Tetrahedron 74 (2018) 477–482

Contents lists available at ScienceDirect

Tetrahedron

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

Iridium-catalyzed asymmetric hydrogenation of 2-substituted 1,4-benzodioxines

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ARTICLE INFO

Article history:
Received 18 October 2017
Received in revised form
2 December 2017
Accepted 8 December 2017
Available online 9 December 2017

Keywords:
Asymmetric hydrogenation
Iridium
Tropos phosphine-oxazoline ligand
2-Substituted 1,4-benzodioxines
Chiral 1,4-benzodioxanes

ABSTRACT

An Ir-catalyzed asymmetric hydrogenation of 2-substituted 1,4-benzodioxines was developed for the preparation of chiral 1,4-benzodioxanes, which are present in numerous biologically active compounds and natural products. Our *tropos* biphenyl phosphine-oxazoline ligand is essential for obtaining good ee. A broad range of substrates were tolerable to the reaction conditions and gave the corresponding hydrogenation products in excellent yields and with moderate to good enantioselectivities using the Ir-complex of our *tropos* phosphine-oxazoline ligand.

1. Introduction

The 1,4-benzodioxane framework has attracted considerable interest because it is a core structural motif in a variety of biologically active compounds and natural products (Fig. 1).[1] For example, Piperoxan is an α-adrenergic blocking agent with considerable stimulating activity and is used to diagnose pheochromocytoma and also acts as an antihypertension agent.[1a] 2-Aryl-1,4-benzodioxanes are subunits of this structure and exhibit important bioactivity. Skeleton **4** belongs to a class of leuketriiene A4 hydrolase inhibitor compounds.[1b] Isovanillyl sweetening agents,[1c] which are 500 times sweeter than sucrose, also contain the 1,4-benzodioxine moiety. Numerous lignans also containing the 2-aryl-1,4-benzodioxane nucleus represent a class of natural products with cytotoxic and hepatoprotective activities.[1d-f] Therefore, reliable and efficient synthetic methodologies for the preparation of these chiral skeletons are highly desired. However, most of the present synthetic methodologies rely on the use of chiral starting materials or large amounts of chirality inducing reagents which are not efficient with regards to atom economy.[2]

It is well-known that the asymmetric catalysis of suitable substrates is an efficient approach towards the synthesis of chiral 1,4-benzodioxanes, with clear advantages with regards to structural diversity and the ability to use only amounts of a chiral source. Asymmetric allylic substitution has been utilized for the preparation of chiral 2-vinyl-1,4-benzodioxanes by several groups.[3] Recently, two newly developed enantioselective reactions for the construction of this chiral skeleton have been reported (Scheme 1).[4,5] The Cai group reported a Pd-catalyzed asymmetric desymmetrization of diols to form chiral 1,4-benzodioxanes bearing a hydroxymethyl group at the 2-position.[4] Tang et al. developed an asymmetric alkene aryloxyarylation catalyzed by a Pd/Antphos catalyst system, yielding chiral 1,4-benzodioxanes possessing tetrasubstituted carbon stereocenters.[5] However, the preparation of chiral 2-aryl-1,4-benzodioxanes using these two methodologies has not been reported using asymmetric catalysis. Asymmetric hydrogenation has attracted considerable attention since the advent of asymmetric catalysis.[6] Although Ir-catalyzed asymmetric hydrogenation was developed later than Rh and Ru-catalysis, such catalyst systems have gained popularity due to their ability to catalyze the asymmetric hydrogenation of unfunctionalized olefins.[7] Ir-catalyzed asymmetric hydrogenation

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https://doi.org/10.1016/j.tet.2017.12.015
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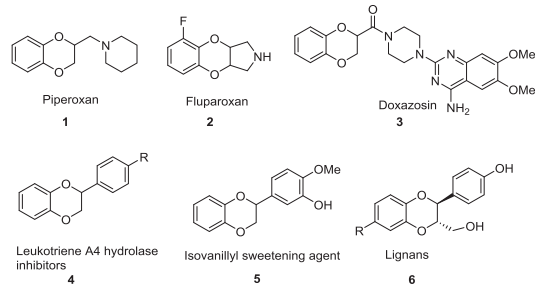
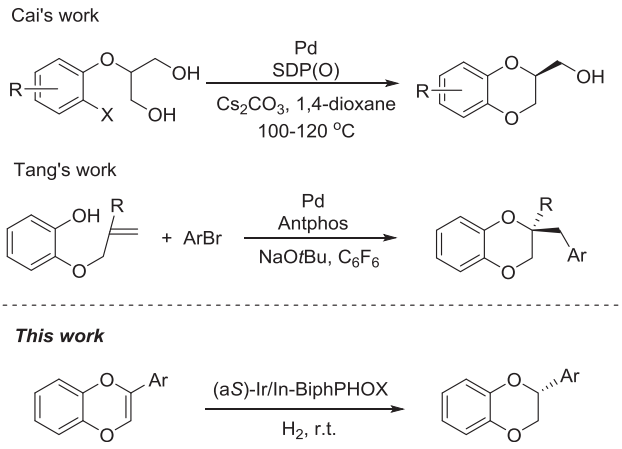


Fig. 1. Example compounds containing the 1,4-benzodioxane fragment.



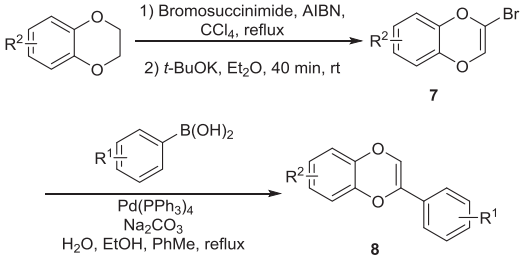
Scheme 1. Synthesis of chiral 1,4-benzodioxane via asymmetric catalysis.

of cyclic compounds has become an efficient protocol for the synthesis of chiral cyclic compounds.[6i,8] The Ir-catalyzed asymmetric hydrogenation of 2-substituted 1,4-benzodioxines provides an attractive route to the preparation of chiral 2-aryl-1,4-benzodioxanes. Herein, we report such a methodology using an Ir-complex of our chiral axially-unfixed biphenyl phosphine-oxazoline ligand (Scheme 1).[9]

2. Results and discussion

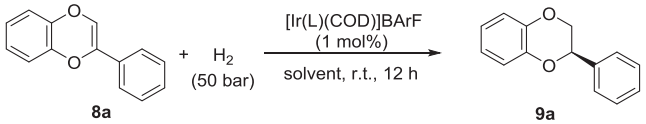
2-Substituted 1,4-benzodioxines could be prepared easily in 3 steps from 1,4-benzodioxane.[10] After a photo-induced dibromination and an elimination reaction, compound **7** could be prepared in large quantities. Cross-coupling of **7** with a series of arylboronic acids gave different 2-substituted 1,4-benzodioxines in moderate to high yields (Scheme 2).

Our study began with the asymmetric hydrogenation of 2-phenyl 1,4-benzodioxines **8a** (Table 1). Firstly, different Ir-complexes of different phosphine-oxazoline ligands were screened (entries 1–8).



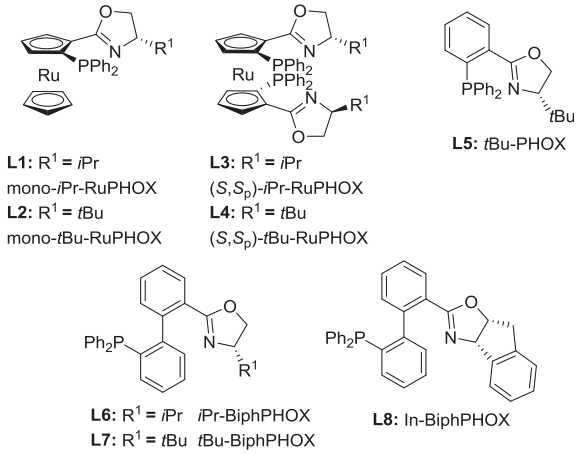
Scheme 2. Synthesis of substrates.

Table 1
Reaction optimization.[a]



Entry	Solvent	Ligand	Yield (%)[b]	ee (%)[c]
1	DCM	**L1**	trace	–
2	DCM	**L2**	>99	−82
3	DCM	**L3**	17	−10
4	DCM	**L4**	>99	−83
5	DCM	**L5**	>99	5
6	DCM	**L6**	91	81
7	DCM	**L7**	>99	70
8	DCM	**L8**	>99	90
9	DCE	**L8**	>99	88
10	Toluene	**L8**	ND[k]	–
11	THF	**L8**	NR[k]	–
12	MeOH	**L8**	NR[k]	–
13[d]	DCM	**L8**	>99	90
14[e]	DCM	**L8**	>99	90
15[f]	DCM	**L8**	91	88
16[g]	DCM	**L8**	87	90
17[h]	DCM	**L8**	ND[k]	–
18[i]	DCM	**L8**	66	88
19[j]	DCM	**L8**	ND[k]	–

[a] Reaction conditions: ratio of substrate/catalyst (S/C) = 100, 2 mL solvent, H_2 (50 bar).
[b] Determined by ^1H NMR spectroscopy.
[c] Enantioselectivity was determined by HPLC using a chiral column.
[d] H_2 (20 bar).
[e] H_2 (10 bar).
[f] H_2 (5 bar).
[g] 4Å MS (50 mg) as an additive.
[h] HOAc (0.1 equiv.) as an additive.
[i] Na_2CO_3 (0.1 equiv.) as an additive.
[j] I_2 (0.1 equiv.) as an additive.



[k] ND = a complex mixture not determined; NR = no reaction.

The type of ligand greatly influences this catalytic reaction (entries 2–8). When planar chiral ruthenocene-derived P-N ligands were used,[11] ligands bearing the sterically bulky *t*Bu group on the oxazoline ring(s) gave hydrogenated product **9a** in excellent conversion and good ee, while those bearing an *i*Pr group exhibited poor catalytic activity and enantio-inducing ability (entry 2 vs 1, 4 vs 3). Ligands bearing bis-(phosphine-oxazoline) groups provided similar behaviour to those bearing a mono-(phosphine-oxazoline) moiety (entry 1 vs 3, 2 vs 4). This suggests that these two (phosphine-oxazoline) functionalities present in **L3** and **L4** do not interact with each