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Reversal of Enantioselectivity in the Copper-Aminophenol Sulfonamide Catalyzed Alkynylation of Isatins by Slightly Tuning the Ligand Structure and Basic Additives

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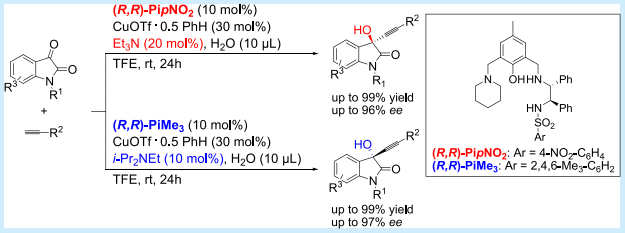
ABSTRACT: A series of new chiral aminophenol sulfonamide ligands with a monochiral arm has been developed for the first Cu(I) catalyzed enantiodivergent alkynylation of isatins. Dramatic reversal of enantioselectivity was accomplished by slightly tuning the substituted benzenesulfonamide and achiral basic additives. A wide range of both terminal alkynes and isatins are tolerated by this new catalyst system with up to 99% yield and 97% *ee*.



Oxindoles with a chiral quaternary stereogenic center containing a hydroxyl group at the 3-position are important structure motifs found in biologically active compounds and natural products.[1] Chiral propargyl alcohols have become an important class of compounds due to their biological activity, unique reactivity, and applicability in the synthesis of complex molecules.[2] It has been found that some compounds with the structure motifs of 3-alkynyl-3-hydroxy-2-oxindoles have important biological activities.[3] The enantioselective alkynylation of isatins is one of the easier and most straightforward approaches to construct optically active 3-alkynyl-3-hydroxy-2-oxindoles. Since Liu and co-workers developed the first highly enantioselective alkynylation of isatins utilizing the bifunctional guanidine/CuI catalyst,[4a] several efficient catalytic systems, including Guo's Cu/phosphine,[4b] Chen's Zn/hydroxy oxazoline,[4c] Wolf's Cu/bisoxazolidine,[4d] Maruoka's Ag/PTC,[4e] Li's Co/bisoxazoline-phosphine,[4f] and Zhang and He's Ag/amidophosphine-urea,[4g] have been developed. Although progress has been achieved, the development of new catalysts for the enantioselective alkynylation of isatins remains challenging and interesting.

The development of a simple methodology for preparing both enantiomers of a chiral compound is important to medical and bioorganic chemistry.[5] Generally, the use of chiral ligands with different configurations is the most straightforward method. However, the two enantiomers of the ligands are not always easily available or economically feasible to synthesize. Besides, the phenomenon of reversal in stereoselectivity with the use of single chiral source derived ligands or catalysts is also a very interesting topic in asymmetric catalysis and organic synthesis.[6] Herein, we describe an enantioselective alkynylation of isatins catalyzed by a Cu(I)/aminophenol sulfonamide complex. Both enantiomers of a series of 3-alkynyl-3-hydroxy-2-oxindoles are readily accessed by slightly tuning the substituted benzenesulfonamide and achiral basic additives.

We recently reported a new type of dinucleating aminophenol sulfonamide ligands (Scheme 1) and their complexes of Cu/Sm,[7a] Ni/Ni,[7b] Co/Co,[7c] and Zn/Sr[7d] as well as their use in asymmetric reactions. Albeit the novel activities observed from the dinucleating ligands, the usage of dual chiral arms requires double chiral materials, which is not economical. In this report, we illustrated an improved ligand design, which reduced the chiral arm to one (**L1**–**L11**, Scheme 1). The redesigned catalytic system enjoys significantly minimized usage of the chiral element in the ligand.

In the preliminary study, the *N*-benzyl-protected isatin **1a** and phenylacetylene **2a** were chosen as model substrates (Table 1). In the presence of aminophenol sulfonamide **L1**/CuOTf (1:1) and Et_3N, only trace 3-alkynyl-3-hydroxyindolinone **3aa** was detected (entry 1, Table 1). As the proportion of CuOTf gradually increased, the reactivity gradually increased (entry 3 vs entries 1 and 2, Table 1). Other achiral basic additives instead of triethylamine were also examined (see the Supporting Information for details). The highest *ee* is obtained in the presence of Et_3N and iPr_2NEt (entries 3 and 4, Table 1). Moreover, without the basic additives, although the reaction activity is greatly reduced, the absolute configuration of the product is reversed (entry 5 vs entry 3 and 4, Table 1). This shows that the achiral base not only affects the reactivity but also affects the interaction

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Scheme 1. Chiral Aminophenol Sulfonamide Ligands

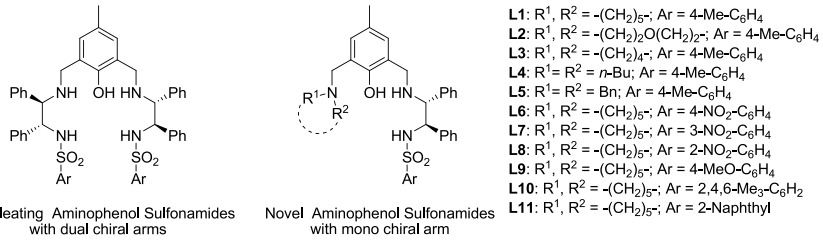
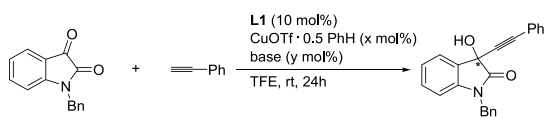


Table 1. Preliminary Screening of Asymmetric Alkynylation of Isatins[a]



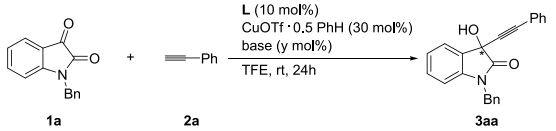
Entry	CuOTf	Base	Yield (%)[b]	*ee* (%)[c]
1	10 mol%	Et_3N (20 mol%)	trace	
2	20 mol%	Et_3N (20 mol%)	54	76 (*R*)
3	30 mol%	Et_3N (20 mol%)	97	77 (*R*)
4	30 mol%	*i*-Pr_2NEt (20 mol%)	54	78 (*R*)
5	30 mol%	none	20	61 (*S*)
6	30 mol%	Et_3N (10 mol%)	97	63 (*S*)
7	30 mol%	Et_3N (30 mol%)	83	73 (*R*)
8	30 mol%	Et_3N (40 mol%)	83	67 (*R*)
9	30 mol%	*i*-Pr_2NEt (10 mol%)	98	62 (*S*)
10	30 mol%	*i*-Pr_2NEt (30 mol%)	62	54 (*R*)
11	30 mol%	*i*-Pr_2NEt (40 mol%)	47	51 (*R*)

[a]Unless otherwise noted, all reactions were carried out with **L1** (10 mol %), CuOTf·0.5PhH, **1a** (0.1 mmol), **2a** (0.4 mmol), and base in trifluoroethanol (1.0 mL) at rt for 24 h. [b]Yield of isolated product. [c]Determined by chiral HPLC.

between the complex and the substrates. Further screening of the amount of the base found that, when the amount of Et_3N or *i*Pr_2NEt is reduced to 10 mol %, the stereoselectivity of the reaction can also be reversed (entries 6−8 vs entry 3, entries 9−11 vs entry 4, Table 1).

Further optimization (Table 2; see the Supporting Information for details) starts with the ligand screening. The results of the achiral arm screening show that the structure motif of piperidine is suitable for this asymmetric reaction (entry 1 vs entries 2−5, Table 2). The screening results of substituted benzenesulfonamides show that *p*-nitrobenzenesulfonamide has the best effect (entries 6−11, Table 2).

Table 2. Further Optimizations[a]



Entry	L	Base	Yield (%)[b]	*ee* (%)[c]
1	**L1**	Et_3N (20 mol%)	94	78 (*R*)
2	**L2**	Et_3N (20 mol%)	95	21 (*R*)
3	**L3**	Et_3N (20 mol%)	88	61 (*R*)
4	**L4**	Et_3N (20 mol%)	79	31 (*R*)
5	**L5**	Et_3N (20 mol%)	44	73 (*S*)
6	**L6**	Et_3N (20 mol%)	92	89 (*R*)
7	**L7**	Et_3N (20 mol%)	97	86 (*R*)
8	**L8**	Et_3N (20 mol%)	27	63 (*R*)
9	**L9**	Et_3N (20 mol%)	83	77 (*R*)
10	**L10**	Et_3N (20 mol%)	73	84 (*R*)
11	**L11**	Et_3N (20 mol%)	89	77 (*R*)
12	**L6**	Et_3N (10 mol%)	97	63 (*R*)
13[d,e]	**L6**	Et_3N (20 mol%)	99	95 (*R*)
14[f]	**L10**	Et_3N (10 mol%)	92	78 (*S*)
15[f]	**L10**	*i*-Pr_2NEt (10 mol%)	99	81 (*S*)
16[d,f]	**L10**	*i*-Pr_2NEt (10 mol%)	99	86 (*S*)

[a]Unless otherwise noted, all reactions were carried out with the ligand (10 mol %), CuOTf·0.5PhH (30 mol %), **1a** (0.1 mmol), **2a** (0.2 mmol), and base in trifluoroethanol (1.0 mL) at rt for 24 h. [b]Yield of isolated product. [c]Determined by chiral HPLC. [d]10 μL of H_2O was added as an additive. [e]0.3 mmol of **2a** was used. [f]0.4 mmol of **2a** was used.

Adding water as an additive and increasing the amount of phenylacetylene can increase the yield and enantioselectivity of the product (entry 13, Table 2). Thus, the optimized reaction conditions for *R*-**3aa** (99% yield, 95% *ee*) entailed the use of CuOTf/**L6** (3:1, 10 mol %) as the catalyst and Et_3N (20 mol %) and H_2O (10 μL) as the additives in trifluoroethanol at rt for 24 h (entry 13, Table 2). To our surprise, when using **L6** as the ligand in the presence of 10 mol % Et_3N, the stereoselectivity of the reaction did not reverse (entry 12, Table 2, vs entry 6, Table 1). Therefore, we reoptimized the reaction conditions to obtain the *S*-enantiomer in high yield with high enantioselectivity (see the Supporting Information for details). The *S*-**3aa** can be obtained in 99% yield with 86%

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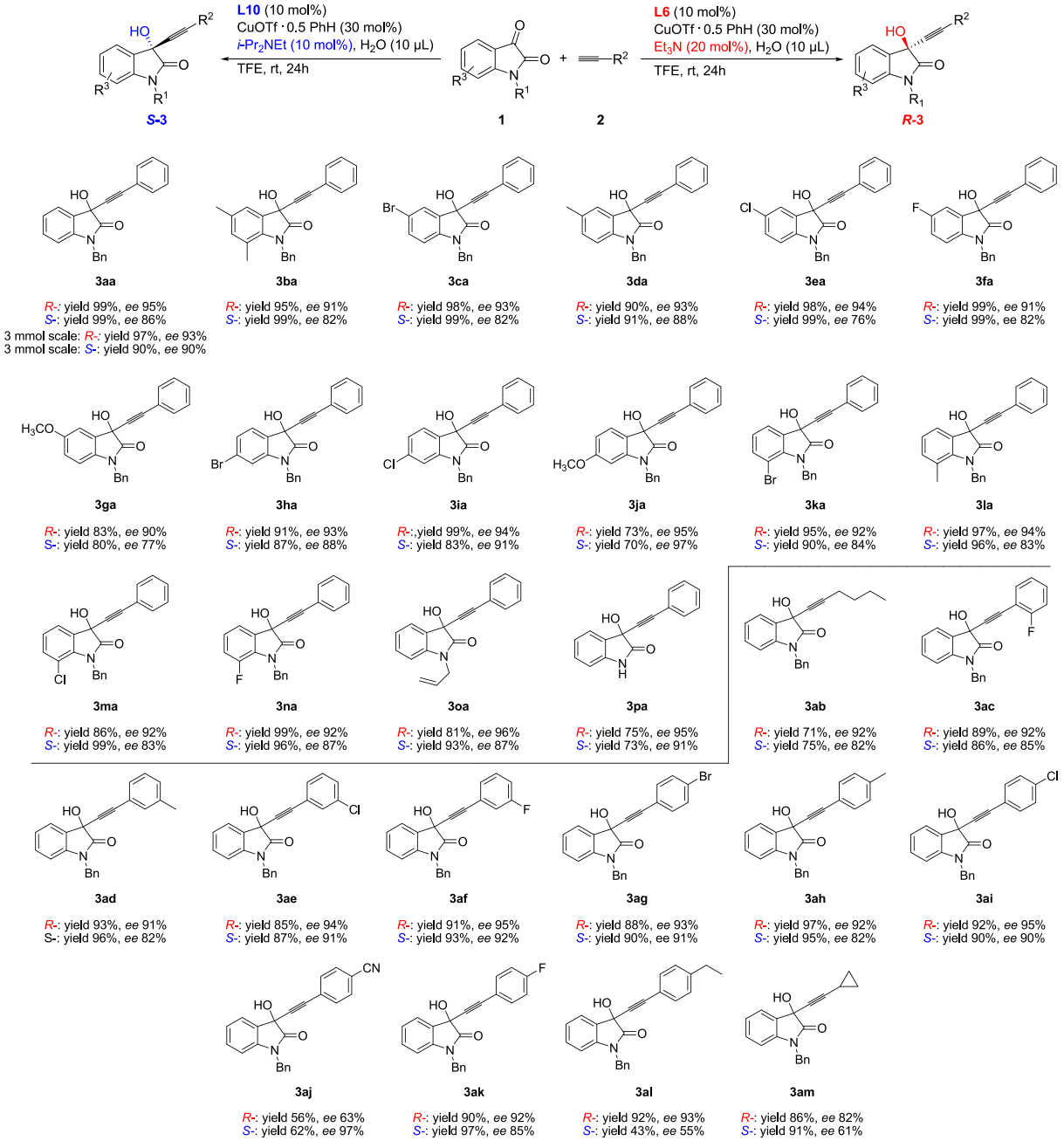
Scheme 2. Substrate Scope



[a]Standard conditions for *R*-**3**: **L6** (10 mol %), CuOTf·0.5PhH (30 mol %), **1** (0.1 mmol), **2** (0.3 mmol), Et_3N (20 mol %), and H_2O (10 μL) in trifluoroethanol (1.0 mL) at rt for 24 h. Standard conditions for *S*-**3**: **L10** (10 mol %), CuOTf·0.5PhH (30 mol %), **1** (0.1 mmol), **2** (0.4 mmol), *i*-Pr_2NEt (10 mol %), and H_2O (10 μL) in trifluoroethanol (1.0 mL) at rt for 24 h.

ee by switching the substituent on the benzenesulfonamide from *p*-NO_2- (**L6**) to 2,4,6-trimethyl- (**L10**) and changing the base from Et_3N (20 mol %) to *i*Pr_2NEt (10 mol %) (entries 14−16, Table 2).

To test the generality of the catalytic systems and the interesting reversal of the enantioselectivity, a wide range of isatins and alkynes were exposed to the optimized reaction conditions (Scheme 2). The reaction could be conducted on a gram scale, and the corresponding products could be obtained in 97% yield (0.99 g) with 93% *ee* for *R*-**3aa** and 90% yield (0.92 g) with 90% *ee* for *S*-**3aa**. To our delight, a complete switch in stereoselectivity was observed for all of the substrates. Generally, isatins having different substituents react with **2a** in good to excellent yields with high enantioselectivities (73−99% yields and 90−95% *ee* for the *R*-products; 70−99% yields and 77−97% *ee* for the *S*-products) regardless of the inductive effect and the position of the substituent (**3aa**−**3na**). *N*-Allyl and *N*-H isatins are also tolerant in this catalytic system (**3oa** and **3pa**). The scope of terminal alkynes was also examined. Most of the tested aromatic alkynes, such as halogen and methyl substituted phenylacetylenes on a phenyl ring, can be employed in this reaction, giving the corresponding products in good to excellent yields with high enantioselectivities (85−97% yields and 91−95% *ee* for the *R*-products; 86−97% yields

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and 82−97% *ee* for the *S*-products) (**3ac**−**3ai** and **3ak**). Linear alkynes exhibited lower reactivity, but the enantioselectivity is maintained (**3ab**). The reactivity of cyclic alkynes is higher than that of linear alkynes, but the enantioselectivity is reduced (**3am**). The strong electron-withdrawing CN group has a neglectable influence on the yield. The *S*-**3aj** was obtained with excellent enantioselectivity, while only moderate *ee* was obtained for the *R*-**3aj**. For *p*-Et-phenylacetylene, satisfactory results were obtained for the *R*-product, but the yield and *ee* of the *S*-product were not good (**3al**).

To gain some insights into the chiral copper complex, the relationship between the *ee* values of product **3aa** and the ligand **L6** or **L10** at different ratios of the ligand to CuOTf (1:2 and 1:3)[8] was investigated (Figure 1).[9] Positive nonlinear

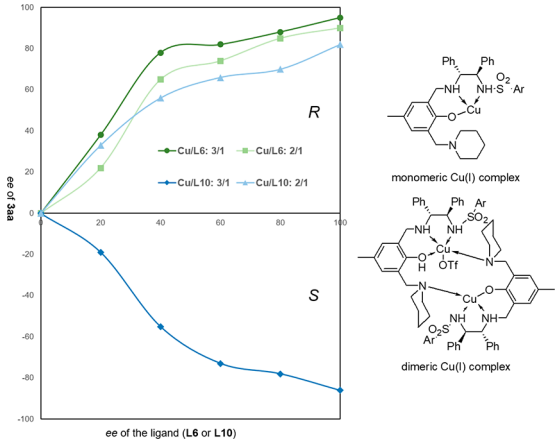

Figure 1. Nonlinear effect studies and the speculated structure of the complexes determined by HRMS (ESI).

effects in all cases were observed, which suggested catalyst aggregation. It is amazing that, when the ratio of **L10** to CuOTf is 1:2, the product stereoselectivity is reversed compared with **L10**/CuOTf in 1/3. And the absolute configuration of the product is the same when the ratio of **L6** to CuOTf is 1/2 and 1/3. The ESI-MS studies were also carried out—only monomeric and dimeric copper complexes were found, and no dinuclear copper complexes were found (for details, see the Supporting Information). The speculated structures of the monomeric and dimeric copper complexes are shown in Figure 1. As the excess of Cu(I) relative to the ligand increases, the yield is improved without affecting the *ee* (entries 1−3, Table 1). In addition, the basic additives can affect the stereoselectivity of the reaction (entries 3−5, Table 1). We speculate that the excess copper would not promote the formation of a dinuclear copper complex but activate the alkynes through the σ-bond and π-system.[10] Combined with the results of positive nonlinear effects, we speculate that the dimeric copper complex (Figure 1) should be the catalytically active species (a proposed catalytic cycle is described in the Supporting Information).

In summary, we have developed a series of new chiral aminophenol sulfonamide ligands with a monochiral arm for the first Cu(I) catalyzed enantiodivergent alkynylation of isatins. Dramatic reversal of enantioselectivity was accomplished by slightly tuning the substituted benzenesulfonamide and achiral basic additives. In contrast to previous results, both enantiomers of a variety of substrates were readily obtained in high enantioselectivity. Further studies are currently underway to elucidate the reason for the enantiodivergence, and the application of these new ligands to develop other asymmetric transformations is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01896.

Experimental details, characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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