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Development of Novel Chloramphenicol Scaffold-Based Chiral Hydroxyl Oxazoline Ligands and Their Application to the Asymmetric Alkynylation of Isatins

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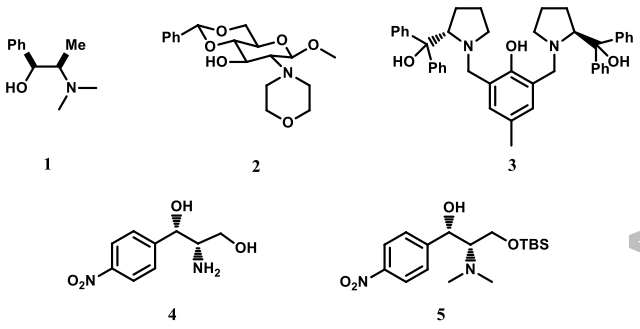
Abstract: The synthesis of new chloramphenicol base-derived chiral hydroxyl oxazoline ligands, and their use in the first $Zn(OTf)_2$-catalyzed enantioselective alkynylation of isatins are described. This transformation features mild reaction conditions, a remarkably broad substrate scope, and excellent functional group tolerance, affording the corresponding tertiary propargylic alcohols in high yields and with high enantioselectivities. The application of chiral hydroxyl oxazolines as ligands in Zn(II)-catalyzed asymmetric alkynylation reactions is unprecedented.

Keywords: asymmetric catalysis, chloramphenicol base, chiral hydroxyl oxazolines, enantioselective alkynylation, isatin

Introduction

The catalytic enantioselective alkynylation of carbonyl compounds is an efficient strategy for the synthesis of optically active propargylic alcohols found in numerous natural products and pharmaceuticals.[1] In 1990, Niwa and Soai first reported the asymmetric synthesis of propargylic alcohols by the enantioselective addition of alkynylzinc reagents to aldehydes in the presence of catalytic amounts of amino alcohol ligands derived from ephedrine.[2] Since then, many chiral ligands, including 2-amino alcohol-type ligands, oxazaborolidine ligands, substituted BINOL ligands, β-sulfonamide alcohol ligands, chiral salen ligands, ProPhenol ligands, and Schiff base amino alcohol ligands have been developed for complexation with different metals (Li, Zn, Cu, Ru, Rh, and Ti) to catalyze enantioselective alkynylations of carbonyl compounds.[3] Among these catalytic systems, zinc complexes have attracted considerable attention owing to their superior catalytic efficiency and environmentally friendliness, with the latter fulfilling the requirements of green and sustainable science. However, the asymmetric alkynylation of carbonyl compounds mediated by truly catalytic amounts of zinc remains an underdeveloped field, with few chiral ligands disclosed to date. For example, Carreira and coworkers reported a pioneering method for the enantioselective addition of terminal alkynes to aldehydes using catalytic amounts of zinc metal and *N*-methylephedrine (**1**) as ligand. Prior to their report, stoichiometric R_2Zn had always been employed.[4]



Scheme 1. Structures of chiral amino alcohol ligands.

Later, Davis and coworkers examined amino alcohol **2**, prepared from a carbohydrate scaffold, as a ligand in the $Zn(OTf)_2$-catalyzed addition of alkynes to aldehydes.[5] More recently, Cook and Wolf reported using ProPhenol ligand **3** for the asymmetric addition

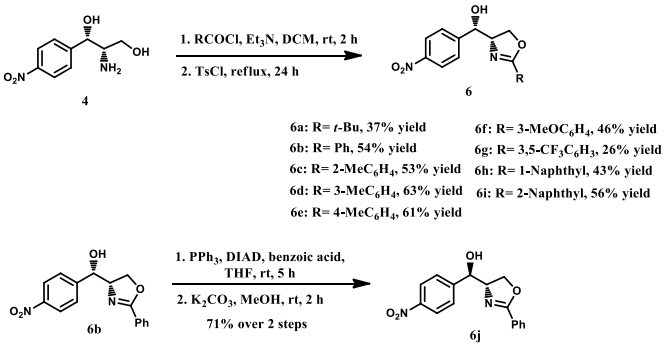
of terminal ynamides to trifluoromethyl ketones to afford CF_3-substituted tertiary propargylic alcohols in up to 99% yield and 96% *ee*.[6] Therefore, almost two decades after the original report, the development of zinc-catalyzed asymmetric alkynylation is still going strong marked by quests for ligands.

In recent years, our group has developed numerous chiral organocatalysts and ligands derived from chloramphenicol base **4**, a by-product of chloramphenicol production, as chiral scaffolds for a variety of highly stereoselective asymmetric transformations.[7] Owing to its easy accessibility, low cost, and good asymmetric induction, we envisioned that the chloramphenicol scaffold could be used as a chiral ligand in the asymmetric alkynylation of carbonyl substrates to produce alcohol products effectively and sustainably. In fact, a literature survey indicated that two elegant precedents exist. Novel amino alcohol ligand **5** derived from chloramphenicol base **4** was developed by Jiang and coworkers and successfully applied to the Zn(II)-catalyzed enantioselective alkynylation of aldehydes and α-ketoesters to generate the desired propargylic alcohols in good yields with excellent *ee* values.[8][9] However, the substrate scope of carbonyl compounds applicable in Jiang's system seems restricted to aldehydes and α-ketoesters. It is desirable to develop novel chiral ligands or catalyst derived from chloramphenicol base for other asymmetric alkynylation transformations.

The catalytic asymmetric alkynylation of isatins remains a formidable challenge, with only two successful examples reported. In 2016, Liu and Feng *et al*. disclosed using copper iodide and a chiral guanidine ligand to synthesize 3-alkynyl-3-hydroxyoxindoles by the addition of terminal alkynes to isatins in high yields and enantioselectivities. [10] Meanwhile, Guo and coworkers achieved the same transformation by employing a catalytic system consisting of Cu(I) and chiral phosphine ligands.[11] To our knowledge, a Zn(II)-catalyzed asymmetric alkynylation of isatins has not been reported. Herein, we describe the preparation of a series of novel chloramphenicol base-derived chiral hydroxyl oxazoline ligands and their application to the Zn(II)-catalyzed enantioselective alkynylation of isatins.

Results and Discussion

Synthesis of hydroxyl chiral oxazolines ligands derived from chloramphenicol base

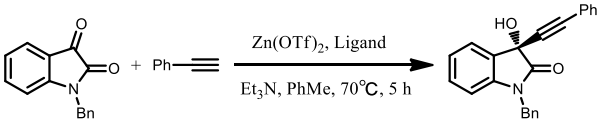


Scheme 2. Synthesis of chiral hydroxyl oxazoline ligands **6a**–**6j**.

Chiral hydroxyl oxazoline ligands **6a**–**6i** were readily prepared from chloramphenicol base **4** in a two-step one-pot procedure (Scheme **2**).[12] In brief, chloramphenicol base was reacted with various acyl chlorides in the presence of Et_3N to afford amides, which were then directly treated with TsCl and Et_3N in boiling dichloromethane to afford desired chiral hydroxyl oxazoline ligands **6a**–**6i**. Chiral ligand **6j** was synthesized by inverting the C-1 configuration in alcohol **6b** under Mitsunobu reaction conditions (PPh_3/DIAD/benzoic acid/THF), followed by carboxylate hydrolysis with K_2CO_3 in methanol. [7d]

Zinc-catalyzed enantioselective alkynylation of isatins using ligands 6a–6j

Table 1. Screening of chiral ligands for enantioselective alkynylation of isatins.



7a 8a 9a

Entry [a]	Ligand	Yield (%)[b]	Ee (%)[c]
1	**5**	88	29
2	**6a**	69	3
3	**6b**	92	40
4	**6c**	51	36
5	**6d**	93	50
6	**6e**	75	32
7	**6f**	81	40
8	**6g**	trace	—
9	**6h**	74	26
10	**6i**	95	61
11	**6j**	31	–18

[a] Unless otherwise noted, reactions were performed in a sealed tube with **7a** (0.2 mmol), **8a** (0.6 mmol), $Zn(OTf)_2$ (0.04 mmol), ligand (0.044 mmol), and Et_3N (0.1 mmol) in PhMe (0.15 mL). [b] Isolated yields. [c] Determined by chiral-phase HPLC.

In a first attempt, we conducted the reaction of 1-benzylindoline-2,3-dione (**7a**) with phenylacetylene (**8a**) using $Zn(OTf)_2$ and amino alcohol ligand **5** at 70 °C. Desired adduct **9a** was isolated in 88% yield, but

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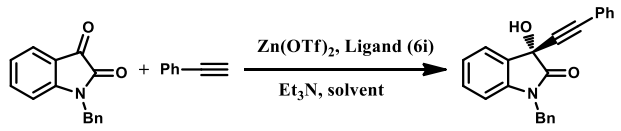
with poor enantioselectivity (Table 1, entry 1). We then turned our attention to chiral hydroxyl oxazoline ligands (Table 1, entries 2–11). Among the first five chiral ligands examined (**6a**–**6e**), ligand **6d**, bearing a methyl moiety at the C-3 position of the phenyl ring, performed best, affording product **9a** in a 93% isolated yield with 50% *ee*. Pleasingly, after further optimization, the alkynylation of isatins proceeded efficiently in the presence of ligand **6i**, bearing a bulky 2-Naph group, affording **9a** in 95% yield with 61% *ee* (Table 1, entry 10). Copper catalysts such as $Cu(OTf)_2$ failed to promote the alkynylation under similar reaction conditions (see Table S1 in the Supporting Information). Interestingly, ligand **6j**, bearing the opposite stereochemistry to ligand **6b** at C-1, gave a low yield (31%) and opposite enantioselectivity (–18% *ee*) under the same reaction conditions (Table 1, entries 11 and 3).

Table 2. Optimization of reaction conditions with ligand **6i**.



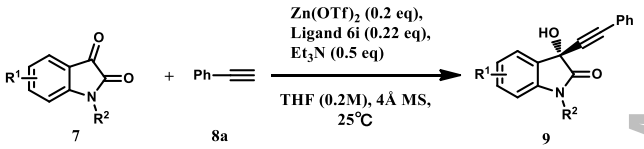
Entry[a]	Temp (℃)	Time (h)	Solvent	Yield (%)[b]	Ee (%) [c]
1[d]	50	10	PhMe	77	69
2	25	48	PhMe	trace	—
3	25	48	$CHCl_3$	75	57
4	25	48	THF	54	87
5[e]	25	40	THF	93	77
6[e, f]	25	40	THF	91	92
7[e, g]	25	48	THF	49	91
8[e, f, h]	25	48	THF	50	84

[a] Unless otherwise noted, reactions were performed in a sealed tube with **7a** (0.2 mmol), **8a** (0.6 mmol), $Zn(OTf)_2$ (0.04 mmol), ligand (0.044 mmol), and Et_3N (0.1 mmol) in solvent (0.5 mL). [b] Isolated yields. [c] Determined by chiral-phase HPLC. [d] Reaction was performed in PhMe (0.15 mL). [e] 4 Å MS additive. [f] Reaction was performed in THF (1 mL). [g] Reaction was performed in THF (2 mL). [h] $Zn(OTf)_2$/Ligand **6i** (1/1.1, 10 mol%), base (25 mol%).

Having identified **6i** as the best catalyst, we next examined the influence of temperature on the reaction. Reducing the reaction temperature to 50 °C resulted in a lower yield, but increased the enantioselectivity (Table 2, entry 1). However, due to the poor solubility of the ligand in PhMe, only partial reaction occurred at 25 °C (Table 2, entry 2). The solvent significantly affected the reactivity and enantioselectivity of the asymmetric alkynylation of **7a** at room temperature (Table 2, entries 2–4), with THF found to be the best solvent in terms of enantioselectivity (87% *ee*). The addition of 4 Å molecular sieves (MS) boosted the reaction yield to 93%, but gave a lower *ee* of 77% (Table 2, entry 5). To our delight, both excellent yield and enantioselectivity were realized by decreasing the substrate concentration from 0.4 M to 0.2 M (Table 2, entry 6). However, further dilution of the substrate to only 0.1 M resulted in a diminished yield (Table 2, entry 7). A reaction with 10 mol% catalyst and 25 mol% base was also carried out, in which both the yield and enantioselectivity decreased (Table 2, entry 8).

With optimized reaction conditions in hand, we then investigated the substrate scope of isatins (Table 3). This protocol was applicable to various substituted *N*-benzylisatins, affording corresponding products **9** in generally good yields (75–90%) with high enantioselectivities (83–93% *ee*), regardless of the electronic character and position of the substituent (entries 1–12). Next, the effect of isatin *N*-substituents on the reaction was studied. Compared with the benzyl-substituted substrate (entry 1), those bearing methyl (entry 13), allyl (entry 14), and *p*-methoxybenzyl (PMB; entry 15) substituents were transformed into the desired products in decreased yields (60–77%), but with excellent enantioselectivities (93–98% *ee*).

Table 3. Substrate scope for isatins.



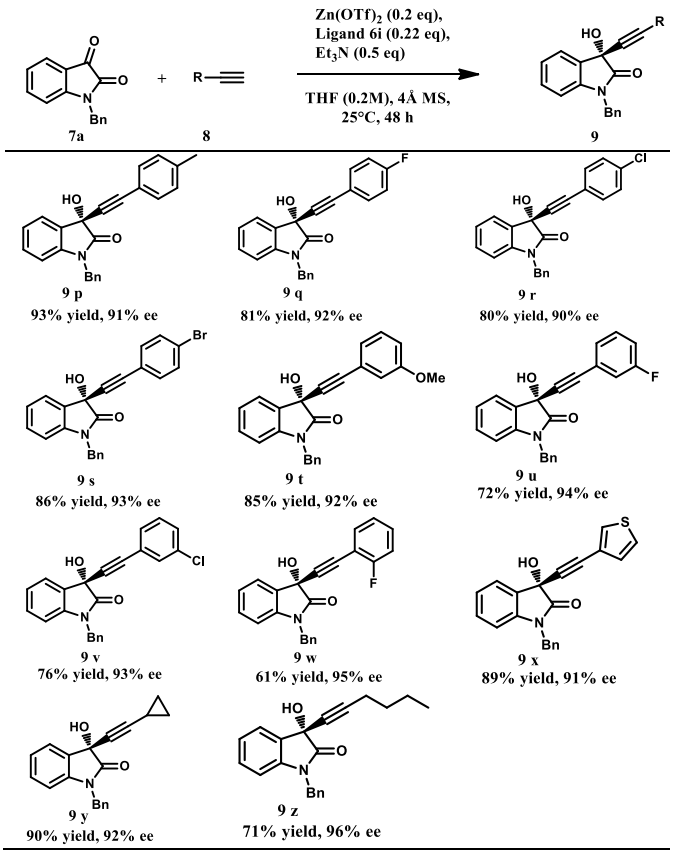
Entry[a]	R^1, R^2	Time (h)	Yield(%)[b]	Ee (%)[c, d]
1	H, Bn	40	91(**9a**)	92 (*S*)
2	4-Cl, Bn	48	86(**9b**)	93
3	4-Br, Bn	48	83(**9c**)	92
4	5-MeO, Bn	40	92(**9d**)	89
5	5-F, Bn	40	96(**9e**)	83
6	5-Br, Bn	40	92(**9f**)	92
7	6-F, Bn	48	76(**9g**)	92
8	6-Cl, Bn	48	75(**9h**)	87
9	7-CF_3, Bn	32	88(**9i**)	90
10	7-Br, Bn	35	87(**9j**)	89
11	7-F, Bn	35	94(**9k**)	87
12	7-Cl, Bn	35	90(**9l**)	85
13	H, Me	60	60(**9m**)	93
14	H, allyl	48	77(**9n**)	95
15	H, PMB	60	67(**9o**)	98

[a] Unless otherwise noted, reactions were performed in a sealed tube with **7** (0.2 mmol), **8a** (0.6 mmol), $Zn(OTf)_2$ (0.04 mmol), ligand (0.044 mmol), and Et_3N (0.1 mmol) in THF (1 mL). [b] Isolated yields. [c] Determined by chiral-phase HPLC. [d] The absolute configuration of **9a** was determined as *S* by comparing the sign of the optical rotation of the major enantiomer with known data. [10, 11]

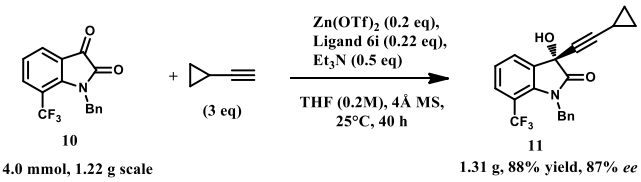
We next focused our attention on the alkynylation of isatin **7a** using a variety of terminal alkynes **8** (Table 4). The substituents on phenylacetylenes could be varied, with high *ee* values obtained (Table 4, **9p**–**9w**). However, terminal alkynes bearing electron-

withdrawing groups exhibited lower reactivities than those bearing electron-donating groups, resulting in a decreased yield (**9p** vs. **9q**). A heteroaryl-substituted alkyne was also tolerated in the reaction, affording product **9x** in excellent yield and enantioselectivity. The developed methodology was further extended to aliphatic alkynes, furnishing the corresponding propargylic alcohol products with 92% *ee* (**9y**) and 96% *ee* (**9z**).

Table 4. Substrate scope for terminal alkynes.[a–d]



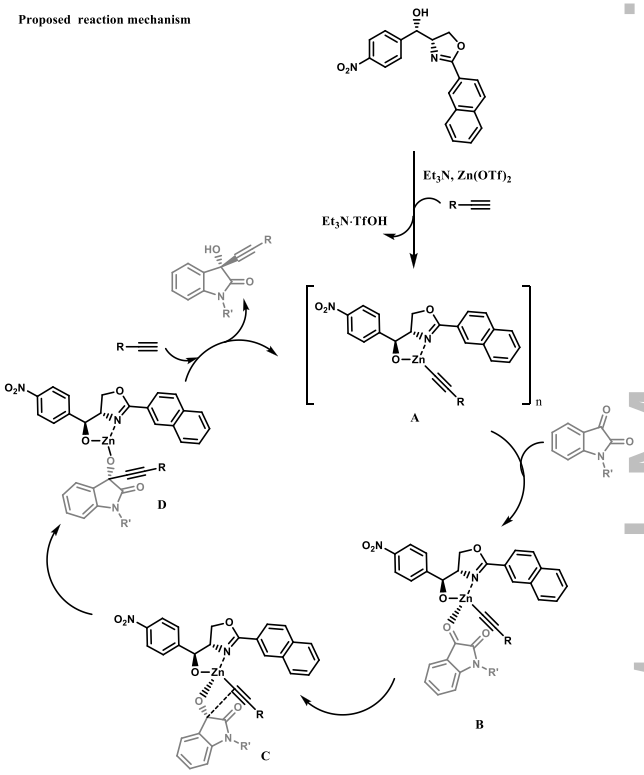
[a] Unless otherwise noted, reactions were performed in a sealed tube with **7a** (0.2 mmol), **8** (0.6 mmol), $Zn(OTf)_2$ (0.04 mmol), ligand (0.044 mmol), and Et_3N (0.1 mmol) in THF (1 mL). [b] Isolated yields. [c] Determined by chiral-phase HPLC. [d] The configuration was determined by analogy to **9a**.



Scheme 3. Gram-scale reaction.

To show the synthetic potential of our developed catalytic system, the Zn(II)-catalyzed enantioselective alkynylation reaction between substrate **10** and cyclopropyl acetylene was carried out on a gram scale, furnishing the corresponding propargylic alcohol product **11** in high yield (88%) with high enantioselectivity (87% *ee*) (Scheme 3).

A possible mechanism for the asymmetric alkynylation of isatins is shown in Scheme 4. Catalyst $Zn(OTf)_2$ first interacts with the chiral hydroxyl oxazoline ligand and terminal alkyne, giving activated Zn-acetylide complex **A** with the loss of triethylamine trifluoromethanesulfonate[13]. Species **A** then interacts with the isatin *N*-substituents, leading to the formation of **B**. The terminal alkyne then migrates to the electron-deficient carbonyl carbon from the least-hindered *Re* face to give **D** via transition structure **C,** as previously suggested in the literature.[14] Finally, protonation of Zn(II) species **D** by the alkyne itself leads to the formation of alkynylation product **9** along with the regeneration of complex **A** for the next catalytic cycle.



Scheme 4. Proposed mechanism for alkynylation of isatin.

Conclusion

In summary, we have developed a series of new chiral hydroxyl oxazoline ligands derived from chloramphenicol base for the first Zn(II)-catalyzed enantioselective alkynylation of isatins. This reaction afforded a wide range of chiral 3-alkynyl-3-hydroxyoxindoles in high yields and with excellent enantioselectivities. Notably, this is the first application of chiral hydroxyl oxazoline ligands to Zn(II)-catalyzed asymmetric alkynylation reactions. We believe that this novel mode of asymmetric induction will provide a new approach in this field. Further investigation into applications of these new

ligands in other asymmetric transformations is in progress.

Experimental Section

General Procedure

To a mixture of $Zn(OTf)_2$ (14 mg, 0.04 mmol), **6i** (15 mg, 0.044 mmol), 4Å MS (100 mg) and Et_3N (15 μL, 0.1 mmol), THF (0.5 mL) was added under N_2 atmosphere and the mixture was stirred at 25 °C for 2 h. Then phenylacetylene (65μl, 0.6 mmol) was added to the mixture. After stirring for 1 h at 25 °C, isatin **7a** (47 mg, 0.20 mmol) and THF (0.5 mL) were added in one portion. The mixture was stirred at 25 °C until the starting material was completely consumed (TLC monitoring). After completion, the mixture was quenched with sat. aq NH_4Cl (10mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to dryness. The crude product was purified by column chromatography (PE/EtOAc=8/1 to 5/1) to give **9a** as a white solid; yield: 62.2 mg (91%, 92% *ee*).

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