Published in final edited form as:

Angew Chem Int Ed Engl. 2019 March 11; 58(11): 3402–3406. doi:10.1002/anie.201814074.

Catalytic Enantioselective Ynamide Additions to Isatins: Concise Access to Oxindole Alkaloids

Max Moskowitz and Prof. Christian Wolf*

Department of Chemistry, Georgetown University, 37th and O Streets, Washington, D.C. 20057 (USA)

Abstract

The highly enantioselective addition of terminal ynamides to a variety of isatins, catalyzed by a bisoxazolidine copper complex under mild, base-free reaction conditions, is described. The reaction is broad in scope, scalable, applicable to unprotected isatins and provides efficient access to 3-hydroxyoxindoles carrying a tetrasubstituted chirality center with excellent yields and enantioselectivities. Synthetically versatile, multifunctional 3-hydroxyindolinones are obtained via hydration, partial hydrogenation or hydroxyacyloxylation of the ynamide moiety at room temperature and exhaustive hydrogenation followed by reductive detosylation and spontaneous cyclization affords cinchonamidines alkaloids.

Graphical Abstract

Terminal ynamide additions to isatins are accomplished with high yields and enantioselectivities via base-free Cu(I)-bisoxazolidine catalysis. This approach provides efficient access to chimonamidines and 3-hydroxyindolinones carrying a tetrasubstituted chirality center with a synthetically versatile ynamide moiety.

* cw27@georgetown.edu.

Conflict of interests

The Wolf bisoxazolidine ligand **L6** is commercially available at Strem Chemicals (#07-0488) under license from Georgetown University. C. Wolf is one of the listed inventors on US patent 7,763,734.

Keywords

Asymmetric catalysis; ynamides; chimonamidine; bisoxazolidines; isatins

The natural occurrence and pharmaceutical relevance of chiral oxindoles displaying a tetrasubstituted stereogenic carbon center at the 3-position has received considerable attention from medicinal and synthetic chemists in recent years.¹ This is particularly the case for the family of 3-substituted 3-hydroxyindolin-2-ones, which share an important structural motif commonly found in alkaloids such as chimonamidine and various emerging drug candidates.² To this end, we noticed that few reports on the asymmetric synthesis of chimonamidine **I**, all suffering from low overall yields, have appeared in the literature.^{2cgi} Retrosynthetic analysis pointed toward an unprecedented 3-(aminoethynyl)-3-hydroxyindolin-2-one scaffold **II** that could be generated via catalytic enantioselective addition of terminal ynamides to isatins **III** of which a wide variety is commercially available (Figure 1). In comparison to alkyne additions,³ incorporation of an ynamide moiety into readily available isatins could generate unique synthetic opportunities via late stage functionalization of the highly polarized *N*-substituted triple bond, for example to 3-substituted 3-hydroxyindolin-2-ones carrying 1,3-amino alcohol, β -hydroxy amide, β -hydroxy enamine or α -acyloxyenamide functionalities. We envisioned a catalytic asymmetric method producing the key scaffold **II** which would ultimately streamline access to multifunctional 3-hydroxyoxindoles **IV-VII** and chimonamidine or other important alkaloids.

Internal ynamides have been used in a wide range of cycloadditions, cycloisomerizations, cross-couplings, ring-closing metathesis and other valuable transformations.⁴ Although terminal ynamides are readily available building blocks,⁵ they remain underutilized compared to both internal ynamides and regular alkynes which have been exploited in countless asymmetric 1,2-addition reactions with carbonyl electrophiles.⁶ This might be attributed to the difficulty with the enamide like reactivity of ynamides and the formation of keteniminium intermediates which is conceptually different from the generally accepted C-C bond formation pathways of alkynes.⁷ Catalytic enantioselective additions with terminal ynamides which are poor nucleophiles under neutral conditions have neither been accomplished with isatins nor applied in natural product synthesis to date.

We began our search for a catalytic asymmetric method that affords the key 3-(aminoethynyl)-3-hydroxyindolin-2-one scaffold **II** using *N*-ethynyl-*N*-butylbenzenesulfonamide, **1**, and the *N*-protected isatins **2** and **3** as test compounds. At the onset of our reaction screening efforts, we investigated the suitability of previously reported catalytic enantioselective alkynylation protocols.^{3,6} The zinc triflate catalyzed ynamide addition using amino alcohols or bisoxazolines **L1-L4** as ligands and stoichiometric amounts of diisopropylethylamine as base gave the desired alkynylated oxindole products **4** and **5** in high yields but with negligible asymmetric induction (Table 1, entries 1-4). Results did not improve with copper iodide or under organocatalytic conditions with thiourea **L5** (entries 5-7). We then turned our attention to bisoxazolidines, a broadly useful class of chiral ligands developed in our laboratory.⁸ The fully saturated oxazolidine moieties in this ligand

type combines a unique ring topology with distinct steric and electronic properties that are remarkably different from bisoxazoline analogues and very useful for asymmetric catalysis.⁹ We were very pleased to find that copper(I) catalysis with bisoxazolidine **L6** gave **4** in quantitative yields and 79% ee under base free conditions (entry 8). Additional screening of various copper and zinc catalysts did not further improve results (entries 9-12 and SI). After optimization of the reaction temperature, however, we isolated **4** in 93% yield and 90% ee (entry 16). Solvent screening using *N*-phenyl isatin, **3**, as substrate showed that chloroform gives superior results and we obtained **5** in 99% yield and with 98% ee (entries 17-21). Interestingly, excellent results were also obtained when bisoxazolidine ligands **L7-L9** were employed in the optimized protocol (entries 22-24).

The catalysis is ligand-accelerated and no reaction was observed after 48 hours in the absence of **L6** (entries 13 and 14). Further analysis revealed that the ynamide addition does not occur in the presence of Hünig's base unless a catalyst is added and the replacement of the ynamide with phenylacetylene in our base-free protocol did not give the corresponding alkynylation product. The ynamide addition proceeded sluggishly when we added two equivalents of Et₃N, producing almost racemic **5** in 27% yield at 50 °C (entry 15).¹⁰ These observations are in agreement with the enamide-like nucleophilicity of ynamides mentioned above, i.e. a base-free C-C bond formation course via a keteniminium intermediate followed by tautomerization toward the 3-(aminoethynyl)-3-hydroxyindolin-2-one scaffold.¹¹ Several examples of enamide-like additions of ynamides to Lewis acid activated carbonyl electrophiles under base-free conditions have been described.¹² A plausible reaction mechanism that is in agreement with our observations and these reports is shown in Scheme 1.¹³ This reaction course is fundamentally different from the generally agreed alkynylation pathway which is initiated by base-promoted deprotonation and generation of an end-on metal-acetylide complex prior to the attack at a carbonyl electrophile.

The optimized protocol was then applied to a range of isatins (Scheme 2). The presence of halogens in various positions does not interfere with the reaction and the 3-(aminoethynyl)-3-hydroxyindolin-2-ones **6-9** were obtained in 87-97% yield and 95-96% ee. Similar results were obtained with isatins carrying a methyl, methoxy or trifluoromethoxy group. The corresponding products **10-12** were produced in 93-97% yield and with high enantioselectivity. The reaction also proceeds smoothly with *N*-aryl ynamides. When *N*-ethynyl-*N*-phenyltolylsulfonamide was applied in the same protocol we obtained **13** in quantitative amounts and in 99% ee. Importantly, the reaction tolerates the easily removable PMP group at the isatin nitrogen which further widens the general usefulness. The catalytic ynamide addition to *N*-PMP isatin gave **14** in high yield and with 97% ee. Retrosynthetic analysis of chimonamidine revealed that the ynamide must bear a methyl group rather than the *n*-butyl substituent used in the preceding examples. The protocol was therefore modified using *N*-ethynyl-*N*-methyltolylsulfonamide as ynamide to afford **15** and **16**. Importantly, **15** can be produced with our Cu(I)-bisoxazolidine catalyzed method in 99% yield and 96% ee on the gram scale. Finally, we found that the nitrogen protection is not a requirement for this reaction and free isatin was converted toward **17** with 75% yield and 91% ee.

Having established the wide substrate scope of the catalytic enantioselective addition of terminal sulfonynamides to isatins we continued with the investigation of the synthetic

versatility of the highly functionalized 3-(aminoethynyl)-3-hydroxyindolin-2-one motif. The incorporation of the chiral propargylic alcohol unit exhibiting a polarized triple bond into the biologically important 3-hydroxyoxindole scaffold enables unique modifications that are distinct from traditional alkyne chemistry, and this affords several new synthetic opportunities (Scheme 3). Complete Pd catalyzed hydrogenation of **5** gave the saturated sulfonamide **18** in 81% yield which was encouraging for our efforts to develop a streamlined asymmetric route toward chimonamidines (*vide infra*). During optimization of this procedure, we found that careful control of reaction time and catalyst loading allows highly diastereoselective formation of (*Z*)- β -hydroxy enamines which are important precursors for the synthesis of aminocyclopropyl carbinols, 1,3-amino alcohols and other multifunctional compounds.¹⁴ The partial hydrogenation of **5** using 2 mol% of Pd/C generated (*Z*)-**19** in almost quantitative yield.¹⁵ Alternatively, the *N*-tosyl ynamine moiety can be exploited to install a terminal amide bond via hydration under acidic conditions or be converted to α -acyloxyenamides, which are sought-after *N,O*-ketene acetals with important applications in rearrangement reactions,¹⁶ via hydroxyacyloxylation with a carboxylic acid. The amide **20** and the α -acyloxyenamide **21** were obtained in excellent yields from **16** with either aqueous HCl or benzoic acid at room temperature. It is noteworthy that the practical 2-step synthesis of **18-21** from isatins would not be possible via traditional nucleophilic additions with alkynes which underscores the significance of our copper(I)-bisoxazolidine catalyzed ynamide addition method.

The synthesis of chimonamidines required deprotection of the sulfonamide group after triple bond saturation and subsequent transamidation with the nascent secondary amino function. First, we prepared **22** by hydrogenation of **16** in 92% yield following the procedure described above (Scheme 4). The deprotection step was very challenging because sulfonamides are notoriously difficult to cleave and this was further complicated by the presence of the acid-sensitive chiral alcohol and the isatin lactam ring. Several literature methods proved unsuccessful or produced low yields and considerable amounts of by-products. After extensive screening and reaction optimization we found that reductive removal of the sulfonamide group in **22** with magnesium turnings in methanol occurs smoothly and with concomitant transamidation in a single step yielding 85% of (*S*)-chimonamidine, **23**, with 96% ee. Altogether, this furnishes **23** in high enantiopurity and in 77% yield over three reactions starting from *N*-methyl isatin, **2**. We were successful in growing a single crystal of chimonamidine **23** by slow evaporation of a hexane/ethyl acetate solution (SI).¹⁷ To the best of our knowledge, this is the first example of a natural product synthesis utilizing a terminal ynamide in a catalytic enantioselective nucleophilic addition reaction. This approach to oxindole alkaloids is very efficient and it compares favorably with previous reports on asymmetric chimonamidine synthesis.^{2c,g,i} The reductive tosyl deprotection was also successfully applied in the synthesis of the chimonamidine derivative **24**, which demonstrates that the ynamide chemistry is well suited for the production of a variety of medicinally interesting alkaloids.

In conclusion, the first catalytic enantioselective addition of terminal ynamides to isatins has been developed and successfully applied in the total synthesis of chimonamidine. This method uses (CuOTf)₂·Tol and a commercially available bisoxazolidine ligand under base-

free conditions, and it affords a series of synthetically versatile 3-(aminoethynyl)-3-hydroxyindolin-2-ones in high yields and enantiomeric excess from readily available starting materials. The introduction of the ynamide moiety provides a unique entry to a variety of multifunctional chiral oxindole building blocks including 1,3-amino alcohols, β -hydroxy amides, β -hydroxy enamines and α -acyloxyenamides which were produced in high yields and without erosion of enantiopurity. As a result, the synthesis of chimonamidines can now be achieved by highly enantioselective, upscalable ynamide additions to isatins followed by hydrogenation and tosyl deprotection under mild conditions. This 3-step approach compares favorably with literature protocols and establishes efficient access to important oxindole alkaloids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We are grateful for financial support from the NIH (GM106260).

References

- [1]. a) Ishimaru T, Shibata N, Horikawa T, Yasuda N, Nakamura S, Toru T, Shiro M, *Angew. Chem. Int. Ed* 2008, 47, 4157; b) Ma S, Han X, Krishnan S, Virgil SC, Stoltz BM, *Angew. Chem. Int. Ed* 2009, 48, 8037; c) Bui T, Syed S, Barbas CF, III, *J. Am. Chem. Soc* 2009, 131, 8758; [PubMed: 19499923] d) Antonchick AP, Gerding-Reimers C, Catarinella M, Schürmann M, Preut H, Ziegler S, Rauh D, Waldmann H, *Nat. Chem* 2010, 2, 735; [PubMed: 20729892] e) Tan B, Candeias NR, Barbas CF, *Nat. Chem* 2011, 3, 473; [PubMed: 21602863] f) Guo C, Song J, Huang J-Z, Chen P-H, Luo S-W, Gong L-Z, *Angew. Chem. Int. Ed* 2012, 51, 1046; g) Wu L, Falivene L, Drinkel E, Grant S, Linden A, Cavallo L, Dorta R, *Angew. Chem. Int. Ed* 2012, 51, 2870; h) Xie W, Jiang G, Liu H, Hu J, Pan X, Zhang H, Wan X, Lai Y, Mae D, *Angew. Chem. Int. Ed* 2013, 52, 12924; i) Mitsunuma H, Shibasaki M, Kanai M, Matsunaga S, *Angew. Chem. Int. Ed* 2012, 51, 5217; j) Zong L, Du S, Chin KF, Wang C, Tan C-H, *Angew. Chem. Int. Ed* 2015, 54, 9390; k) Zhao J, Fang B, Luo W, Hao X, Liu X, Lin L, Feng X, *Angew. Chem. Int. Ed* 2015, 54, 241; l) Yu J-S, Liao F-M, Gao W-M, Liao K, Zuo R-L, Zhou J, *Angew. Chem. Int. Ed* 2015, 54, 7381; m) Engl OD, Fritz SP, Wennemers H, *Angew. Chem. Int. Ed* 2015, 54, 8193; n) Wu M-Y, He W-W, Liu X-Y, Tan B, *Angew. Chem. Int. Ed* 2015, 54, 9409; o) Biswas P, Paul S, Guin J, *Angew. Chem. Int. Ed* 2016, 55, 7756; p) Sankar MG, Garcia-Castro M, Golz C, Strohmman C, Kumar K, *Angew. Chem. Int. Ed* 2016, 55, 9709; q) Kong W, Wang Q, Zhu J, *Angew. Chem. Int. Ed* 2016, 55, 9714; r) Balaraman K, Wolf C, *Angew. Chem. Int. Ed* 2017, 56, 1390; s) Balaraman K, Ding R, Wolf C, *Adv. Synth. Catal* 2017, 359, 4165; [PubMed: 29755308] t) Ding R, Wolf C, *Org. Lett* 2018, 20, 892. [PubMed: 29360370]
- [2]. Selected examples: a) Sano D, Nagata K, Itoh T, *Org. Lett* 2008, 10, 1593; [PubMed: 18348568] b) Itoh T, Ishikawa H, Hayashi Y, *Org. Lett* 2009, 11, 3854; [PubMed: 19655732] c) Chen W-B, Du X-L, Cun L-F, Zhang X-M, Yuan W-C, *Tetrahedron* 2010, 66, 1441; d) Guo Q, Bhanushali M, Zhao C-G, *Angew. Chem. Int. Ed* 2010, 49, 9460; e) Hara N, Nakamura S, Funahashi Y, Shibata N, *Adv. Synth. Catal* 2011, 353, 2976; f) Yang Y, Moinodeen F, Chin W, Ma T, Jiang Z, Tan C-H, *Org. Lett* 2012, 14, 4762; [PubMed: 22946651] g) Zhu B, Zhang W, Lee R, Han Z, Yang W, Tan D, Huang K-W, Jiang Z, *Angew. Chem. Int. Ed* 2013, 52, 6666; h) Ding R, Wolf C, *J. Org. Chem* 2017, 82, 1273; [PubMed: 28032765] i) Reddy UVS, Chennapuram M, Seki K, Ski C, Anusha B, Kwon E, Okuyama Y, Uwai K, Tokiwa M, Takeshita M, Nakano H, *Eur. J. Org. Chem* 2017, 3874; j) Moskowitz M, Balaraman K, Wolf C, *J. Org. Chem* 2018, 83, 1661 [PubMed: 29313686] For asymmetric synthesis of isoindolinones, see: Li T, Zhou C, Yan X, Wang J, *Angew. Chem. Int. Ed* 2018, 57, 4048.

- [3]. a) Xu N, Gu D-W, Zi J, Wu X-Y, Guo X-X, *Org. Lett* 2016, 18, 2439; [PubMed: 27152462] b) Chen Q, Tang Y, Huang T, Liu X, Lin L, Feng X, *Angew. Chem. Int. Ed* 2016, 55, 5286; c) Chen L, Huang G, Liu M, Huang Z, Chen F-R, *Adv. Synth. Catal* 2018, 360, 3497.
- [4]. a) Zificsak CA, Mulder JA, Hsung RP, Rameshkumar C, Wei L-L, *Tetrahedron* 2001, 57, 7575; b) Evano G, Coste A, Jouvin K, *Angew. Chem. Int. Ed* 2010, 49, 2840; c) DeKorver KA, Li H, Lohse AG, Hayashi R, Lu Z, Zhang Y, Hsung RP, *Chem. Rev* 2010, 110, 5064; [PubMed: 20429503] d) Wang X-N, Yeom H-S, Fang L-C, He S, Ma Z-X, Kedrowski BL, Hsung RP, *Acc. Chem. Res* 2014, 47, 560; [PubMed: 24164363] e) Adcock HV, Chatzopoulou E, Davies PW, *Angew. Chem. Int. Ed* 2015, 54, 15525; f) Straker RN, Majhail MK, Willis MC, *Chem. Sci* 2017, 8, 7963; [PubMed: 29568442] g) Zeng X, Li J, Ng CK, Hammond GB, Xu B, *Angew. Chem. Int. Ed* 2018, 57, 2924; h) Gao Y, Wu G, Zhou Q, Wang J, *Angew. Chem. Int. Ed* 2018, 57, 2716; i) Mansfield SJ, Christensen KE, Thompson AL, Ma K, Jones MW, Mekareeya A, Anderson EA, *Angew. Chem. Int. Ed* 2017, 56, 14428; k) Marien N, Reddy BN, De Vleeschouwer F, Goderis S, Van Hecke K, Verniest G, *Angew. Chem. Int. Ed* 2018, 57, 5660.
- [5]. a) Hamada T, Ye X, Stahl SS, *J. Am. Chem. Soc* 2008, 130, 833; [PubMed: 18166058] b) Mansfield SJ, Campbell CD, Jones MW, Anderson EA, *Chem. Commun* 2015, 51, 3316; c) Tu Y, Zeng X, Wang H, Zhao J, *Org. Lett* 2018, 20, 280. [PubMed: 29281293]
- [6]. a) Wang X-N, Hsung RP, Qi R, Fox SK, Lv M-C, *Org. Lett* 2013, 15, 2514; [PubMed: 23646900] b) Wang X-N, Hsung RP, Fox SK, Lv M-C, Qi R, *Heterocycles* 2014, 88, 1233; [PubMed: 24791059] c) Cook AM, Wolf C, *Chem. Commun* 2014, 50, 3151; d) Cook AM, Wolf C, *Tetrahedron Lett* 2015, 56, 2377; [PubMed: 26085692] e) Cook AM, Wolf C, *Angew. Chem. Int. Ed* 2016, 55, 2929; f) Zhao J, Yang J, Wang C, Xu S, *Angew. Chem. Int. Ed* 2018, 57, 10.1002/anie.201811586.
- [7]. Laub HA, Evano G, Mayr H, *Angew. Chem. Int. Ed* 2014, 53, 4968.
- [8]. a) Wolf C, Liu S, *J. Am. Chem. Soc* 2006, 128, 10996; [PubMed: 16925396] b) Liu S, Wolf C, *Org. Lett* 2007, 9, 2965; [PubMed: 17602638] c) Liu S, Wolf C, *Org. Lett* 2008, 10, 1831; [PubMed: 18386903] d) Yearick Spangler K, Wolf C, *Org. Lett* 2009, 11, 4724; [PubMed: 19743819] e) Xu H, Wolf C, *Synlett* 2010, 2765; f) Wolf C, Moskowitz M, *J. Org. Chem* 2011, 76, 6372; [PubMed: 21623640] g) Xu H, Wolf C, *Angew. Chem. Int. Ed* 2011, 50, 12249; h) Xu H, Wolf C, *Chem. Commun* 2010, 46, 8026; i) Wolf C, Zhang P, *Adv. Synth. Catal* 2011, 353, 760.
- [9]. Wolf C, Xu H, *Chem. Commun* 2011, 47, 3339.
- [10]. Under these conditions, phenylacetylene addition to isatin **3** occurs smoothly to give 99% yield of racemic product.
- [11]. For examples of ynamide transformations via keteniminium ion intermediates, see a) Lecomte M, Evano G, *Angew. Chem. Int. Ed* 2016, 55, 4547; b) Baldassari LL, de la Torre A, Li J, Lüdtke DS, Maulide N, *Angew. Chem. Int. Ed* 2017, 56, 15723; c) Patil DV, Kim SW, Nguyen QH, Kim H, Wang S, Hoang T, Shin S, *Angew. Chem. Int. Ed* 2017, 56, 3670; d) Pinto A, Kaiser D, Maryasin B, Di Mauro G, Gonzalez L, Maulide N, *Chem. Eur. J* 2017, 24, 2515.
- [12]. a) Kurtz KCM, Hsung RP, Zhang Y, *Org. Lett* 2006, 8, 231. [PubMed: 16408882] b) You L, Al-Rashid ZF, Ghosh SK, Li G, Hsung RP *Synlett* 2007, 1656. c) Wang X-N, Ma Z-X, Deng J, Hsung RP, *Tetrahedron Lett* 2015, 56, 3463. [PubMed: 26028784] d) Yabuuchi Y, Kuzuguchi T, Yoshimura T, Matsuo J-i., *Org. Lett* 2016, 18, 4951. [PubMed: 27648942] For asymmetric catalysis with enamides: e) Matsubara R, Kobayashi S, *Acc. Chem. Res* 2008, 41, 292. [PubMed: 18281949]
- [13]. The bisoxazolidine ligand undergoes N,N'-coordination to Cu(I).
- [14]. a) Valenta P, Carroll PJ, Walsh PJ, *J. Am. Chem. Soc* 2010, 132, 14179; [PubMed: 20853837] b) Gopalaiah K, Kagan HB, *Chem. Rev* 2011, 111, 4599. [PubMed: 21568332]
- [15]. Reddy AS, Swamy KCK, *Angew. Chem. Int. Ed* 2017, 56, 6984.
- [16]. a) Smith DL, Goundry WRF, Lam HW, *Chem. Commun* 2012, 48, 1505; b) Xu S, Liu J, Hu D, Bi X, *Green Chem* 2015, 17, 184.
- [17]. The CCDC numbers for the compounds **16** and **23** are 1882888 and 1882889, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

Previous work (ref. 2c,g,i):

This work:

Figure 1.
Synthetic utility of ynamide catalysis with isatins.

Scheme 1.
Plausible base-free reaction mechanism.

Scheme 2.

Catalytic enantioselective synthesis of 3-aminoalkynyl-3-hydroxyoxindoles. The absolute configuration of **16** was determined by crystallographic analysis of a single crystal obtained by slow evaporation of a hexanes/ethyl acetate solution (SI). The other configurations were assigned by analogy.

Scheme 3.

Selective modifications of the 3-(aminoethynyl)-3-hydroxyindolin-2-one motif.

Scheme 4.

Total synthesis of chimonamidines and X-ray structure of **23**. The absolute configuration of **16** was determined by crystallographic analysis of a single crystal obtained by slow evaporation of a hexane/ethyl acetate solution (SI). The other configurations were assigned by analogy.

Table 1.

Optimization of the asymmetric addition of ynamides to isatins.^a

Entry	R	Catalyst	Ligand	Conditions	Yield (%) ^b	Ee (%) ^d
1	Me	Zn(OTf) ₂	L1	C ₆ H ₆ , DIPEA, 25 °C	99	<1
2	Me	Zn(OTf) ₂	L2	DCE, DIPEA, 25 °C	86	<1
3	Me	Zn(OTf) ₂	L3	DCE, DIPEA, 25 °C	94	2
4	Me	Zn(OTf) ₂	L4	DCE, DIPEA, 25 °C	89	1
5	Me	CuI	L3	DCM, DIPEA, 25 °C	64	16
6	Me	CuI	L4	DCM, DIPEA, 25 °C	51	17
7	Me	/	L5	DCE, DIPEA, 25 °C	54	4
8	Me	(CuOTf) ₂ ·Tol	L6	CHCl ₃ , 25 °C	99 ^c	79
9	Me	(CuOTf) ₂ ·Tol	L4	CHCl ₃ , 25 °C	<5 ^c	n.d.
10	Me	CuI	L6	CHCl ₃ , 25 °C	<50 ^c	80
11	Me	CuI	L3	CHCl ₃ , 25 °C	<50 ^c	9
12	Me	Zn(OTf) ₂	L6	CHCl ₃ , 25 °C	<5 ^c	n.d.
13	Me	/	/	CHCl ₃ , DIPEA, 25 °C	n.r.	n.d.
14	Me	(CuOTf) ₂ ·Tol	/	CHCl ₃ , DIPEA, 25 °C	n.r.	n.d.
15	Ph	(CuOTf) ₂ ·Tol	L6	CHCl ₃ , Et ₃ N, 50 °C	27	2
16	Me	(CuOTf) ₂ ·Tol	L6	CHCl ₃ , 0 °C	93	90
17	Ph	(CuOTf) ₂ ·Tol	L6	CH ₂ Cl ₂ , 0 °C	97	90
18	Ph	(CuOTf) ₂ ·Tol	L6	THF, 0 °C	36	96
19	Ph	(CuOTf) ₂ ·Tol	L6	Et ₂ O, 0 °C	42	68
20	Ph	(CuOTf) ₂ ·Tol	L6	MTBE, 0 °C	61	66

Entry	R	Catalyst	Ligand	Conditions	Yield (%) ^b	Ee (%) ^d
21	Ph	(CuOTf) ₂ ·Tol	L6	CHCl ₃ , 0 °C	99	98
22	Ph	(CuOTf) ₂ ·Tol	L7	CHCl ₃ , 0 °C	98	85
23	Ph	(CuOTf) ₂ ·Tol	L8	CHCl ₃ , 0 °C	99	91
24	Ph	(CuOTf) ₂ ·Tol	L9	CHCl ₃ , 0 °C	93	90

[a] Reaction Conditions: Ynamide (0.3 mmol, 1.5 equiv.), isatin (0.2 mmol, 1 equiv.), catalyst (5 mol%), ligand (15 mol%), base (1.1 equiv.) in 0.1 mL of solvent.

[b] Isolated yield.

[c] Conversion determined by HPLC.

[d] Ee determined by chiral HPLC on a Phenomenex Lux 5μ Cellulose-3 column (mobile phase = 85:15 hexanes-EtOH, flow rate = 1.0 mL/min, λ = 254 nm), n.r. = no reaction, n.d. = not determined.