ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

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Cite this: *Org. Chem. Front.*, 2018, **5**, 3098

Dual photoredox and nickel-catalyzed desymmetric C–O coupling reactions: visible light-mediated enantioselective synthesis of 1,4-benzodioxanes†

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Received 1st August 2018,
Accepted 15th September 2018

DOI: 10.1039/c8qo00805a

rsc.li/frontiers-organic

1,4-Benzodioxane widely exists as the core structure in many therapeutic agents and bioactive natural compounds. Hence, to access this kind of molecule, an enantioselective desymmetric C–O cross coupling reaction has been developed through dual visible light photoredox and nickel catalysis. Notably, the use of an axially chiral 2,2′-bipyridine ligand is the key to success. A series of chiral 1,4-benzodioxanes were afforded in high yields and moderate to good enantioselectivity under mild reaction conditions.

Chiral 1,4-benzodioxanes are a kind of important molecule that show a variety of important biological activities. As highlighted in Fig. 1, many chiral natural products and drugs possess the basic 1,4-benzodioxane core.[1] Given their attractive biological significance, synthetic chemists have devoted their attention to the efficient synthesis of chiral 1,4-benzodioxanes in the past few decades.[2] Among the developed protocols, transition-metal-catalyzed intramolecular C–O cross-coupling reactions have been determined to be a direct and efficient method. In an earlier report by Buchwald and co-workers, chiral 1,4-benzodioxanes were successfully obtained through a Pd-catalyzed intramolecular C–O coupling of optically active alcohols (Scheme 1a).[3] Recently, catalytic asymmetric desymmetrizations have been established to be an efficient and general approach to access chiral heterocycles from *meso* substrates.[4,5] In particular, Cai and co-workers smartly used this strategy to realize the synthesis of chiral 1,4-benzodioxanes from 2-(2-halophenoxy)-propane-1,3-diols (Scheme 1b) through asymmetric Pd or Cu catalysis.[6] Nonetheless, elevated temperatures are usually necessary for these reactions; from the

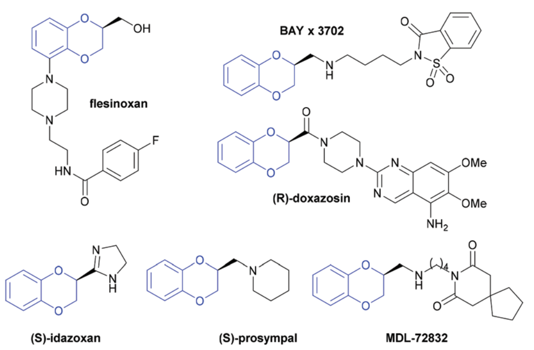
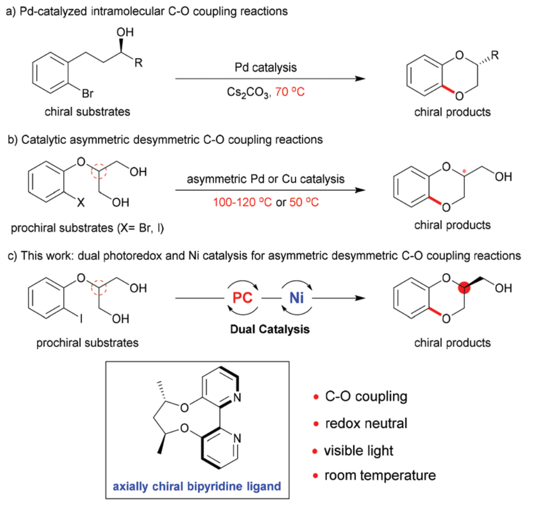


Fig. 1 Selected examples of bioactive 1,4-benzodioxanes.



Scheme 1 Synthetic methods for chiral 1,4-benzodioxanes.

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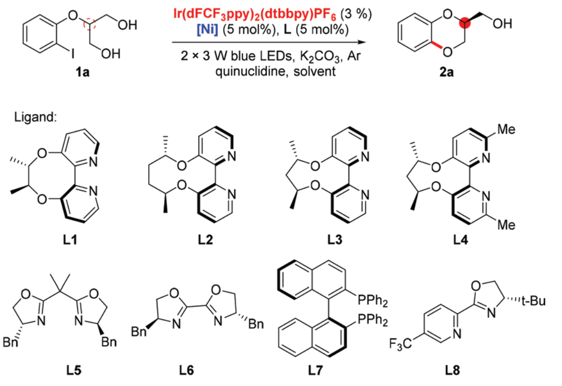
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8qo00805a

perspective of substantial and environmentally friendly synthesis, exploiting new and alternative catalyst systems featuring mild reaction conditions is still highly desirable.

Recently, dual visible light photoredox and transition metal catalysis has been regarded as a powerful tool in modern organic synthesis.[7] Introducing visible light photocatalysis into the transition-metal-catalyzed cross-coupling reactions leads to new organometallic reactivities through photo-induced electron or energy transfer processes. This strategy gives remarkably mild conditions for carbon–carbon and carbon–heteroatom bond formation, which is usually helpful to realize the asymmetric process.[8] However, this dual photo-/transition metal catalysis usually changes the reaction pathway, which would make the traditionally efficient chiral ligand inefficient. We noticed that bipyridine ligands are the most used ligands in such dual catalysis systems,[9] but there are no reports on the use of the chiral bipyridine ligand[10] to achieve the asymmetric coupling reactions. Considering our research interests in the heterocycle synthesis through visible light photocatalysis[11] and transition metal catalysis,[12] herein we have described the first example of dual photoredox and nickel-catalyzed asymmetric desymmetric C–O coupling reactions by utilizing the chiral bipyridine ligand (Scheme 1c). This protocol would afford a novel approach to chiral 1,4-benzodioxanes under extremely mild conditions.

Initially, we used 4,4-di-*tert*-butyl bipyridine (dtbbpy) as the ligand, and $NiCl_2$·glyme and $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ as catalysts, to test the asymmetric desymmetric C–O coupling reaction under the irradiation of 2 × 3 W blue LEDs. The successful conversion of 2-(2-iodophenoxy)propane-1,3-diol (**1a**) into the racemic product **2a** proved the bipyridine to be efficient for the dual photoredox and Ni catalysis system. Encouraged by this result, we started to examine the axially chiral 2,2′-bipyridine ligands.[10d–f] To our delight, the use of ligand **L1** did promote the coupling reaction well, giving the chiral product in 63% yield and 71 : 29 er (Table 1, entry 2). To improve the reaction efficiency and selectivity, we further evaluated many other chiral bipyridine ligands and found that the ligand **L3** stands out as the most efficient one, delivering the product in 77% yield and 84 : 16 er. Preliminary results indicated that a suitable dihedral angle seems important for the enantio-control (Table 1, entries 2–4). Additionally, introducing two additional methyl groups at the *ortho* positions of bipyridine ligand **L3** did not give the desired product (Table 1, entry 5). For comparison with the chiral bipyridine ligands, we also performed the coupling reaction with some other chiral nitrogen- and phosphine-ligands that were previously used in such Cu-, Ni- and Pd-catalyzed asymmetric coupling reactions. As a result, low conversions and enantioselectivities were observed. With **L3** as the best ligand, we continued to examine the effect of nickel salts and solvents (Table 1, entries 10–14); $NiCl_2$·glyme and THF are the optimal choice (Table 1, entry 10, 75% yield, 82 : 18 er). The reaction efficiency can be slightly improved by using 30 W blue LEDs (Table 1, entry 15, 87% yield, 87 : 13 er). Moreover, control experiments demonstrated that a Ni catalyst, a photocatalyst and visible light are all indispensable for the present transformation (Table 1, entries 16–18). The absolute configuration of **2a** was determined to be *S* by comparing with the reported results.[6g]

Table 1 Optimization of the reaction conditions[a]

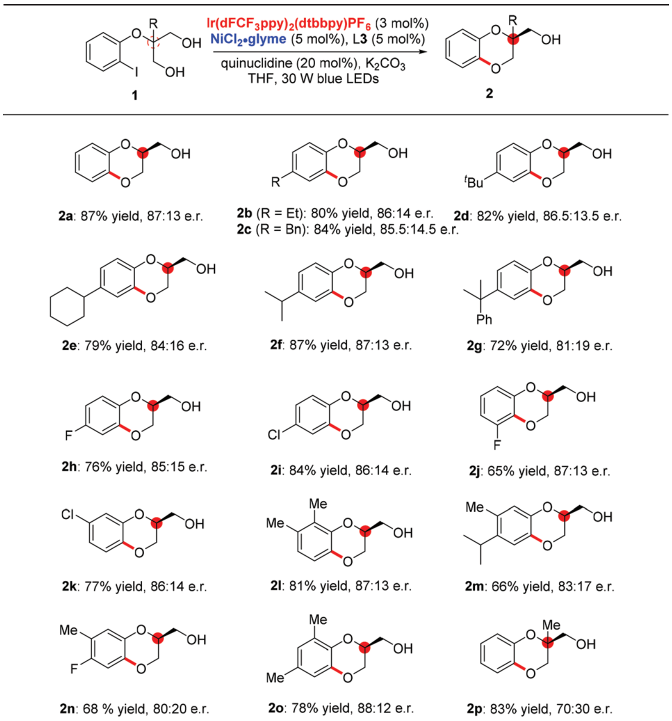


Entry	[Ni]	Ligand	Solvent	Yield[b] (%)	er[c]
1	$NiCl_2$·glyme	dtbbpy	THF	89	—
2	$NiCl_2$·glyme	**L1**	THF	63	71 : 29
3	$NiCl_2$·glyme	**L2**	THF	74	74 : 26
4	$NiCl_2$·glyme	**L3**	THF	77	84 : 16
5	$NiCl_2$·glyme	**L4**	THF	<5	—
6	$NiCl_2$·glyme	**L5**	THF	12	59 : 41
7	$NiCl_2$·glyme	**L6**	THF	10	58 : 42
8	$NiCl_2$·glyme	**L7**	THF	<5	—
9	$NiCl_2$·glyme	**L8**	THF	19	66 : 34
10	$NiBr_2$·glyme	**L3**	THF	75	82 : 18
11	$Ni(cod)_2$	**L3**	THF	81	81 : 19
12	$NiCl_2$·glyme	**L3**	DME	56	77 : 23
13	$NiCl_2$·glyme	**L3**	DCM	47	78 : 22
14	$NiCl_2$·glyme	**L3**	Toluene	<5	—
15[d]	**$NiCl_2$·glyme**	**L3**	**THF**	**87**	**87 : 13**
16[d]	—	**L3**	THF	<5	—
17[d,e]	$NiCl_2$·glyme	**L3**	THF	<5	—
18[d,f]	$NiCl_2$·glyme	**L3**	THF	<5	—

[a] Unless noted otherwise, the reactions were performed with **1a** (0.30 mmol), [Ni] (5 mol%), **L** (5 mol%), $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ (3 mol%), K_2CO_3 (0.30 mmol), quinuclidine (20 mol%), in anhydrous THF (3.0 mL) at room temperature under the irradiation of 2 × 3 W blue LEDs for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Replaced with 30 W blue LEDs. [e] Without a photocatalyst. [f] In the dark.

With the optimal conditions in hand, we next probed the generality of a dual photoredox/Ni catalyst system for the desymmetric C–O coupling reactions. As highlighted in Table 2, most coupling reactions proceeded well, yielding the desired products in good to excellent yields and with moderate to good enantioselectivities. Substrates bearing electron-donating groups (*e.g.*, CH_3, Et, Ph, Bn, *n*-Pr, *t*-Bu, *etc.*) proved to be suitable for this reaction; the corresponding products **2a–2g** were obtained in 72–87% yields and 81 : 19–87 : 13 er. Halide-contained substrates **1h** and **1i** were also applicable, being converted to the products with good results. The substituent position has no obvious effect on the enantioselectivity of cross-coupling reactions. Substrates **1j–1o** with Me, i-Pr, Cl and F at the *para*-, *meta*- or *ortho*-position of the benzene ring all reacted smoothly to give the corresponding products in

Table 2 Scope of the desymmetric C–O coupling reactions for the synthesis of chiral 1,4-benzodioxanes[a,b,c]



2a: 87% yield, 87:13 e.r.
2b (R = Et): 80% yield, 86:14 e.r.
2c (R = Bn): 84% yield, 85.5:14.5 e.r.
2d: 82% yield, 86.5:13.5 e.r.
2e: 79% yield, 84:16 e.r.
2f: 87% yield, 87:13 e.r.
2g: 72% yield, 81:19 e.r.
2h: 76% yield, 85:15 e.r.
2i: 84% yield, 86:14 e.r.
2j: 65% yield, 87:13 e.r.
2k: 77% yield, 86:14 e.r.
2l: 81% yield, 87:13 e.r.
2m: 66% yield, 83:17 e.r.
2n: 68 % yield, 80:20 e.r.
2o: 78% yield, 88:12 e.r.
2p: 83% yield, 70:30 e.r.

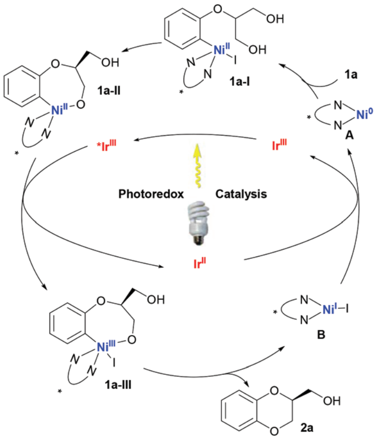
[a] Unless noted otherwise, reactions were performed with **1** (0.30 mmol), NiCl$_2$·glyme (5 mol%), **L3** (5 mol%), Ir(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$ (3 mol%), K$_2$CO$_3$ (0.30 mmol), quinuclidine (20 mol%), in anhydrous THF (3.0 mL) at room temperature under the irradiation of 30 W blue LEDs for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

65–81% yields and 80 : 20–88 : 12 er. The enantioselective formation of quaternary stereocenters is a challenge in asymmetric synthesis. We also tested our dual catalyst system to produce the chiral 1,4-benzodioxane containing an oxa-quaternary stereocenter. As shown in Table 2, a good yield and moderate enantioselectivity were obtained for product **2p**.

To explore the utility of such coupling reactions, a gram-scale reaction was further carried out. When **1a** (10 mmol scale) was subjected to the standard conditions, the corresponding product **2a** was obtained in a comparable result (Scheme 2, 82% yield and 85 : 15 er).

On the basis of our observations and the related literature,[9f] a plausible mechanism for the desymmetric C–O coupling reaction is proposed in Scheme 3. Initially, the substrate **1a** undergoes an oxidative addition to the chiral Ni(0) catalyst and generates a Ni(II) aryl complex **1a-I**. At this stage, the axially chiral 2,2′-bipyridine ligand exhibits a chiral environment and ligand exchange (displacement of the iodo ion with the substrate alcohol) would produce the Ni(II) aryl alkoxide (**1a-II**), which was proposed to be the enantio-determining step. Meanwhile, visible light irradiation of the iridium(III) photocatalyst Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ would produce the long-lived photoexcited *Ir^{III} state. At this juncture, the nickel and photoredox cycles would merge *via* the SET process between the Ni(II) complex **1a-II** and the excited state of Ir(III) photocatalyst, generating the critical Ni(III) aryl alkoxide **1a-III** and the reduced state of Ir(II) photocatalyst. Then this species would undergo a reductive elimination to forge the desired C–O bond and give the final product **2a**. Finally, reduction of Ni(I) to Ni(0) by Ir(II) species completed the whole cycle.

Scheme 2 Scale-up preparation of **2a**.



Scheme 3 Proposed mechanisms.

In conclusion, we have developed a new dual photoredox and nickel catalyst system for asymmetric desymmetric C–O coupling reactions. The use of axially chiral 2,2′-bipyridine ligands was determined to be vital for the successful implementation of this protocol, which produced a variety of chiral 1,4-benzodioxanes in good reaction efficiency and moderate to good selectivity. We believe that this study opens a new route for the asymmetric construction of carbon–heteroatom bonds *via* dual visible light photoredox and transition metal catalysis utilizing the axially chiral 2,2′-bipyridine ligands.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 21472057, 21572074, 21772052 and 21772053) and the Natural Science Foundation of Hubei Province (2015CFA033 and 2017AH047) for the support of this research. We sincerely thank Prof. Y.-G. Zhou for assistance in the supply of axially chiral 2,2′-bipyridine ligands and valuable suggestions about ligand preparation and fruitful discussions.

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