Asymmetric Catalysis

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Copper/Guanidine-Catalyzed Asymmetric Alkynylation of Isatins

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Abstract: *The highly enantioselective alkynylation of isatins, catalyzed by a bifunctional guanidine/CuI catalyst under mild reaction conditions, is described. The reaction is broad in scope with respect to alkyl/aryl-substituted terminal alkynes and substituted isatins, thus affording bioactive propargylic alcohols in excellent yields and enantioselectivities.*

The catalytic asymmetric alkynylation of carbonyl compounds is a fundamental reaction in organic chemistry and allows an efficient way to construct optically active propargylic alcohols, which are versatile intermediates and building blocks for the synthesis of useful natural products and drugs.[1] In terms of atom economy and operating simplicity, utilizing readily available alkynylide nucleophiles for C–C bond formations which do not require strong bases, such as carbanions,[2] metalated amides,[3] alkoxides,[4] and hydroxides[5] is desirable. The catalytic in situ generation of metalated terminal alkynes under reaction conditions compatible with electrophilic addition of carbonyl compounds is well appreciated.[6] Moreover, in comparison with the asymmetric alkynylation of aldehydes,[7–9] the reaction of ketones[10] to form a tetrasubstituted carbon center has been very limited. Initiated by the pioneering work of Carreira and co-workers on the alkynylation of aldehydes,[8a,b] Jiang and co-workers utilized the Zn^{II}/N-methylephedrine derivative/Et_3N system in the asymmetric alkynylation of α-ketoesters at 70 °C.[11] Ohshima, Mashima, and co-workers[12] reported an efficient asymmetric alkynylation of ethyl trifluoropyruvate catalyzed by a C_1-symmetric Rh/phebox complex. Both Zn^{II} and Rh^{III} weaken the terminal C(sp)–H so that weakly basic amines or acetate counterions can effect deprotonation with concomitant generation of the corresponding metal alkynilides. The groups of Chan[10d,i] and Wang[10h] realized the $Cu(OTf)_2$/chiral camphorsulfonamide promoted alkynylation of ketones in the presence of a stoichiometric amount of alkynylzinc. The complexation of terminal alkynes with copper(I) in the presence of amines is well known,[13] and both Cu^I/diphosphine and Cu^I/pybox complexes in the catalytic alkynylation of trifluoromethyl ketones gave only moderate enantioselectivity (up to 52% *ee*),[14a] and good results in the reaction of isochroman ketals.[14b]

3-Substituted 3-hydroxyoxindole scaffolds are common in various natural products and biologically active compounds.[15] For example, 3-alkynyl-3-hydroxyindolin-2-ones, analogues of efavirenz, show a biological effect on *Echinococcus multilocularis* metacestodes.[16] Racemic derivatives have been synthesized through the addition of terminal alkynes to isatins by using either *n*BuLi, $ZnEt_2$, or CuI/DBU.[17] Meanwhile, ketimines derived from isatins have been employed in copper(I)-catalyzed stereoselective alkynylations for the total synthesis of KAE609.[18] Herein, we have developed an asymmetric version for enantioselective alkynylation of isatins to generate products useful for pharmacological evaluation. Otherwise, chiral guanidine derivatives have been developed as useful organocatalysts[19] and ligands[20] in recent years. Our group successfully explored chiral guanidine/Cu^I complexes in the asymmetric C–H insertion of terminal alkynes with α-diazoesters and other reactions.[21] Taking inspiration from the known chemistry of copper(I) and acetylenes, as well as the promising application of chiral guanidine ligands in asymmetric catalysis, we sought to extend chiral guanidine/Cu^I catalysts for the asymmetric alkynylation of isatins. Following an expanded screening of ligand structures, we observed that a new bifunctional guanidine ligand bearing an acyclic guanidine unit and a sulfonamide unit was a good candidate (Figure 1). The chiral guanidine **L6** in combination with CuI and 2,4,6-collidine leads to the generation of the desired 3-alkynyl-3-hydroxyoxindoles. Herein, we report our progress in promoting the copper-catalyzed enantioselective alkynylation of isatins where a range of terminal alkynes and substituted isatins are tolerated, thus affording 3-alkynyl-3-hydroxyoxindoles in high yield and with excellent enantioselectivity under mild reaction conditions.

In our preliminary study, we chose the N-benzyl-protected isatin[22] **1a** and phenylacetylene (**2a**) as model substrates

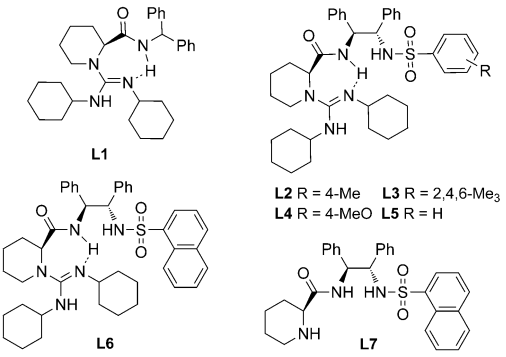

Figure 1. Structures of chiral guanidines and amide.

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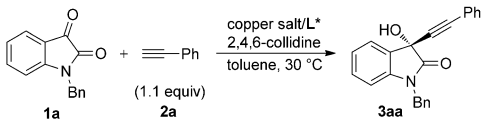
Table 1: Optimization of the reaction conditions.



Entry	L*	Base	[Cu]	Yield [%][b]	*ee* [%][c]
1[a]	**L1**	–	CuI	8	0
2[a]	**L2**	–	CuI	28	67
3[a]	**L2**	Li_2CO_3	CuI	21	55
4[a]	**L2**	Cy_2NH	CuI	22	51
5[a]	**L2**	DMAP	CuI	7	30
6[a]	**L2**	pyridine	CuI	8	47
7[a]	**L2**	2,6-lutidine	CuI	34	78
8[a]	**L2**	2,4,6-collidine	CuI	50	81
9[d]	**L2**	2,4,6-collidine	CuI	87	82
10[d]	**L2**	2,4,6-collidine	CuCl	4	61
11[d]	**L2**	2,4,6-collidine	CuBr	5	82
12[d]	**L2**	2,4,6-collidine	$Zn(OTf)_2$	NR	–
13[d]	**L3**	2,4,6-collidine	CuI	92	89
14[d]	**L4**	2,4,6-collidine	CuI	55	77
15[d]	**L5**	2,4,6-collidine	CuI	74	81
16[d]	**L6**	2,4,6-collidine	CuI	98	96
17[e]	**L6**	2,4,6-collidine	CuI	89	96
18[f]	**L6**	2,4,6-collidine	CuI	34	95
19[d]	**L7**	2,4,6-collidine	CuI	trace	−26

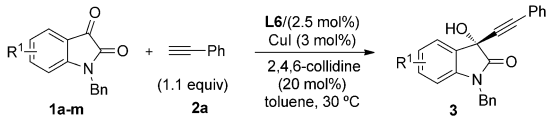
[a] Unless otherwise noted, all reactions were carried out with **L*** (10 mol%), copper salt (10 mol%), **1a** (0.10 mmol), **2a** (0.11 mmol), and base (20 mol%) in toluene (0.5 mL) at 30°C for 2 days. [b] Yield of isolated product. [c] Determined by chiral-phase HPLC. [d] CuI (12 mol%), base (40 mol%) for 4 days. [e] **L**/CuI (1/1.2, 2.5 mol%), base (20 mol%) for 3 days. [f] **L**/CuI (1/1.2, 1.0 mol%), base (20 mol%) for 3 days. DMAP = 4-(*N*,*N*-dimethylamino)pyridine.

(Table 1). In the presence of CuI, the guanidine-amide **L1** gave the racemic 3-alkynyl-3-hydroxyindolinone **3aa** in only 8% yield (entry 1). Upon investigating a variety of chiral guanidines in combination with CuI, we determined that installing a sulfonamide unit into the guanidine progenitor increased both the yield and the enantioselectivity. The sulfonamide moiety might act as the hydrogen-bond donor for the activation of isatin. The CuI/**L2** catalyst can deliver the product **3aa** in 28% yield and 67% *ee* (entry 2 versus entry 1). The efficiency of achiral basic additives, which play an important role in forming copper(I) acetylide with terminal alkynes,[23] was then examined. Li_2CO_3 and dicyclohexylamine gave no improvement for the outcomes (entries 3 and 4), and DMAP and pyridine decreased the reactivity dramatically (entries 5 and 6). Delightedly, when the reaction was carried out with 20 mol% of 2,4,6-collidine, **3aa** was obtained in 50% yield and 81% *ee* (entry 8). A better yield can be achieved by increasing the amount of the base and CuI (entry 9; see the Supporting Information). The evaluation of the copper salts showed that the reactivity decreased dramatically when either CuBr or CuCl was used (entries 9–11). $Zn(OTf)_2$ could not promote the alkynylation under the present reaction conditions (entry 12). We next identified the optimal subunits of the chiral guanidine ligand (Figure 1) and found that the substituent on the phenylsulfonyl moiety of the guanidine ligand affected the selectivity and the reactivity (entries 13–16). Increasing the steric hindrance of the phenylsulfonyl moiety resulted in higher enantioselectivity and yield (**L3** versus **L2** and **L5**), while **L4**, having an electron-donating substituent at *para*-position, decreased both the yield and the *ee* value, thus indicating the importance of the NH bond of sulfonamide. The guanidine **L6**, bearing a 1-naphthyl group, achieved the best result of 98% yield and 96% *ee* (entry 16). Remarkably, a promising reactivity profile was finally established using 2.5 mol% of **L6**/CuI, and **3aa** was afforded with an encouraging *ee* value of 96% with an 89% yield upon isolation (entry 17). Further decreasing the catalyst loading to 1 mol% resulted in a dramatically lower yield (entry 18). Removing the amidine unit of the guanidine gave the amide **L7**, which afforded trace amounts of product with a reversal of enantioselection (entry 19), thus indicating that the guanidine moiety of **L6**, like the sulfonamide moiety, had a great influence on enantiofacial control and activation.

To determine the substrate scope, a wide variety of isatins was exposed to the optimized reaction conditions (Table 2). Generally, isatins having electron-withdrawing substituents react with **2a** in good yields and enantioselectivities (95–99% yields and 94–97% *ee*) regardless of the position of the substituent (entries 2–5, and 8–13). With methoxy and trifluoromethoxy substituents at the five-position, the reactions were resulted in high enantioselectivities, albeit with slightly reduced yields (entries 6 and 7). A gram-scale synthesis of **3aa** was achieved and maintained similar yield and enantioselectivity (entry 1). The absolute configuration of **3aa** was determined to be *S* by X-ray crystallography analysis,[24] and the others show a similar stereoarrangement based on the CD spectra analysis (see the Supporting Information).

Next, variation of the terminal alkynes was studied using the 5-fluoro-substituted isatin **1c** as the electrophile (Table 3). By using aryl-substituted alkynes **2b–h**, the reactions pro-

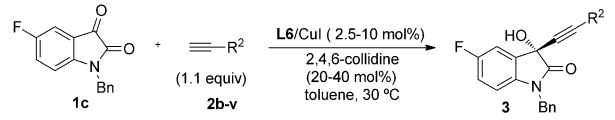
Table 2: Substrate scope for isatins.[a]

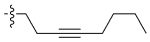
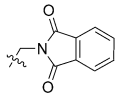


Entry[a]	**1**: R^1	Yield [%][b]	*ee* [%][c]
1[d]	**1a**: H	89 (**3aa**)	96 (*S*)[24]
2	**1b**: 4-Cl	95 (**3ba**)	95
3	**1c**: 5-F	99 (**3ca**)	96
4	**1d**: 5-Br	98 (**3da**)	94
5	**1e**: 5-I	99 (**3ea**)	94
6	**1f**: 5-MeO	86 (**3fa**)	97
7	**1g**: 5-F_3CO	87 (**3ga**)	94
8	**1h**: 7-F	98 (**3ha**)	96
9	**1i**: 7-Cl	98 (**3ia**)	97
10	**1j**: 7-Br	99 (**3ja**)	97
11	**1k**: 7-I	96 (**3ka**)	97
12	**1l**: 7-F_3C	99 (**3la**)	93
13	**1m**: 7-F_3CO	98 (**3ma**)	96

[a] All reactions were carried out with **L6**/CuI (1/1.2, 2.5 mol%), **1**·(0.20 mmol), **2a** (0.22 mmol), and 2,4,6-collidine (20 mol%) in toluene (0.5 mL) at 30°C for 3 days. [b] Yield of isolated product. [c] Determined by chiral-phase HPLC. [d] **1a** (5.0 mmol) and **2a** (1.1 equiv).

Table 3: Substrate scope for terminal alkynes.

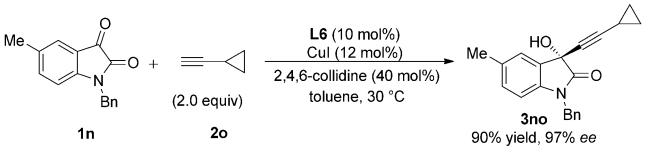


Entry	**2**: R^2	Yield [%][d]	*ee* [%][e]
1[b]	**2b**: 2-FC_6H_4	98 (**3cb**)	96
2[a]	**2c**: 3-FC_6H_4	99 (**3cc**)	93
3[b]	**2d**: 4-FC_6H_4	89 (**3cd**)	93
4[b]	**2e**: 3-ClC_6H_4	90 (**3ce**)	93
5[a]	**2f**: 3-MeC_6H_4	92 (**3cf**)	95
6[a]	**2g**: 4-MeC_6H_4	99 (**3cg**)	96
7[b]	**2h**: 3-$MeOC_6H_4$	89 (**3ch**)	94
8[a]	**2i**: Bn	90 (**3ci**)	96
9[a]	**2j**: CH_2OCOEt	85 (**3cj**)	96
10[a]	**2k**: CH_2OCOPh	90 (**3ck**)	95
11[a]	**2l**: CH_2OtBu	91 (**3cl**)	95
12[a]	**2m**: CH_2NHBoc	79 (**3cm**)	89
13[a]	**2n**: *i*Pr	86 (**3cn**)	95
14[a]	**2o**: 	89 (**3co**)	96
15[a]	**2p**: 	70 (**3cp**)	93
16[a]	**2q**: 	80 (**3cq**)	94
17[a]	**2r**: 	97 (**3cr**)	95
18[c]	**2s**: nC_5H_{11}	80 (**3cs**)	94
19[c]	**2t**: $nC_{10}H_{21}$	78 (**3ct**)	89
20[c]	**2u**: 	89 (**3cu**)	94
21[a]	**2v**: 	97 (**3cv**)	95

[a] Unless otherwise noted, all reactions were carried out with **L6** (2.5 mol%), CuI (3 mol%), **1c** (0.20 mmol), **2** (0.22 mmol) and 2,4,6-collidine (20 mol%) in toluene (0.5 mL) at 30°C for 3 days. [b] **L6**/CuI (1/1.2, 5 mol%). [c] **L6**/CuI (1/1.2, 10 mol%) and 2,4,6-collidine (40 mol%) at 30°C for 4 days. [d] Yield of isolated product. [e] Determined by chiral-phase HPLC. Boc = *tert*-butoxycarbonyl.

ceeded well (89–99% yields and 93–96% *ee*; entries 1–7). The electronic properties and positions of the substituents on the phenyl group had a slight effect on the activity (**3cb–ch**). A re-optimization of the catalyst loading to 5 mol% for the reaction of 2-fluoro-, 4-fluoro-, 3-chloro-, and 3-methoxy-substituted phenylacetylene resulted in good yields and excellent enantioselectivities. With alkyl-substituted alkynes possessing functional groups, such as propionate, benzoate, ether, or amine, the corresponding products **3cj–cm** were generated in 79–90% yields and 89–96% *ee* (entries 9–12). Moreover, alkynes bearing branched and cyclic alkyl groups, or an alkene group, could be successfully utilized, thus forming the products **3cn–cr** in 70–97% yields and 93–96% *ee* (entries 13–18). With alkynes having longer substituted alkyl groups (**2s–u**), it was advantageous to use a higher amount of catalyst to compensate for the reduction in reaction rate while maintaining high levels of enantiocontrol (78–89% yield and 89–94% *ee*, entries 19 and 20).

The reaction between the 5-methylisatin **1n** and cyclopropylacetylene (**2o**) proceeded smoothly, thus generating the desired product **3no** in 90% yield and 97% *ee* (Scheme 1). This product presented a greater activity than



Scheme 1. Synthesis of the biologically active product **3no**.

efavirenz against HIV-1 replication and was not significantly cytotoxic.[25] The readily available of class of optically active 3-alkynyl-3-hydroxyindolin-2-ones will allow the selection of compounds to establish structure–activity relationships.

In summary, the highly enantioselective direct addition of terminal alkynes to isatins has been developed. A new bifunctional chiral guanidine ligand in combination with CuI was proven efficient for the alkynylation under mild reaction conditions. Good levels of reactivity and excellent enantioselectivities were obtained across a diverse range of alkyl- and aryl-substituted terminal alkynes, as well as with various substituted isatins. This reaction provides an efficient route to enantiomerically enriched propargylic alcohols which demonstrate potent bioactivities. Further work to uncover the reaction mechanism and the application of the catalyst to develop other novel asymmetric reactions is ongoing in our laboratories.

Experimental Section

To a mixture of CuI (3 mol%), **L6** (2.5 mol%) and **1** (0.20 mmol) was added in toluene (0.5 mL) under an inert atmosphere. The mixture was stirred for 30 min at 30°C, followed by the additions of base (20–40 mol%) and **2** (0.22 mmol). The resulting mixture was stirred for 3 days at 30°C and the product **3** was purified by flash chromatography.

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