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Cobalt/Bisoxazolinephosphine-Catalyzed Asymmetric Alkynylation of Isatins

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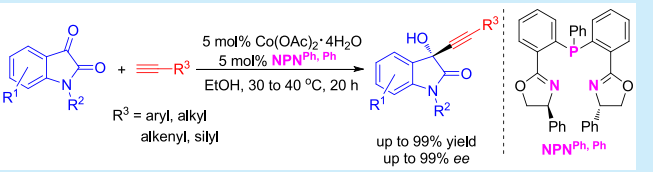
ABSTRACT: A new catalyst system based on $Co(OAc)_2$/bisoxazolinephosphine has been developed to catalyze the direct addition of terminal alkynes to isatins under base-free conditions. Chiral propargyl alcohols with an oxindole skeleton could be prepared in up to 99% yield and 99% ee with the help of the chiral tridentate ligand. A variety of functionalized aliphatic or aromatic alkynes and isatins were utilized in this method, and gram-scale synthesis could be achieved with 1 mol % catalyst.



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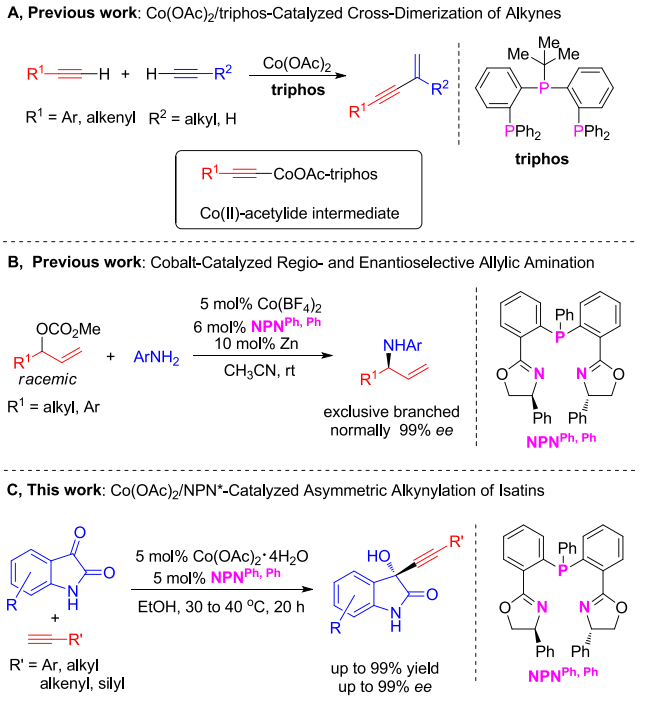
The transition-metal-catalyzed direct addition of terminal alkynes to unsaturated carbon−carbon or carbon−heteroatom bonds provides not only atom-economic methods to prepare complex molecules with versatile alkyne functions but also an opportunity to construct chiral scaffolds.[1] Although a variety of metals, for example, Zn,[2] Cu,[3] Rh,[4] Ir,[5] Co,[6] Ni,[7] or Ag,[8] have been reported to catalyze the asymmetric functionalization of terminal alkynes with the help of chiral ligands, there is still much room to develop new catalyst systems to solve the problems such as the low reaction efficiency, homocoupling of terminal alkynes, or the use of precious transition metal catalysts and a large amount of alkynes. Recently, we reported the $Co(OAc)_2$/triphos-catalyzed gem-cross-dimerization of the aromatic alkynes and aliphatic alkynes, in which an internal acetate was proposed to promote the formation of Co(II)-acetylide intermediate (Scheme 1, **A**).[9a] We envisioned that not only is the Co(II)-acetylide intermediate able to coordinate with another alkyne, but also it is possible to activate carbonyl groups to accelerate the addition to carbon−heteroatom double bonds. The simultaneous activation of the terminal alkyne and carbonyl group within one catalyst was expected to improve the catalysis efficiency. On the other hand, chiral tridentate bisoxazoline-phosphine (NPN*) ligand was successfully used in the Co-catalyzed regio- and enantioselective allylic amination and alkylation reactions (Scheme 1, **B**).[10] NPN* ligands were proven to be suitable ligands to provide a chiral environment in the cobalt complexes. Inspired by the two reactions above, we expect that $Co(OAc)_2$/NPN* can be a new highly reactive catalyst in the enantioselective direct addition of terminal alkynes to carbonyl groups.

The 3-substituted 3-hydroxyoxindole structure can be found in many natural products and biologically active molecules.[11] The highly enantioselective addition of alkynes to isatin derivatives has been realized only recently. Liu[12] and Guo[13] reported the elegant Cu(I)-catalyzed addition reactions in the

Scheme 1. Asymmetric Catalysis by Cobalt and Chiral Bisoxazolinephosphine Ligands



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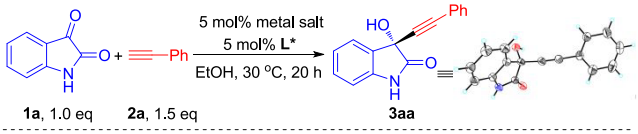
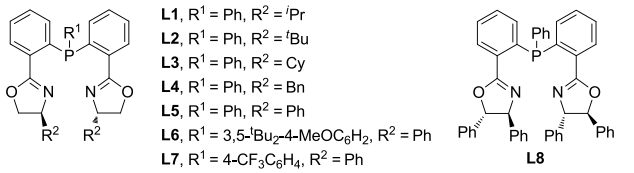
presence of base with chiral guanidine and phosphine ligands, respectively, in which a 3 day reaction time is normally necessary. The Zn/chiral hydroxyl-oxazoline-catalyzed version was reported by Chen. However, 20 mol % Zn complex and 3 equiv of alkynes have to be used.[14] Maruoka developed the hybrid catalyst system with noble metal AgOAc and chiral-phase-transfer-catalyst to promote the addition to trityl protected isatins in high yields and selectivities.[15] Herein, we present our preliminary result on the $Co(OAc)_2$/NPN*^{Ph,Ph}-catalyzed asymmetric alkynylation of isatins (Scheme 1, **C**). Chiral propargyl alcohols with the oxindole skeleton could be prepared in up to 99% yield and mostly 99% ee from alkyl, aryl or silyl alkynes and unprotected isatins under base-free conditions. Different useful function groups could be tolerated under this condition, and gram-scale synthesis was achieved with 1 mol % Co-complex.

We began our studies with the unprotected isatin **1a** and phenylacetylene **2a** as the model substrates (Table 1). Several

Table 1. Optimization of Co-Catalyzed Asymmetric Alkynylation of Isatin[a]





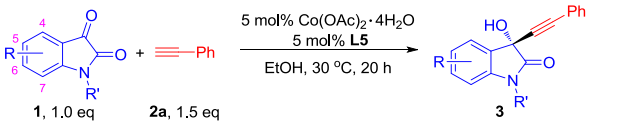
entry	catalyst precursor	ligand	yield[b] (%)	ee[c] (%)
1	$Co(OAc)_2{\cdot}4H_2O$	**L1**	99	29
2	$Co(OAc)_2{\cdot}4H_2O$	**L2**	<5	
3	$Co(OAc)_2{\cdot}4H_2O$	**L3**	99	12
4	$Co(OAc)_2{\cdot}4H_2O$	**L4**	92	0
5	$Co(OAc)_2{\cdot}4H_2O$	**L5**	96	99
6	$Co(OAc)_2{\cdot}4H_2O$	**L6**	99	97
7	$Co(OAc)_2{\cdot}4H_2O$	**L7**	93	97
8	$Co(OAc)_2{\cdot}4H_2O$	**L8**	76	83
9	$Co(OAc)_2{\cdot}4H_2O$		<5	
10	$Co(OBz)_2$	**L5**	92	99
11	$Fe(OAc)_2$	**L5**	<5	
12	$Ni(OAc)_2$	**L5**	67	98
13	$Cu(OAc)_2$	**L5**	<5	
14	$Zn(OAc)_2$	**L5**	<5	

[a]All reactions were run with 5 mol % catalyst precursor and 5 mol % ligand on a 0.25 mmol scale at 30 °C for 20 h; the ellipsoids of **3aa** were drawn at the 30% probability level. [b]Yield of isolated product. [c]The enantiomeric excess values were determined by HPLC analysis with a chiral column.

bisoxazolinephosphine ligands with different R^2 substitutions on the oxazoline moiety were evaluated first in ethanol at 30 °C. To our delight, the high efficiency was observed with isopropyl-, cyclohexyl-, benzyl-, and phenyl-based ligands (**L1**, **L3**−**L5**). Among them, reaction with **L5** leads to the isolation of **3aa** in 96% yield and 99% ee (entry 5). However, less than 5 mol % of **3aa** was obtained with **L2** bearing a bulky t-butyl group (entry 2). A neglectable effect was observed when ligands with an electron-donating or withdrawing phenyl substituted R^1 were tested (entries 6 and 7). The reaction with **L8** derived from the 2-amino-1,2-diphenylethanol gave lower yield and enantioselectivity (entry 8). Chiral pyridine bisoxazoline ligands (pybox) lead to no conversion (see the Supporting Information). The control experiment without ligand affords no product (entry 9). The reaction with $Co(OBz)_2$ as the catalyst precursor leads to comparable yield and ee (entry 10). Some other salts from the first row transition metals were examined in the presence of **L5**. The acetate salts of Fe, Cu, and Zn are not able to catalyze the same reaction (entries 11, 13, and 14). Reaction by $Ni(OAc)_2$ gave **3aa** with the same level 98% ee, although a lower 67% yield was obtained (entry 12). The absolute configuration of **3aa** was assigned to be *S* by single-crystal X-ray diffraction analysis.

With the optimized reaction conditions in hand, we first examined the scope of the isatins (Table 2). The effect of

Table 2. Reaction Scope of Isatins[a]



entry	R, R′	3	yield[b] (%)	ee[c] (%)
1	5-MeO, H	**3ba**	97	99
2	5-CF_3O, H	**3ca**	95	99
3	5-F, H	**3da**	96	99
4	5-Cl, H	**3ea**	99	99
5	5-Br, H	**3fa**	96	99
6	5-NO_2, H	**3ga**	97	98
7	7-CF_3, H	**3ha**	92	99
8	7-CO_2Me, H	**3ia**	98	99
9	4,7-Cl_2, H	**3ja**	78	92
10	H, Me	**3ka**	86	98
11	H, Ph	**3la**	91	95
12	H, Bn	**3ma**	92	97
13	H, allyl	**3na**	83	98

[a]All reactions were run with 5 mol % cobalt catalyst and 5 mol % ligand on a 0.25 mmol scale at 30 °C for 20 h. [b]Yield of isolated product. [c]The enantiomeric excess values were determined by HPLC analysis with a chiral column.

different electron-donating or electron-withdrawing groups at the 5-position in the unprotected isatin was evaluated (entries 1−6). Functional groups including methoxide, halogens, and the nitro group could be tolerated. 95−99% yields and 98−99% ee's were obtained for **3ba**−**3ga**. CF_3 and CO_2Me substituents at the 7-position have a neglectable influence on the reaction efficiency and selectivities (entries 7 and 8). Slightly reduced yield and ee were obtained when the 4,7-dichloroisatin was used (entry 9). The substituent effect on the nitrogen atom in isatins was further tested. Simple methyl, phenyl, benzyl, and allyl groups substituted isatins could be converted to the propargyl alcohols smoothly in excellent enantioselectivities, albeit with slightly reduced yields (entries 10−13).

The scope of the aromatic alkynes was studied with the unprotected isatin **1a** as the model substrate (Table 3). First, the reaction with 1.2 equiv of simple phenylacetylene **2a** could be conducted at a 10 mmol scale under the catalysis of 1 mol % cobalt complex (entry 1). 2.44 g of **3aa** was isolated in 99% yield and 98% ee, which indicates that the reaction could be used in the gram-scale synthesis. Bromides at para-, meta-, and

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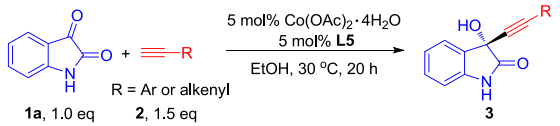
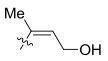
Table 3. Reaction Scope of Aromatic or Alkenyl Alkynes[a]



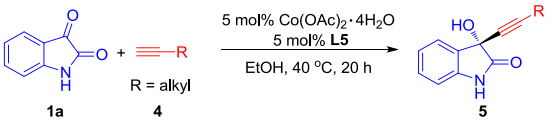
entr	R	3	yield (%)[b]	*ee* (%)[c]
1	C_6H_5	**3aa**	99[d]	98[d]
2	4-BrC_6H_4	**3ab**	94	99
3	3-BrC_6H_4	**3ac**	99	99
4	2-BrC_6H_4	**3ad**	99	98
5	4-$CHOC_6H_4$	**3ae**	77	99
6	4-CNC_6H_4	**3af**	83	99
7	4-$CF_3C_6H_4$	**3ag**	93	99
8	4-$CO_2MeC_6H_4$	**3ah**	96	98
9	4-$NO_2C_6H_4$	**3ai**	69	99
10	4-$OMeC_6H_4$	**3aj**	96	92
11[e]	4-$NH_2C_6H_4$	**3ak**	76	93
12	3-OHC_6H_4	**3al**	97	98
13	3-thiophenyl	**3am**	99	96
14	3-pyridyl	**3an**	93	99
15		**3ao**	92	94
16		**3ap**	97	99

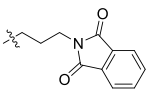
[a]All reactions were run with 5 mol % cobalt catalyst and 5 mol % ligand on a 0.25 mmol scale at 30 °C for 20 h unless otherwise noted. [b]Yield of isolated product. [c]The enantiomeric excess values were determined by HPLC analysis with a chiral column. [d]The reaction was conducted at the 10 mmol scale with 1 mol % $Co(OAc)_2$ and **L5** at 40 °C for 30 h. [e]At 0 °C.

ortho-positions could be tolerated in this reaction condition without erosion of efficiency and selectivities (entries 2−4). The function groups like electron-withdrawing aldehyde, cyano, trifluoromethyl, and ester groups have neglectable influence on the yields and ee's (entries 5−8), while the reaction of **1i** with a strong electron-withdrawing nitro group leads to a 69% yield (entry 9). Terminal aromatic alkynes with electron-donating groups could be converted to the products **3** with high yields and ee's, in which the protection of the free amino and hydroxyl groups is not necessary (entries 10−12). Alkynes with heterocyclic 3-thiophenyl and 3-pyridyl groups or alkenyl substitutions were also utilized in this direct addition reaction to give the corresponding propargyl alcohols in excellent yields and enantioselectivities (entries 13−16).

The reaction of aliphatic alkynes is normally more sluggish compared to aromatic alkynes, which is probably due to the lower acidity of aliphatic alkynes.[12,13] In the $Co(OAc)_2$/**L5** system, this problem could be easily solved by raising the reaction temperature from 30 to 40 °C. As shown in Table 4, the reactions of simple n-octyl, benzyl, and cyclopropyl substituted alkynes with **1a** afforded products **5aa**−**5ac** in high yields with excellent enantioselectivities (entries 1−3). Terminal alkynes with primary and even tertiary hydroxyl groups could react under the same condition without protection to give the diols in high efficiency and selectivities (entries 4−7). Similarly, the reaction of **1a** and 1.2 equiv of **4e**

Table 4. Reaction Scope of Aliphatic Alkynes[a]



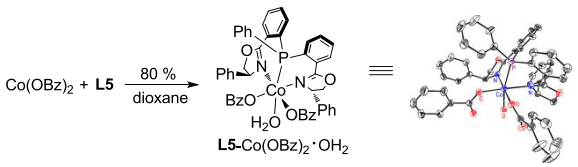
entr	R	5	yield (%)[b]	*ee* (%)[c]
1	n-C_8H_{17}	**5aa**	86	99
2	CH_2Ph	**5ab**	87	99
3	cyclopropyl	**5ac**	92	92
4	CH_2OH	**5ad**	71	99
5	CH_2CH_2OH	**5ae**	92 (85)[d]	99 (98)[d]
6		**5af**	83[e]	98[e]
7		**5ag**	78[e]	99[e]
8	CH_2CH_2Br	**5ah**	86	99
9	$CH_2CH_2CH_2Cl$	**5ai**	98	99
10	CH_2OBn	**5aj**	86	99
11	CH_2CH_2OTs	**5ak**	83	99
12	CH_2S-tol	**5al**	82	99
13	CH_2NHBoc	**5am**	82	99
14	$CH_2CH_2CH_2CN$	**5an**	92	99
15		**5ao**	81	99
16	$SiMe_3$	**5ap**	73[e]	98[e]

[a]All reactions were run with 5 mol % cobalt catalyst and 5 mol % ligand on a 0.25 mmol scale at 30 °C for 20 h unless otherwise noted. [b]Yield of isolated product. [c]The enantiomeric excess values were determined by HPLC analysis with a chiral column. [d]The reaction was conducted at the 10 mmol scale with 1 mol % $Co(OAc)_2$ and **L5** f at 60 °C for 30 h. [e]At 60 °C.

could be conducted with 1 mol % $Co(OAc)_2$ and **L5** in a 10 mmol scale (entry 5). 1.84 g of **5ae** was isolated in 85% yield and 98% ee. Other functional groups like halogens, ether, tosylate, sulfide, amide, cyano, and phthalimide in aliphatic alkynes could be tolerated without significant influence on the outcome of the reactions. **5ah**−**5ao** were isolated in 81−98% yields and 99% ee's (entries 8−15). Finally, trimethylsilyl acetylene **4p** was successfully applied in this addition reaction to afford **5ap**, which allows the synthesis of the terminal propargyl alcohol by removing the TMS group (entry 16).

The structure of the cobalt complex was investigated to understand the role of the chiral ligand. As shown in Scheme 2, **L5**-$Co(OBz)_2{\cdot}H_2O$ was synthesized in 80% yield by mixing $Co(OBz)_2$ and **L5** in dioxane. A crystal suitable for single-

Scheme 2. Structure of the Chiral Cobalt Complex with Ellipsoids at the 15% Probability Level



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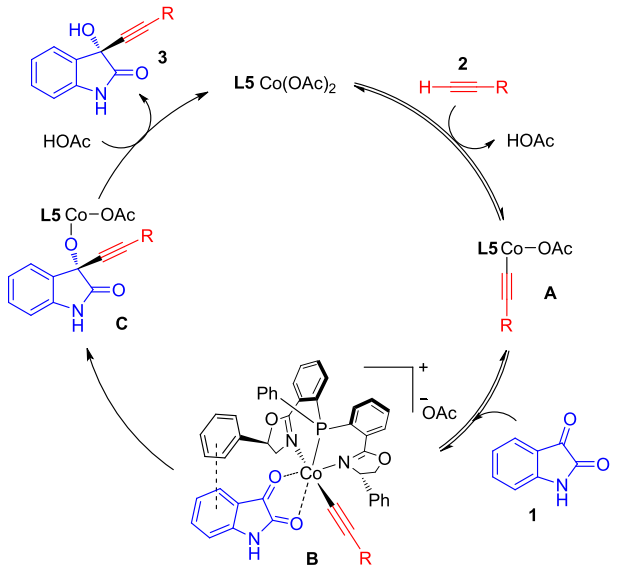
crystal X-ray diffraction analysis was obtained by slow diffusion of cyclohexane to the dioxane solution. In the solid state, Co(II) adopts a six-coordinate octahedron geometry with one extra water molecule. The benzoate anions coordinate with cobalt in a ^{1}k mode. Similar to the Co(II)/NPN* and Co(I)/NPN* complexes we isolated previously,[10a] the NPN tridentate ligand occupies half of the coordination sphere in the facial manner and provides the chiral environment for the addition step.

Based on the literature reports and the experiments above, a catalytic cycle was proposed in Scheme 3. The exchange of

Scheme 3. Proposed Catalytic Cycle



water with terminal alkynes allows the coordination of alkynes with the cobalt center and enhancement of the acidity of the sp C−H bond. The internal acetate promoted deprotonation of the alkynes generates the Co(II)-acetylide intermediate **A** and releases HOAc. **A** undergoes a dissociation of the acetate anion and the further coordination with the carbonyl groups in isatins **1** to form cationic intermediate **B**. The $\pi-\pi$ stacking between the phenyl ring on one of the oxazolines and the aromatic ring in the isatin molecule locks the orientation of the other three coordination atoms in only one possibility as shown in **B**. Intramolecular addition of the acetylide to the activated carbonyl group from the *Re* face of the isatin affords the Co-alkoxide **C** with an *S* chiral center. Ligand exchange of **C** with HOAc or solvent EtOH releases the product **3** and regenerates the active catalyst **L5**-Co$(OAc)_2$. The oxidative state of the cobalt complex does not change during the catalytic cycle.

In summary, we have developed a new catalyst system for the asymmetric alkynylation of carbonyl groups based on Co$(OAc)_2$ and chiral bisoxazolinephosphine ligand. The highly enantioselective direct addition of aryl, alkyl, and silyl terminal alkynes bearing different functional groups to a variety of isatin derivatives was realized under neutral conditions. Propargyl alcohols with the biologically important oxindole skeleton could be prepared under base-free conditions with 1 mol % cobalt complex in gram scale. The extension of the scope to other unsaturated carbon−carbon or carbon−heteroatom bonds is ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01486.

Detailed experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra, and X-ray crystal structure of **3aa** and Co$(OBz)_2$·**L5** (PDF)

Accession Codes

CCDC 1989113 and 1989116 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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