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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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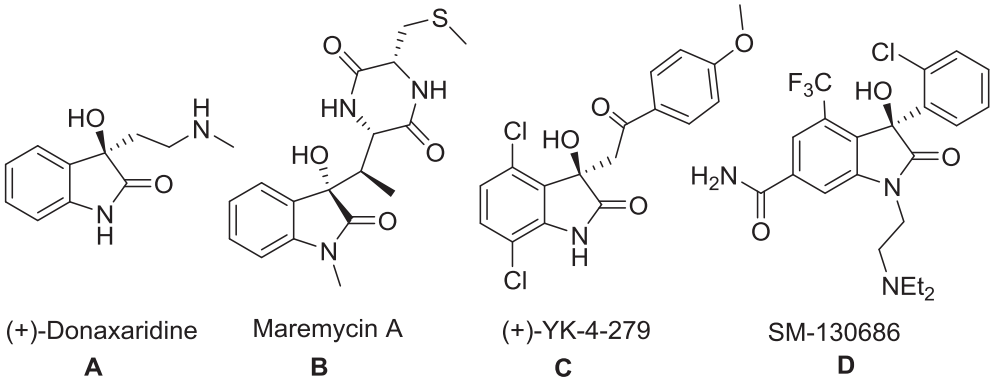
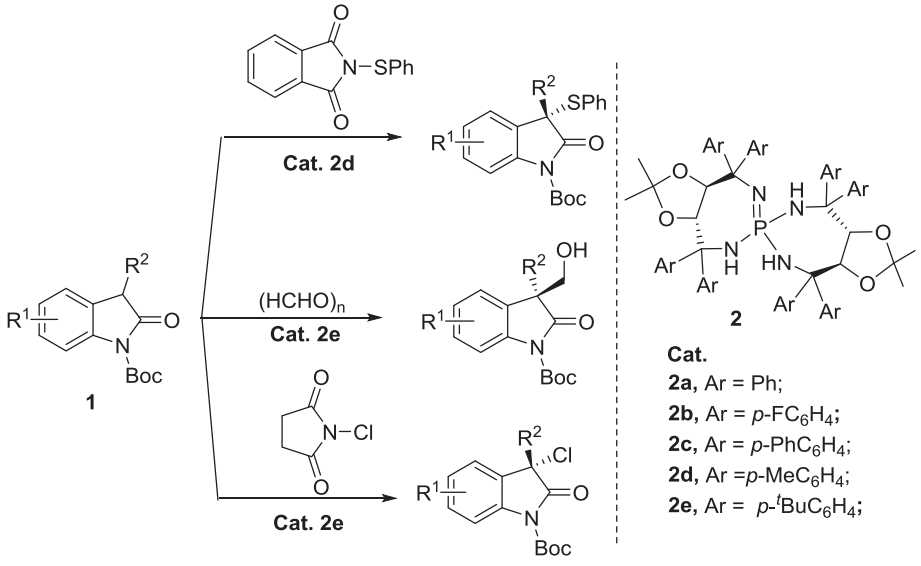
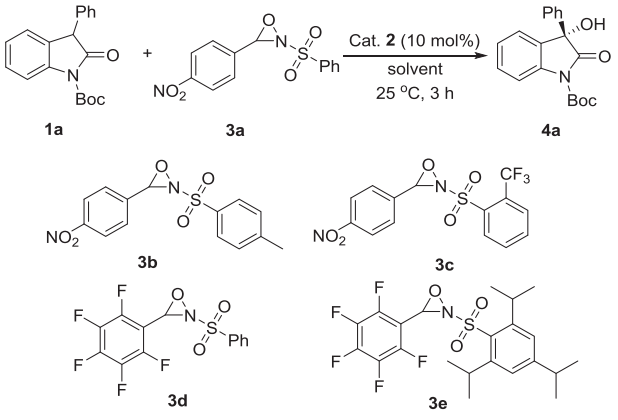


Fig. 1. Selected samples of 3-substituted-3-hydroxy-2-oxindoles.



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

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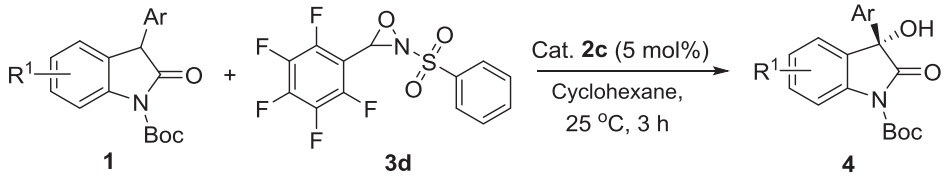
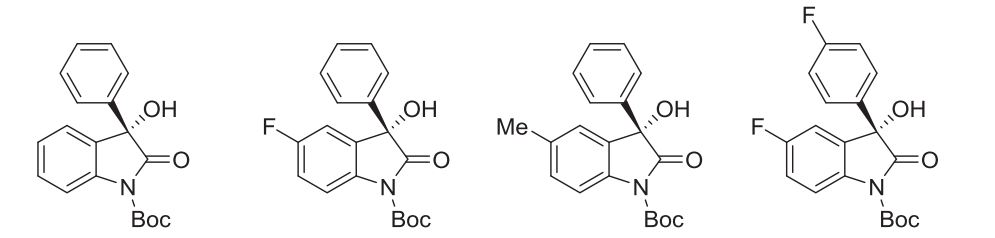
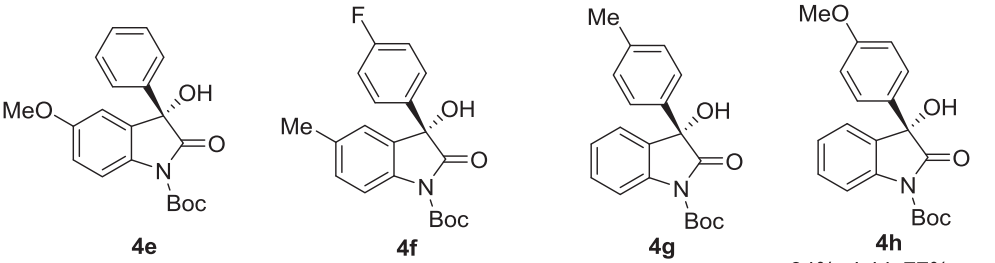
Table 1 (*continued*)

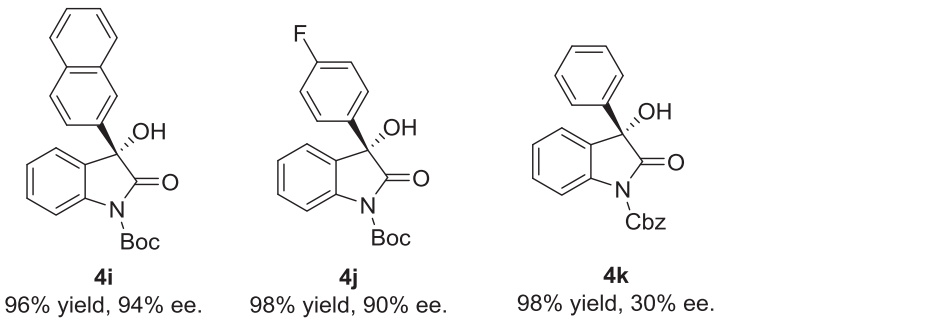
Entry	Cat. **2**	Solvent	**3**	Yield [%][b]	*ee* [%][c]
8	**2c**	Toluene	**3d**	95	75
9	**2c**	Toluene	**3e**	91	53
10	**2c**	EtOAc	**3d**	99	60
11	**2c**	DCM	**3d**	99	59
12	**2c**	$CHCl_3$	**3d**	99	66
13	**2c**	Et_2O	**3d**	98	14
14	**2c**	THF	**3d**	99	76
15	**2c**	MeCN	**3d**	99	34
16	**2c**	Cyclohexane	**3d**	99	83
17	**2c**	*i*-PrOH	**3d**	35	54
18	**2c**	Mesitylene	**3d**	99	73
19[d]	**2c**	Cyclohexane	**3d**	99	85
20[e]	**2c**	Cyclohexane	**3d**	99	84
21[f]	**2c**	Cyclohexane	**3d**	99	83

[a] Reactions were performed on a 0.1 mmol scale of *N*-Boc-protected oxindole **1a** using oxaziridine **3** (0.1 mmol, 1.0 equiv.) and catalyst in solvent (2 mL) at 25 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis on a chiral stationary phase.
[d] 5 mol% catalyst **2c** was used as catalyst.
[e] 1 mol% catalyst **2c** was used as catalyst and the reaction time was 24 h.
[f] 2.0 equiv. of **3d** was used in the reaction.









Scheme 2. Substrate Scope of 3-Aryl Substituted Oxindoles.

in asymmetric hydroxylation of *N*-protected 3-substituted oxindoles with oxaziridine as the oxidant.[12]

We began the study with the hydroxylation reaction of *N*-Boc-protected 3-phenyl-2-oxindole **1a** with racemic **3a** (N-3-(4-nitrophenyl)-2-(phenylsulfonyl)-1,2-oxaziridine) as the model reaction to investigate the reaction conditions and to optimize the catalyst at room temperature. We first attempted the reaction by using toluene as solvent to screen the catalysts **2a–2e**. It was found that catalyst **2c** was the most suitable catalyst in this reaction and the product **4a** was achieved in the highest enantioselectivity with excellent yield after 3 h (98% yield, 60% *ee*; Table 1, entry 3). Of note, Mannich adducts of **1a** with aryl sulfonimines were not observed by thin-layer chromatography experiments since the aryl sulfonimines can be generated from oxaziridines as byproducts in this reaction. Then we examined the oxidants of oxaziridine derivatives with 10 mol% catalyst **2c** in toluene (Table 1, entries 6–9), it was found that **3d** with pentafluorophenyl substituted oxaziridine improved the enantioselectivity without loss in efficiency (95% yield, 75% *ee*). After that we optimized the reaction conditions by screening solvents at room temperature (Table 1, entries 10–18). As shown in Table 1, the results showed that tetrahydrofuran (THF) and mesitylene gave comparable enantiomeric excess of 76% and 73%, respectively (Table 1, entries 14 and 18). We were delighted to observe that non-polar solvent of cyclohexane led to **4a** in 99% yield with good enantioselectivity of 83% *ee* (Table 1, entry 16). The protic solvent of isopropanol gave **4a** in 35% yield with 54% *ee* (Table 1, entry 17). Further study of catalyst loading showed that 5 mol% catalyst **2c** was enough to afford **4a** in 99% yield with 85% *ee* (Table 1, entry 19). However, less catalyst loading results in very sluggish reaction (Table 1, entry 20). Of note, the absolute configuration of compound **4a** was determined to be "(*S*)" by comparison of the optical rotation value to the reported literature value.[3] Furthermore, two equivalents of racemic **3d** were employed in this reaction, **4a** was obtained in 99% yield with 83% ee. The recovered **3d** were obtained in 87% yield and 15% enantiomeric excess were determined by HPLC (Table 1, entry 21).

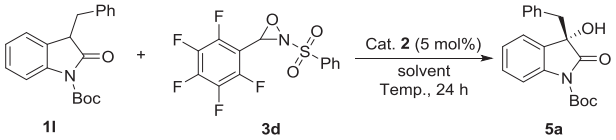
With the optimized reaction conditions in hand, we then explored the generality of the reaction scope with various *N*-protected 3-aryloxindole derivatives. The reaction scope was summarized in Scheme 2, all reactions were completed within 3 h at 25 °C in the presence of 5 mol% catalyst **2c** with cyclohexane as solvent. The desired oxindole products **4a–4k** were afforded in excellent yields (94–99%) and moderate to excellent level of enantioselectivities of 30–94% *ee*. Generally, *N*-Boc-protected 3-aryloxindole derivatives gave satisfactory results of both reactivity and enantioselectivity (**4a–4j**; Scheme 1). *N*-Cbz-protected product of **4k** was produced efficiently in 98% yield under the optimal conditions, however, the enantioselectivity were decreased to 30% *ee* in comparison of **4a** (Scheme 1, 85% *ee* of **4a** vs 30% *ee* of **4k**).

When the optimized reaction conditions were applied to 3-benzyl substituted *N*-Boc-oxindole of **1l**, the enantioselectivity was very poor (20% *ee*) although with excellent yield of 99% after 24 h (Table 2, entry 1). Thus, the catalysts **2a–2e** were screened again with the hydroxylation reaction of **1l** with 3d in cyclohexane as solvent. It was found that the catalyst 2d achieved the best enantioselectivity (58% *ee*) with the desired product 5a (Table 1, entries 1–5). By using 5 mol% 2d as catalyst, the solvent effect was investigated (Table 1, entries 6–10), toluene as solvent gave comparable results in comparison of cyclohexane (Table 2, 57% *ee* of entry 6 vs 58% *ee* of entry 4). In order to improve the enantioselectivity, changing the reaction temperature from 25 °C to −20 °C led to a significant increase in enantioselectivity to 77% *ee* (Table 2, entry 11). Further decreasing the temperature to −30 °C did not give better results (Table 2, entry 12).

After optimizing the reaction conditions, we started to evaluate the substrate scope of this reaction by varying the structure of 3-benzyl substituted *N*-Boc-oxindoles. As shown in Scheme 3, the desired oxindole products **5a–5l** were afforded in excellent yields (91–99%) and moderate to good enantioselectivities of 23–78% *ee* were achieved. As can be seen, a number of substituted *N*-Boc-oxindoles regardless of the electronic nature of the substituents, such as methyl, fluoro or methoxy on the aryl groups of both oxindole skeleton and the 3-arylmethylene substituents, reacted efficiently with **3d** to afford the desired products **5b–5l** efficiently (Scheme 3).

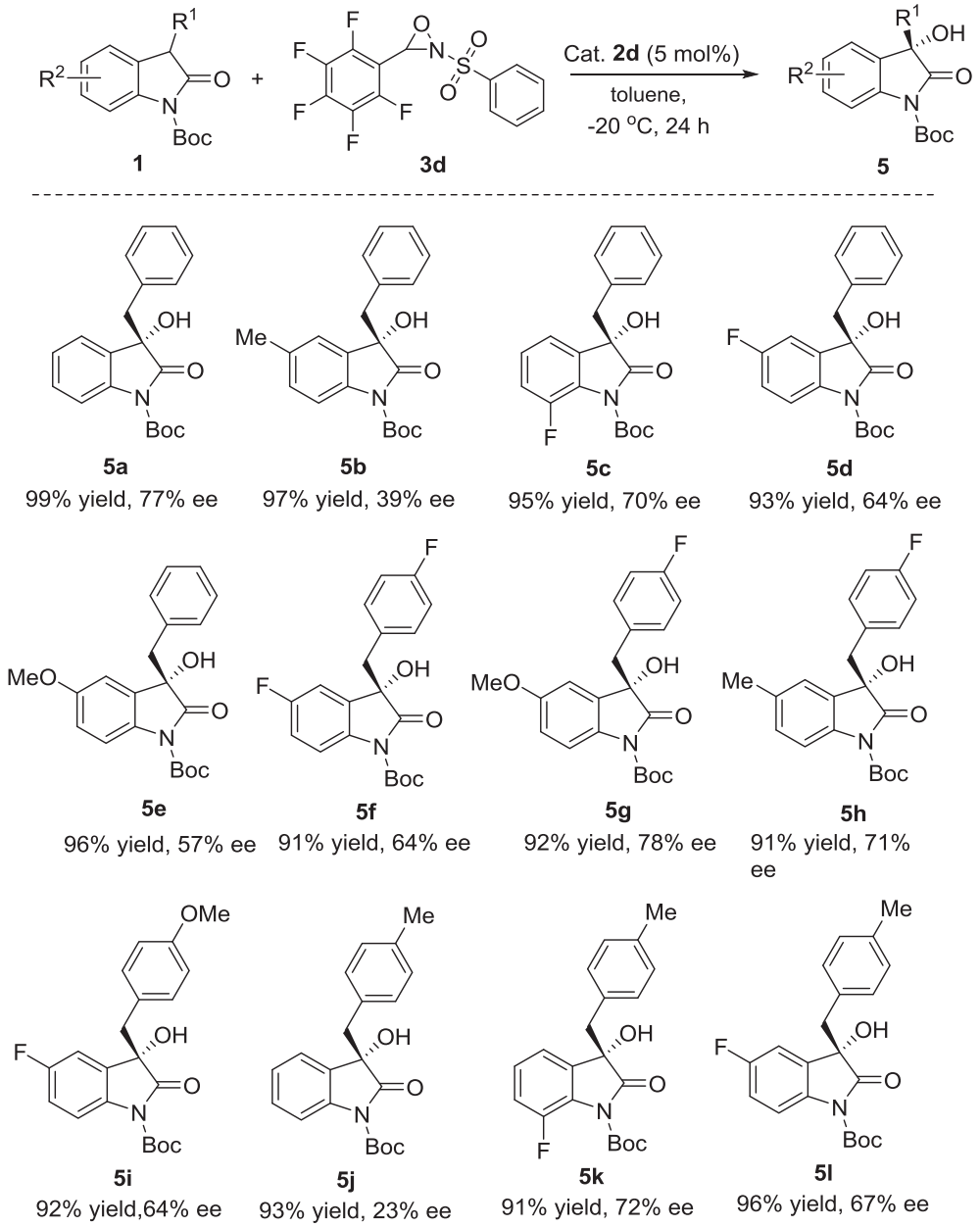
In conclusion, we have developed an iminophosphorane catalyzed enantioselective hydroxylation of *N*-protected 3-substituted oxindoles by using oxaziridines as the hydroxyl reagents. The reaction proceeded smoothly under mild conditions, and the desired oxindole products were obtained in excellent yields of 91–99% and moderate to excellent level of enantiomeric excess

Table 2
Screening of reaction conditions for asymmetric hydroxylations.[a]



Entry	Cat. 2	Solvent	Temp. [°C]	Yield [%][b]	*ee* [%][c]
1	2c	Cyclohexane	25	99	20
2	2a	Cyclohexane	25	99	51
3	2b	Cyclohexane	25	99	11
4	2d	Cyclohexane	25	99	58
5	2e	Cyclohexane	25	99	40
6	2d	Toluene	25	99	57
7	2d	EtOAc	25	99	47
8	2d	DCM	25	99	55
9	2d	Et_2O	25	99	40
10	2d	THF	25	99	45
11	2d	Toluene	−20	99	77
12	2d	Toluene	−30	95	71

[a] Reactions were performed on a 0.1 mmol scale of *N*-Boc-protected oxindole **1l** using oxaziridine **3d** (0.1 mmol, 1.0 equiv.) and 5 mol% catalyst in solvent (2 mL) for 24 h.
[b] Isolated yield.
[c] Determined by HPLC analysis on a chiral stationary phase.



Scheme 3. Substrate Scope of 3-Alkyl Substituted Oxindoles.

(up to 94% *ee*). Studies on the catalytic potentials of these chiral phosphorus-based catalysts are in progress in our laboratories. It is believed that these base catalysts will be suitable for a wide range of catalytic reactions, whose studies in this direction are also underway.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.05.018.

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