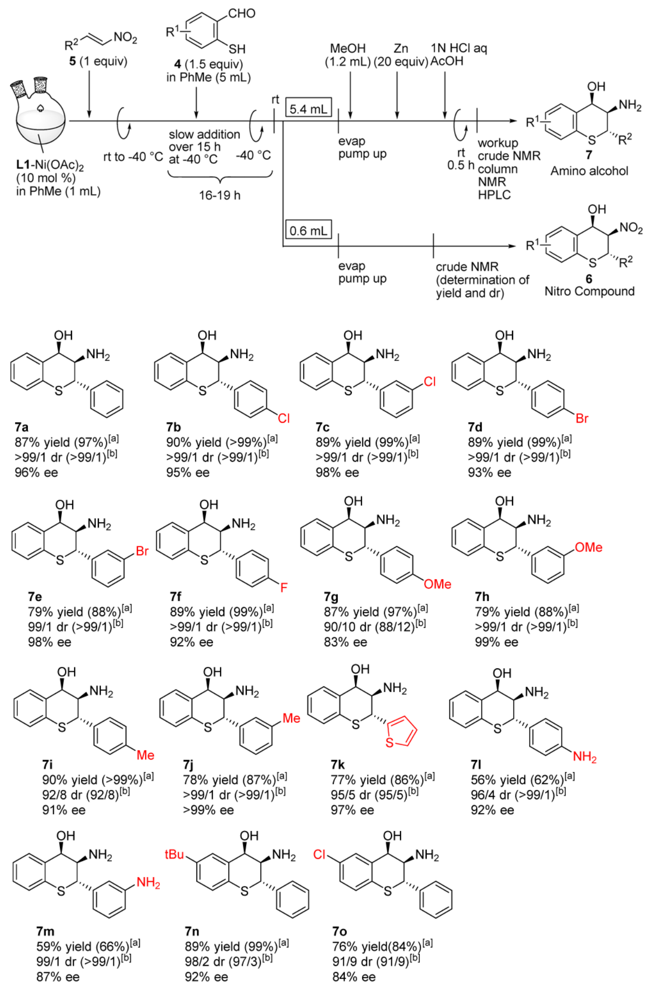
[a]Values in parentheses are diastereomeric ratios after silica gel column chromatography. [b]−20 °C, $CHCl_3$ solvent.

nitroalkene resulted in a reduced yield of the desired product **6p** as well as asymmetric induction.

During the experimental trials shown in Scheme 2 we observed the partial epimerization of the newly obtained (2*S*,3*R*,4*R*)-thiochromanes (**6**) to the more stable *all-trans* (2*S*,3*R*,4*S*)-isomers (**6a′**) following purification using silica gel column chromatography. The epimerization of the hydroxy group at the C4 position is explained by an equilibrium between the retro-Henry reaction and recyclization. To avoid the retro-Henry reaction, a portion of the crude (2*S*,3*R*,4*R*)-thiochromane (**6**) was isolated and subsequently reduced to the corresponding amine (**7**), as described in Scheme 3. To accomplish this reduction, the **L1**−Ni-catalyzed Michael/Henry reaction was first performed on a 6.0 mL scale, following which 5.4 mL of the reaction mixture was reduced with zinc nanopowder in acidic media to give the corresponding amino alcohol **7**, while the remaining 0.6 mL was analyzed by crude ^{1}H NMR to confirm the original diastereoselectivity of the thiochromane. In all cases, the amino alcohols (**7**) were obtained in good to excellent yields without loss of stereoselectivity. In the case of the Michael/Henry product obtained using *p*- and *m*-nitro-*β*-nitrostyrene, both the nitro group on the thiochromane ring and on the benzene ring were reduced to give the diamines **7l** and **7m** in a one-pot reduction process.

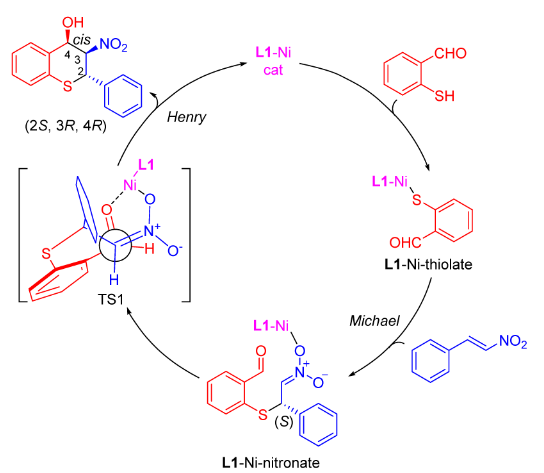
A proposed mechanism explaining the manner in which the (2*S*,3*R*,4*R*)-thiochromanes (**6**) are synthesized from the **L1**−Li-catalyzed Michael/Henry reaction is provided in Scheme 4. The process begins with the **L1**−Ni-catalyzed Michael reaction of the 2-mercaptobenzaldehyde with the *β*-nitrostyrene. As a prelude to this reaction, the high affinity which thiol has for the nickel center leads to formation of an **L1**−Ni-tholate intermediate. The corresponding [**L1**−Ni-thiolate + H]$^+$ species was observed during ESI-MS analysis based on the presence of an ion peak at *m*/*z* 966.0162 (see the Supporting

Scheme 3. Reduction of (2*S*,3*R*,4*R*)-Thiochromanes 6



[a]Since only 90% of the reaction solution (i.e., 5.4 mL) was applied to the reduction, yields estimated by multiplying by 1.11 are given in parentheses. [b]The value in parentheses is the dr of **6** as determined by crude ^{1}H NMR of 10% of the reaction mixture (i.e., 0.6 mL).

Scheme 4. Proposed Catalytic Cycle for the L1−Ni-Catalyzed Michael/Henry Reaction



Information). The 2-mercaptobenzaldehyde, which is present in excess, displaces the **L1** from the nickel center to generate an achiral nickel thiolate which reduces asymmetric induction in the Michael/Henry reaction, as observed in entries 2–4 of Table 1. By using the (*S*,*S*)-diphenylethylenediamine-derived **L1**–Ni catalyst, the stereochemistry at the C2 position of the resulting thiochromane is forced into the (*S*)-configuration by nucleophilic attack of the **L1**–Ni-thiolate at the *Si*-face of the *β*-nitrostyrene. Since the **L1**–Ni-catalyzed Michael reaction of benzenethiol with *β*-nitrostyrene results in a low level of asymmetric induction (<5% ee), the formyl group of the 2-mercaptobenzaldehydes must also interact with the **L1**–Ni catalyst to contribute to the asymmetric induction. During the Michael reaction of the **L1**–Ni-thiolate with the *β*-nitrostyrene, the corresponding Ni-nitronate is generated, leading to the formation of a 6-membered transition state complex which includes the Ni atom. The long C–S bonds in this complex force the 6-membered ring of the thiochromane to adopt a strained half-boatlike conformation in which the eclipsed interaction between the carbonyl and nitro groups is increased if the carbonyl group remains in the equatorial position. The Henry reaction then proceeds from the transition-state complex (TS1), in which the C4–O–Ni bond is in the pseudoaxial position, to give the (2*S*,3*R*,4*R*)-thiochromane.

In conclusion, the (*S*,*S*)-diphenylethylenediamine-derived **L1**–Ni complex was found to catalyze the tandem asymmetric Michael/Henry reaction of 2-mercaptobenzaldehydes with *β*-nitrostyrenes to give a novel stereoisomer of (2*S*,3*R*,4*R*)-2-aryl-3-nitrothiochroman-4-ols in up to 99% diastereoselectivity with 95% ee. The development of new diversity-oriented asymmetric catalysis using IAP–metal catalysts and the application of these reactions to the synthesis of biologically active scaffolds are presently ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data; copies of ^{1}H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (Japan) and by the Workshop on Chirality in Chiba University (WCCU).

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