



Chiral copper-catalyzed asymmetric monoarylation of vicinal diols with diaryliodonium salts



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ABSTRACT

The copper-catalyzed enantioselective monoarylation of *meso*-1,2-diols by the use of diaryliodonium triflates as aryl sources has been developed. The chiral copper(II) complex catalyzed the asymmetric desymmetrization effectively to afford optically active β -aryloxy alcohols in moderate to high chemical yields and enantioselectivity.

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1. Introduction

The asymmetric transformation of vicinal diols has been energetically pursued because the optically active diol derivatives are highly important as chiral building blocks.^{1,2} In particular, β -aryloxy alcohols prepared from vicinal diols are known as useful synthetic intermediates,³ although the asymmetric monoarylation of vicinal diols is relatively limited. The copper-catalyzed enantioselective monophenylation of vicinal diols with triphenylbismuth diacetate was developed by Brunner et al. and is the only method for this type of transformation.⁴ However, the reaction efficiency, enantioselectivity, and substrate scope in their reports did not reach a sufficient level, leaving a margin for improvement. Therefore, the development of novel synthetic reactions for chiral β -aryloxy alcohols from vicinal diols is still desired.

Recently, diaryliodonium salts have received much attention due to their selectivity, harmlessness, and easy availability.⁵ Based on these advantages, a number of novel and useful reactions with diaryliodonium salts as aryl sources have been developed.^{6,7} Although C–O bond forming reactions with phenols or alcohols were also actively investigated,^{8–11} the asymmetric versions of this type of transformation have never been reported. Herein, we report the chiral copper-catalyzed asymmetric desymmetrization of vicinal diols with diaryliodonium salts.

2. Results and discussion

In the earliest stage of investigation, the chiral copper-catalyzed asymmetric monophenylation of *cis*-1,2-cyclooctanediol **1a** was

examined with a series of diphenyliodonium salts (Table 1). Iodonium salts bearing a halogen or nitrate anion showed low reactivity to give almost racemic **3aa** (entries 1–3). While asymmetric monophenylation with diphenyliodonium triflate led to 90% yield and 59% ee, lower reactivity and enantioselectivity were observed when the counterion was changed from triflate to tetrafluoroborate (entries 4 and 5). Diphenyliodonium hexafluorophosphate afforded a completely racemic product in a good yield (entry 6).

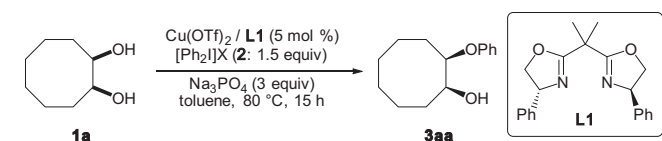
Based on these results, the reaction conditions were optimized using *cis*-1,2-cyclooctanediol **1a** and diphenyliodonium triflate as model substrates (Table 2). Examination of the inorganic bases showed that sodium phosphate tribasic was the reagent of choice (entries 1–5), while *N,N*-diisopropylethylamine promoted the reaction with moderate enantioselectivity (entry 6). In the screening of copper sources, divalent copper salts gave similar or superior results compared to monovalent copper salts, and copper(II) chloride was found to be the most suitable and gave 94% yield and 76% ee (entries 2 and 7–16). The influence of solvents was investigated, and insufficient enantioselectivity was observed with the exception of toluene (entries 2 and 17–20).

Subsequently, the screening of chiral ligands was carried out (Table 3), in which chiral oxazoline-based bidentate or tridentate ligands were employed (Fig. 1). The investigation of substituents at the 4-position in chiral bis(oxazoline) ligands revealed that a simple phenyl group was more effective than electron-rich and larger aryl groups as well as benzyl group (entries 1–5). In addition, an *n*-butyl group on the methylene bridge also proved to be a suitable substituent while an allyl group in addition to a benzyl group led to lower enantioselectivity (entries 6–8). The chiral bis(oxazoline) ligands bearing substituents at the 5-position gave almost racemic products (entries 9 and 10). The asymmetric monophenylation with other various chiral ligands proceeded with moderate

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Table 1
Screening of diphenyliodonium salts in the chiral copper-catalyzed asymmetric monophenylation of *cis*-1,2-cyclooctanediol^a



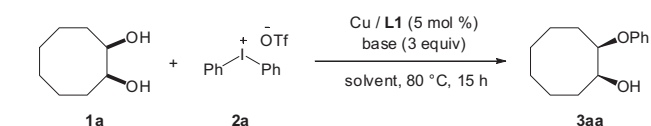
Entry	X	Yield (%)	ee (%)
1	Br	4	3
2	I	1	2
3	NO ₃	15	1
4	OTf	90	59
5	BF ₄	50	29
6	PF ₆	64	0

^a Reaction conditions: *cis*-1,2-cyclooctanediol **1a** (1 mmol), Cu(OTf)₂ (5 mol %), **L1** (5 mol %), diphenyliodonium salt **2** (1.5 mmol), Na₃PO₄ (3 mmol), toluene (1.5 mL), 80 °C, 15 h.

to high yields but the enantioselectivity was quite low (entries 11–18).

Investigation of *meso*-1,2-diols in the chiral copper-catalyzed asymmetric desymmetrization was conducted with diphenyliodonium triflate (**Table 4**). The asymmetric reaction with *cis*-1,2-cyclododecanediol gave the desired product **3ba** with 85% ee, although this substrate showed relatively reduced reactivity compared to *cis*-1,2-cyclooctanediol (entries 1 and 2). In the case of the cyclic *cis*-1,2-diol bearing a π bond, a significant decrease in the levels of reaction progress and enantiocontrol was not observed (entry 3). Cyclic *cis*-1,2-diols with smaller ring sizes led to lower yields and enantioselectivities (entries 1, 4 and 5). The asymmetric

Table 2
Optimization of the reaction conditions in the chiral copper-catalyzed asymmetric monophenylation of *cis*-1,2-cyclooctanediol^a



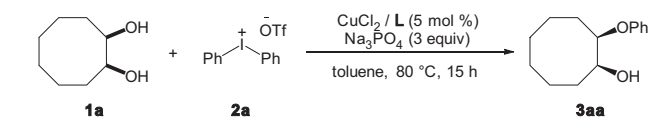
Entry	Cu	Base	Solvent	Yield (%)	ee (%)
1	Cu(OTf) ₂	K ₃ PO ₄	Toluene	21	3
2	Cu(OTf) ₂	Na ₃ PO ₄	Toluene	90	59
3	Cu(OTf) ₂	Li ₃ PO ₄	Toluene	52	9
4	Cu(OTf) ₂	Na ₂ CO ₃	Toluene	50	41
5	Cu(OTf) ₂	NaF	Toluene	88	9
6	Cu(OTf) ₂	DIPEA	Toluene	95	33
7	(CuOTf) ₂ ·tol	Na ₃ PO ₄	Toluene	84	64
8	CuI	Na ₃ PO ₄	Toluene	89	65
9	CuBr ₂	Na ₃ PO ₄	Toluene	93	69
10	CuBr	Na ₃ PO ₄	Toluene	42	39
11	CuCl ₂	Na ₃ PO ₄	Toluene	94	76
12	CuCl	Na ₃ PO ₄	Toluene	89	43
13	CuF ₂	Na ₃ PO ₄	Toluene	9	0
14	Cu(OAc) ₂	Na ₃ PO ₄	Toluene	82	54
15	CuOAc	Na ₃ PO ₄	Toluene	77	67
16	Cu(tfac) ^b	Na ₃ PO ₄	Toluene	82	54
17	Cu(OTf) ₂	Na ₃ PO ₄	DCE ^c	93	2
18	Cu(OTf) ₂	Na ₃ PO ₄	Dioxane	74	11
19	Cu(OTf) ₂	Na ₃ PO ₄	DMA	55	11
20	Cu(OTf) ₂	Na ₃ PO ₄	<i>i</i> -PrOH	27	27

^a Reaction conditions: *cis*-1,2-cyclooctanediol **1a** (1 mmol), diphenyliodonium triflate **2a** (1.5 mmol), Cu (5 mol %), **L1** (5 mol %), base (3 mmol), solvent (1.5 mL), 80 °C, 15 h.

^b tfac: trifluoroacetylacetonate.

^c DCE: 1,2-dichloroethane.

Table 3
Screening of chiral ligands in the chiral copper-catalyzed asymmetric monophenylation of *cis*-1,2-cyclooctanediol^a



Entry	L	Yield (%)	ee (%)
1	L1	94	76
2	L2	96	68
3	L3	75	53
4	L4	51	30
5	L5	78	40
6	L6	87	77
7	L7	84	74
8	L8	71	50
9	L9	81	0
10	L10	8	2
11	L11	59	4
12	L12	60	6
13	L13	49	6
14	L14	64	3
15	L15	65	2
16	L16	56	12
17	L17	82	0
18	L18	77	0

^a Reaction conditions: *cis*-1,2-cyclooctanediol **1a** (1 mmol), diphenyliodonium triflate **2a** (1.5 mmol), CuCl₂ (5 mol %), **L** (5 mol %), Na₃PO₄ (3 mmol), toluene (1.5 mL), 80 °C, 15 h.

monophenylation of the aliphatic linear *meso*-1,2-diol proceeded moderately with 37% ee (entry 6).

The influence of varying diaryliodonium triflates was investigated in the chiral copper-catalyzed asymmetric monoarylation of *cis*-1,2-cyclooctanediol **1a** (**Table 5**). The sterically hindered

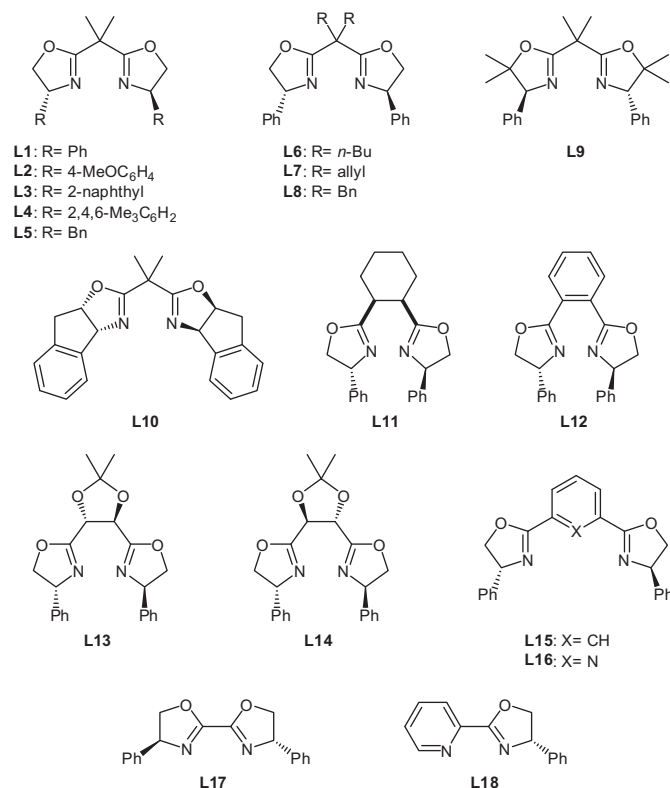


Figure 1. Chiral ligands based on optically active oxazolines.

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