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# Chiral iminophosphoranes organocatalyzed asymmetric hydroxylation of 3-substituted oxindoles with oxaziridines

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ABSTRACT

Enantioselective hydroxylation of *N*-protected 3-substituted oxindoles has been developed *via* chiral iminophosphorane catalysis with oxaziridines as oxidants. As such, a variety of optically active 3-substituted-3-hydroxy-2-oxindoles were obtained in excellent yields (91–99%) and moderate to excellent level of enantiomeric excess (up to 94% *ee*).



## Introduction

The catalytic asymmetric synthesis of chiral 3-substituted-3-hydroxy-2-oxindoles has attracted much interest of organic chemists due to the biological activities associated with oxindole derivatives (A and B; Fig. 1).[1a] For instance, several lead compounds with 3-hydroxy-2-oxindole skeleton were evaluated as clinical candidates in the drug development process (C and D; Fig. 1).[1c] Therefore, great synthetic efforts in the preparation of optically active 3-substituted-3-hydroxy-2-oxindoles resulted in various novel methodologies by enantioselective carbon-oxygen bond construction, which has been a subject of many reviews.[1]

The enantioselective carbon-oxygen (C—O) bond formation of 3-substituted-3-hydroxy-2-oxindoles in a catalytic manner have been achieved in several reported works by using both organometallic catalysis and organocatalysis.[2] In 2006, Shibata and Toru reported an enantioselective hydroxylation of oxindoles using zinc complex with bis(oxazoline) ligand of DBFOX.[3] Later, Itoh et al. employed cinchonidine-derived phase-transfer catalyst with molecular oxygen as an oxidant for this enantioselective hydroxylation.[4] The research group of Feng employed rare-earth metal/N,N'-dioxide complex in asymmetric hydroxyamination of oxindoles with nitrosobenzenes.[5] Similar strategy of organocatalytic enantioselective aminooxygenation of oxindoles was realized by Barbas.[6] The research group of Tan developed pentanidium-catalyzed α-hydroxylation of 3-substituted-2-oxindoles using molecular oxygen in good yields and excellent enantioselectivities.[7] With binaphthyl derived N,N,O-tridentate phenanthroline as an axially chiral ligand, a copper complex was used as catalyst in asymmetric hydroxylation of oxindoles with oxaziridine as an oxidants by Nishiyama in 2015, the corresponding products were afforded in excellent enantioselectivities.[8] Recently, Ooi et al. reported that peroxy trichloroacetimidic acid acted as oxygenating agent in asymmetric α-hydroxylation of 3-substituted oxindoles, the responding products were obtained in excellent enantioselectivities with the catalyst of L-alanine-derived chiral 1,2,3-triazolium bromide.[9] Despite significant advance has been achieved in this field, the exploration of more catalytic systems to deliver oxindoles bearing a chiral 3-hydroxy-substituted quaternary stereocenter is still necessary. We have recently embarked on the development of a class of tartaric acid derived iminophosphoranes as organocatalysts in the asymmetric transformations of 3-substituted oxindoles (Scheme 1).[10,11] We report herein the efficient use of iminophosphoranes as organocatalysts

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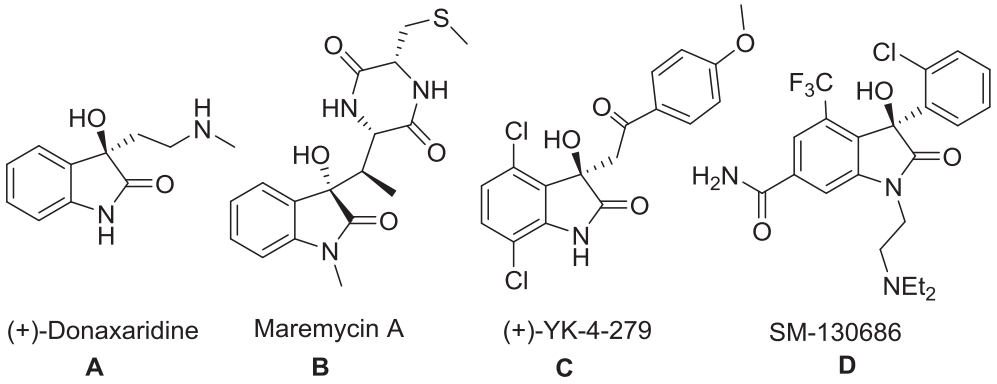
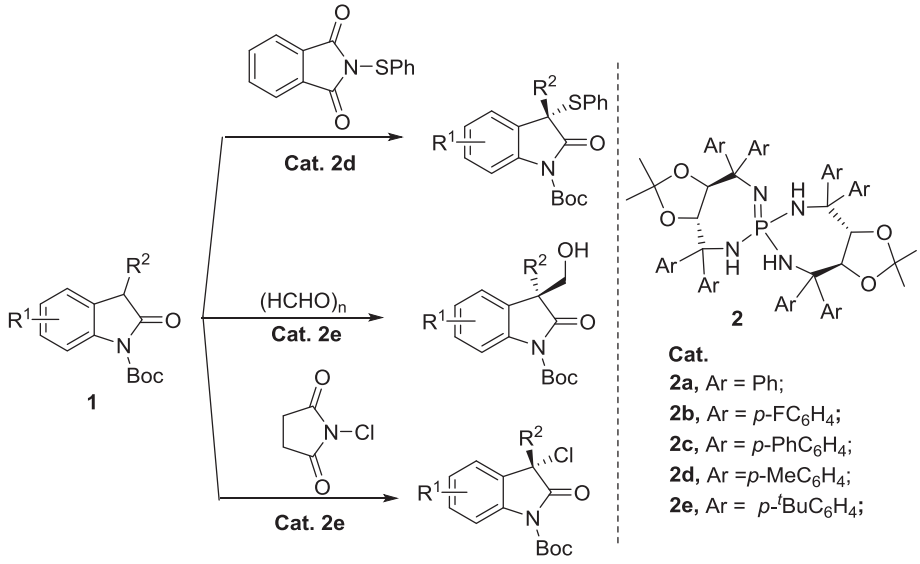
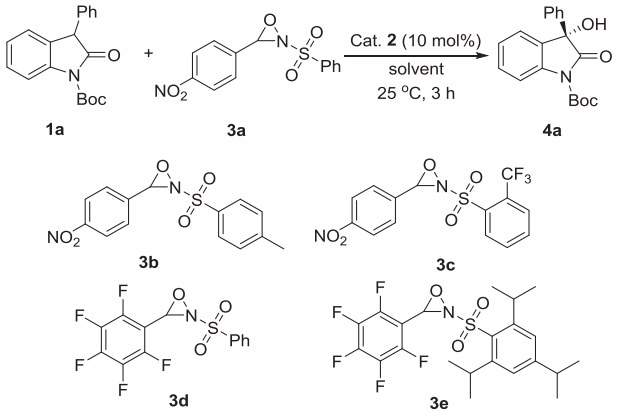



**Fig. 1.** Selected samples of 3-substituted-3-hydroxy-2-oxindoles.




**Scheme 1.** Chiral iminophosphoranes as organocatalysts in the asymmetric reactions of 3-substituted oxindoles.

**Table 1**
Screening of reaction conditions for asymmetric hydroxylation.[a]




| Entry | Cat. **2** | Solvent | **3** | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | **2a** | Toluene | **3a** | 65 | 0 |
| 2 | **2b** | Toluene | **3a** | 76 | 28 |
| 3 | **2c** | Toluene | **3a** | 98 | 60 |
| 4 | **2d** | Toluene | **3a** | 78 | −9 |
| 5 | **2e** | Toluene | **3a** | 99 | 22 |
| 6 | **2c** | Toluene | **3b** | 67 | 60 |
| 7 | **2c** | Toluene | **3c** | 95 | 60 |

(*continued on next page*)