Chinese Chemical Letters 31 (2020) 1859–1862

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Communication

Facile access to chiral 4-substituted chromanes through Rh-catalyzed asymmetric hydrogenation

Lin Tao[a], Qingyang Zhao[b,c], Xumu Zhang[a,b,*], Xiu-Qin Dong[a,**]

[a] Key Laboratory of Biomedical Polymers, Engineering Research Centre of Organosilicon Compounds & Materials, Ministry of Education, College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, China
[b] Department of Chemistry and Shenzhen Grubbs Institute, Southern University of Science and Technology, Shenzhen 518055, China
[c] School of Pharmaceutical Sciences (Shenzhen), Sun Yat-sen University, Shenzhen 518107, China

ARTICLE INFO

Article history:
Received 1 November 2019
Received in revised form 17 December 2019
Accepted 2 January 2020
Available online 2 January 2020

Keywords:
Chiral 4-substituted chromanes
Asymmetric hydrogenation
Excellent enantioselectivity
Gram-scale synthesis
Bisphosphine-thiourea ligand

ABSTRACT

Rh/ZhaoPhos-catalyzed asymmetric hydrogenation of a series of (*E*)-2-(chroman-4-ylidene)acetates was successfully developed to prepare various chiral 4-substituted chromanes with high yields and excellent enantioselectivities (up to 99% yield, 98% *ee*). Moreover, the gram-scale hydrogenation could be performed well in the presence of 0.02 mol% catalyst loading (TON = 5000), the hydrogenation product was easily converted to access other important compounds, which demonstrated the synthetic utility of this asymmetric catalytic methodology.

The chromanes have been respresnted an important subclass of benzopyran structural units, which are key core structures and widely distributed in many natural products, biologically active compounds and drugs [1]. Their great contributions as significant scaffolds have been exhibited with a broad range of biological activities, such as treatment of stomach, aldose reductase inhibitors, anti-cancer, anti-bacterial and anti-arrhythmic (Fig. 1) [2].

Owing to the great importance of these privileged chromanes motifs, much attraction has been obtained to develop efficient synthetic methods. Therefore, some asymmetric catalytic methodologies for the constrution of chiral chromanes promoted by transition metal catalysis and organocatalysis have been well established in the past decades [1i,2b,3–13], such as asymmetric cascade reactions involving *ortho*-hydroxycinnamaldehydes [1i,3] or *ortho*-nitrovinylphenols [2b,4] substrates, asymmetric intramolecular [4 + 2] cyclization of *ortho*-quinone methides with olefins [5] or aldehydes [6], asymmtric conjugate addition of alkynes to 3-alkoxycarbonylcoumarines [7], dynamic kinetic asymmetric acylation of 2-chromanols [8], intramolecular desymmetric aryl C—O coupling reaction of 2-(2-haloaryl)-1,5-diols [9], asymmetric 6-exo-trig Michael addition-lactonization of enone-acid [10], intramolecular ylide annulation [11], allenylidene-ene reactions [12]. Asymmetric catalytic reduction is a direct and powerful synthetic methodology to construct chiral molecules [14]. However, there are limited asymmetric reduction examples concerning the synthesis of chiral chromanes [15,16]. In 2017, Zhang and coworkers described a highly efficient Ir-catalyzed asymmetric hydrogenation of substituted 2*H*-chromenes and substituted benzo[*e*][1,2]oxathiine 2,2-dioxides in high yields with excellent enantioselectivities [15a]. Zhou and coworkers realized Ni-catalyzed asymmetric (transfer) hydrogenation of α,β-unsaturated esters with excellent results, which involved the example of synthesis of chiral 4-substituted chromane [16]. Encouraged by these great achievements and in the continuation of our efforts in the field of asymmetric catalytic hydrogenation, we herein developed Rh-catalyzed asymmetric hydrogenation of (*E*)-2-(chroman-4-ylidene)acetates to afford a series of chiral 4-substituted chromanes with high yields and excellent enantioselectivities (up to 99% yield, 98% *ee*), the gram-scale hydrogenation could be proceeded efficiently in the presence of 0.02 mol% catalyst loading (TON = 5000) (Scheme 1).

We began our initial studies of Rh-catalyzed asymmetric hydrogenation of model substrate ethyl (*E*)-2-(chroman-4-ylidene)acetate **1a**, which was investigated in the presence of various chiral diphosphine ligands, 50 atm H_2 in CH_2Cl_2. As shown

* Corresponding author at: Key Laboratory of Biomedical Polymers, Engineering Research Centre of Organosilicon Compounds & Materials, Ministry of Education, College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, China.
** Corresponding author.
E-mail addresses: zhangxm@sustc.edu.cn (X. Zhang), xiuqindong@whu.edu.cn (X.-Q. Dong).

https://doi.org/10.1016/j.cclet.2020.01.001

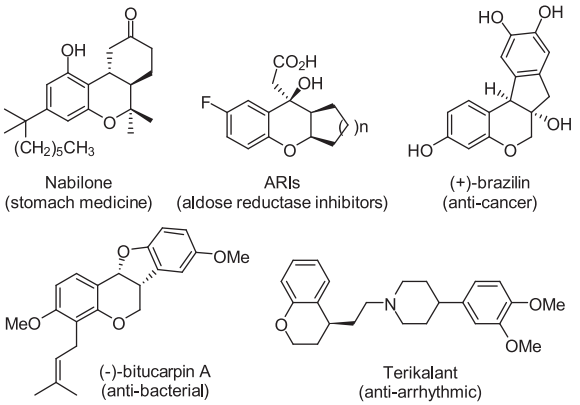
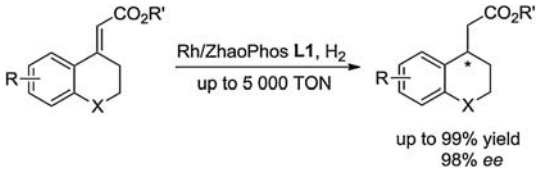
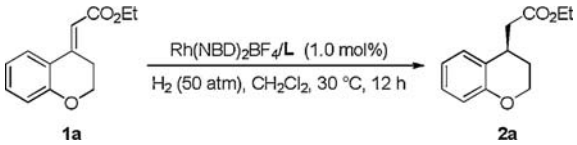


Fig. 1. Some examples of biologically active compounds bearing chiral chromane motifs.



Scheme 1. Rh-catalyzed asymmetric hydrogenation of (*E*)-2-(chroman-4-ylidene) acetates.

Table 1
Screening ligands for Rh-catalyzed asymmetric hydrogenation of ethyl (*E*)-2-(chroman-4-ylidene)acetate **1a**.[a]



Entry	Ligand	Conv. (%) [b]	*ee* (%) [c]
1	ZhaoPhos **L1**	>99	97
2	**L2**	>99	95
3	(*S*)-SegPhos	9	−20
4	(*Rc*, *Sp*)-DuanPhos	13	−60
5	(*S*)-Binap	5	−18
6	(*S*, *S*)-Me-DuPhos	6	−56

[a] Unless otherwise noted, all reactions were carried out with $Rh(NBD)_2BF_4$/ligand/**1a** (0.2 mmol) ratio of 1:1.1:100 in 1.0 mL of solvent under 50 atm of H_2 at 30 °C. The catalyst was precomplexed in CH_2Cl_2 (0.1 mL for each reaction vial).
[b] Determined by ^1H NMR analysis.
[c] Determined by chiral HPLC analysis.

in Table 1, the bisphosphine-thiourea ligands **L1** and **L2** were applied (Fig. 2), which were developed by our group [17], could promote this Rh-catalyzed asymmetric hydrogenation to provide the desired product **2a** in full conversion and excellent enantioselectivities (>99% conversion, 95%–97% *ee*, Table 1, entries 1 and 2). The axially chiral bisphosphine ligands (*S*)-SegPhos and (*S*)-Binap displayed poor catalytic activity and asymmetric induction (5%–9% conversions, 18%–20% *ee*, Table 1, entries 3, 5). Although moderate enatioselectivities could be obtained employing (*Rc*, *Sp*)-DuanPhos and (*S*,*S*)-Me-DuPhos as the ligands, very poor conversions were given (6%–13% conversions, 56%–60% *ee*, Table 1, entries 4, 6). Among the ligands probed, the ligand ZhaoPhos **L1**

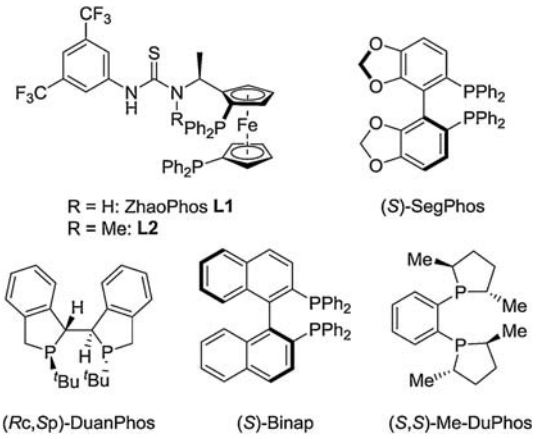
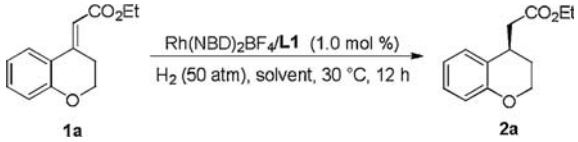


Fig. 2. The structure of chiral diphosphine ligands in this asymmetric hydrogenation.

was proved to be the best with regard to both conversion and enantioselectivity for this Rh-catalyzed hydrogenation.

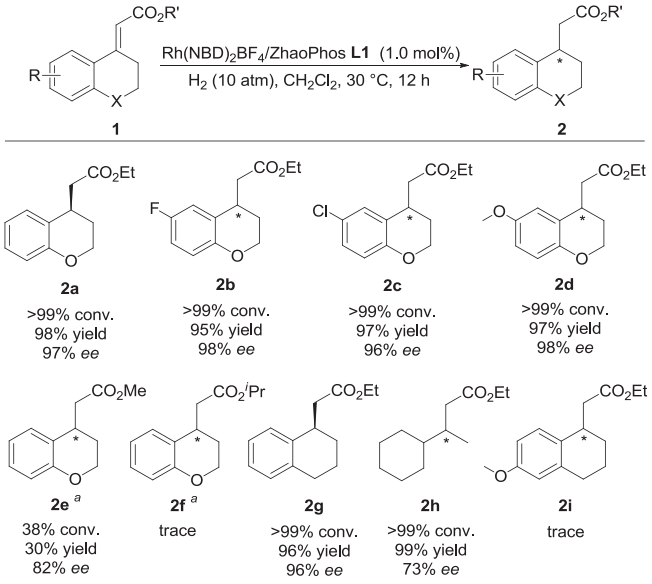
Solvents always played an important role in asymmetric catalytic reactions. As shown in Table 2, the Rh/ZhaoPhos **L1**-catalyzed asymmetric hydrogenation of model substrate ethyl (*E*)-2-(chroman-4-ylidene)acetate **1a** was then investigated in different solvents. Interestingly, nearly these solvents provided the same enantioselectivity. We found that toluene, CH_2Cl_2 and 1,2-dichloroethane (DCE) led to high conversions and excellent enantioselectivities (98% ∼ >99% conversions, 97% *ee*, Table 2, entries 1, 3, 6). In addition, moderate to good conversions were observed with other polar solvents, such as tetrahydrofuran (THF), 1,4-dioxane and ^{i}PrOH (60%–82% conversions, Table 2, entries 8–10). Although MeOH, EtOH and $CHCl_3$ allowed this transformation to proceed with high enantioselectivities, 28%–40% conversions were detected (Table 2, entries 4, 5, 7). Therefore, CH_2Cl_2 was the optimal solvent for this Rh-catalyzed asymmetric hydrogenation. To our delight, when the hydrogen pressure was reduced from 50 atm to 10 atm, this hydrogenation could be still performed

Table 2
Screening solvents for Rh-catalyzed asymmetric hydrogenation of ethyl (*E*)-2-(chroman-4-ylidene)acetate **1a**.[a]



Entry	Solvent	Conv. (%) [b]	*ee* (%) [c]
1	Toluene	98	97
2	CF_3CH_2OH	54	97
3	CH_2Cl_2	>99	97
4	MeOH	40	97
5	EtOH	37	97
6	DCE	98	97
7	$CHCl_3$	28	97
8	THF	82	97
9	1,4-Dioxane	81	97
10	^{i}PrOH	60	97
11[d]	CH_2Cl_2	>99	97

[a] Unless otherwise noted, all reactions were carried out with $Rh(NBD)_2BF_4$/ZhaoPhos **L1**/**1a** (0.2 mmol) ratio of 1:1.1:100 in 1.0 mL of solvent under 50 atm of H_2 at 30 °C. The catalyst was precomplexed in CH_2Cl_2 (0.1 mL for each reaction vial).
[b] Determined by ^1H NMR analysis.
[c] Determined by chiral HPLC analysis.
[d] The reaction was carried out under 10 atm H_2.



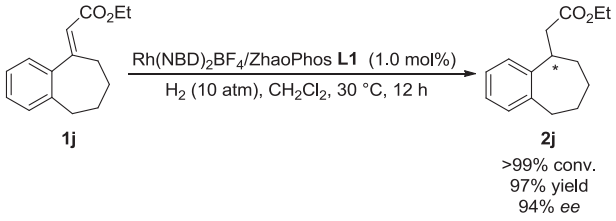
Scheme 2. Substrate scope study. Unless otherwise noted, all reactions were carried out with $Rh(NBD)_2BF_4$/ZhaoPhos **L1**/**1** (0.2 mmol) ratio of 1:1.1:100 in 1.0 mL CH_2Cl_2 under 10 atm of H_2 at 30 °C. Conversion was determined by ^1H NMR analysis. *ee* was determined by chiral HPLC analysis. [a] $Rh(NBD)_2BF_4$/ZhaoPhos **L1** (4.0 mol%), 50 atm H_2, 50 °C.

smoothly with the same results (>99% conversion, 97% *ee*, Table 2, entry 3 *vs.* entry 11).

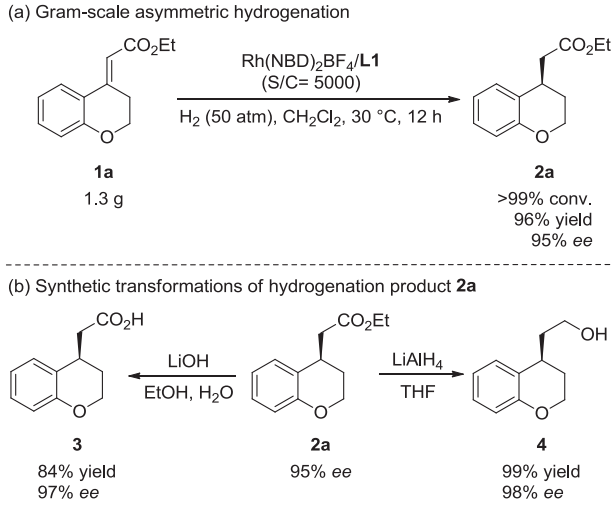
After the optimized reaction conditions were established, we focused on the exploration of the substrate scope generality. These reaction results were summarized in Scheme 2, a variety of substituted (*E*)-2-(chroman-4-ylidene)acetates were hydrogenated to give the corresponding desired chiral 4-substituted chromanes. Whether the electron-deficient or electron-rich groups were at C6-position of the substrates, they were hydrogenated smoothly to prepare products (**2b**-**2d**) in high yields and excellent enantioselectivities (>99% conversion, 95%–97% yields, 96%–98% *ee*). In addition, other substrates with methyl or isopropyl ester groups were applied into this Rh-catalyzed asymmetric hydrogenation. The methyl (*E*)-2-(chroman-4-ylidene)acetate (**1e**) was hydrogenated to give the product (**2e**) with low conversion and moderate enantioselectivity (38% conversion, 30% yield, 82% *ee*). The isopropyl (*E*)-2-(chroman-4-ylidene)acetate (**1f**) with bulky steric hindrance was difficult to be hydrogenated in this catalytic system, and trace conversion was detected. The oxygen atom of the model substrate ethyl (*E*)-2-(chroman-4-ylidene)acetate **1a** was switched to carbon atom forming substrate ethyl (*E*)-2-(3,4-dihydronaphthalen-1(2*H*)-ylidene)acetate **1g**, which was hydrogenated well to afford product **2g** with full conversion, 96% yield and 96% *ee*. In addition, the alkyl substrate **1h** also gave the corresponding product **2h** in high yield and moderate enantioselectivity (>99% conversion, 99% yield, 73% *ee*). However, the substrate (**1i**) with substituted group on the benzene ring at C7-position almost did not work in this reduction, trace conversion was observed.

Encourged by these promising results, the benzo-seven-membered substrate was further investigated in this catalytic system. And we found that ethyl (*E*)-2-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene)acetate **1j** was an excellent substrate pattern, which was hydrogenated efficiently to provide the desired product **2j** with >99% conversion, 97% yield and 94% *ee* (Scheme 3).

In order to demonstrate the synthetic utility of this asymmetric catalytic methodology, a gram-scale Rh/ZhaoPhos **L1**-catalyzed asymmetric hydrogenation of model substrate **1a** was performed in the presence of 0.02 mol% catalyst loading (S/C = 5000) under



Scheme 3. Rh-catalyzed asymmetric hydrogenation of benzo-7-membered substrate ethyl (*E*)-2-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene)acetate **1j**.



Scheme 4. Gram-scale asymmetric hydrogenation and synthetic transformations.

50 atm H_2, and product **2a** was readily obtained in comparable yield nearly without loss of enantioselectivity (>99% conversion, 96% yield, 95% *ee*, Scheme 4a). The enantioenriched hydrogenation product **2a** can be easily converted into other useful chiral molecules. For example, the ester group of the product **2a** was hydrolyzed smoothly, affording the chiral carboxylic acid **3** in 84% yield and without loss of *ee* value (Scheme 4b) [18]. In addition, the reduction of product **2a** with $LiAlH_4$ furnished chiral alcohol **4** in nearly quantitative yield and 98% *ee* (Scheme 4b) [6b].

In conclusion, we successfully developed a highly efficient Rh/ZhaoPhos-catalyzed asymmetric hydrogenation of (*E*)-2-(chroman-4-ylidene)acetates to construct a series of chiral 4-substituted chromanes with high yields and excellent enantioselectivities (up to 99% yield, 98% *ee*). Moreover, the gram-scale hydrogenation could be performed well in the presence of 0.02 mol% catalyst loading (TON = 5000), and hydrogenation product transformations were conducted to access other important compounds, such as chiral carboxylic acid and chiral alcohol.

Declaration of competing interest

The authors declare no competing financial interest.

Acknowledgments

We are grateful for the financial support from the National Natural Science Foundation of China (Nos. 21432007, 21502145, 21602172), Wuhan Morning Light Plan of Youth Science and Technology (No. 2017050304010307), the Fundamental Research Funds for and the Central Universities (No. 2042018kf0202), Shenzhen Nobel Prize Scientists Laboratory Project (No. C17783101), Science and Technology Innovation Committee of

Shenzhen (No. KQTD 20150717103157174) and SZDRC Discipline Construction Program. The Program of Introducing Talents of Discipline to Universities of China (111 Project) is also appreciated.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.01.001.

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