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CuH-Catalyzed Synthesis of 3-Hydroxyindolines and 2-Aryl-3H-indol-3-ones from *o*-Alkynylnitroarenes, Using Nitro as Both the Nitrogen and Oxygen Source

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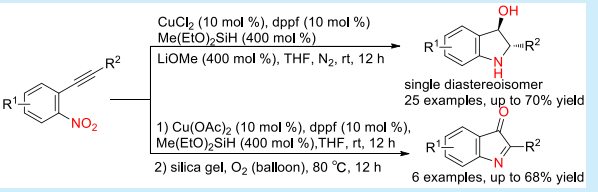
Supporting Information

ABSTRACT: CuH-catalyzed diasterospecific synthesis of 3-hydroxyindolines and 2-aryl-3H-indol-3-ones have been developed from *o*-alkynylnitroarenes in the presence of hydrosilane as the reductant. The protocol employs nitro as both nitrogen and oxygen sources for the intramolecular simultaneous construction of C−N and C−O bonds.



Indolines are of considerable significance in both synthetic and medicinal chemistry, because of a large quantity of naturally occurring bioactive compounds and drugs whose structures incorporate this heterocyclic framework (Figure 1).[1] Accordingly, numerous synthetic methods have been developed for indolines and their derivatives bearing synthetically valuable functional groups.[2] Especially noteworthy among those are indole ring's dearomatic hydrogenation[3] or cyclization,[4] an intramolecular coupling of imine and styrene catalyzed by CuH species,[5] and a Pd-catalyzed C−C coupling procedure involving unactivated methylenes, etc.[6] Despite its attractiveness, most of them required multiple steps using aryl amine functionality as the nitrogen source of the indoline rings. Thus, it is highly desirable to develop more-efficient nitrogen source, such as a nitro group, for the synthesis of indoline rings with step economy.

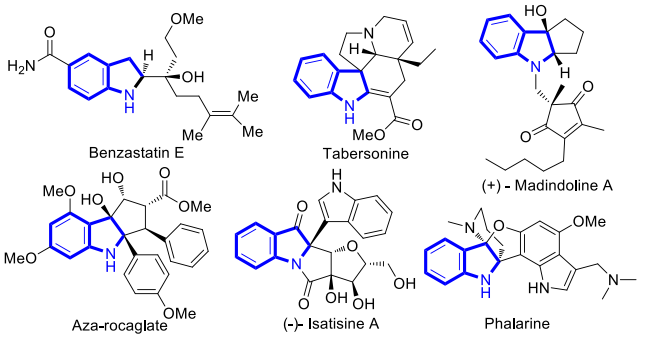


Figure 1. Representative bioactive indolines.

Nitroarenes, directly obtained from the nitration of the parent arenes, are highly versatile and common aromatic building blocks for access to the corresponding aryl amine,[7] and indole[8] involving the use of the nitro group as the nitrogen source via reduction. Nevertheless, given that the N atom in the nitro group has a high oxidation state, it is ideal to explore more redox-economic reactions for further functionalization.

Despite the obvious advantages in step economy, cost efficiency, and orthogonality, currently, only a few methods have recently been developed for directly transforming nitro compounds without the detour into the fully reduced anilines.[9] Considering that CuH species has been demonstrated as a versatile catalyst in a range of reductive couplings,[10] and our continuous interest in the development of new methods for synthesizing indole derivatives,[11,2h] we herein wish to report a diasterospecific access to 3-hydroxyindolines from *o*-alkynylnitroarenes with the nitro group serving as both the nitrogen and oxygen source of 3-hydroxylindolines, via an intramolecular CuH-catalyzed reductive coupling of a nitro group with alkynes.

Initially, we used 1-nitro-2-(*p*-tolylethynyl)benzene (**1a**) as the substrate for the optimization of the reaction conditions. In the presence of CuCl (10 mol %), dppf (10 mol %), and LiO*t*-Bu (400 mol %), the reaction of **1a** with $Me(EtO)_2SiH$ (400 mol %) for 12 h afforded 3-hydroxyindoline **2a** in 27% yield as a single diasteroisomer, along with a large amount of **1a** (see Table 1). The structure of **2a** was ambiguously assigned via single-crystal X-ray analysis (see the Supporting Information (SI)). The hydroxyl and tolyl groups are located on the opposite sides of the indoline ring. A range of other copper catalysts, including CuBr, CuI, $CuCl_2$, and CuF_2 were evaluated (Table 1, entries 2−5), and only $CuCl_2$ gave a higher yield (35%) than CuCl. Screening of bases demonstrated LiOMe to be optimal, giving **2a** in 62% yield (Table 1, entries 6−8). Several other ligands were examined, but proved to have no better yield than dppf (Table 1, entries 9−15).

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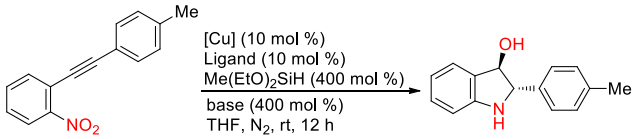
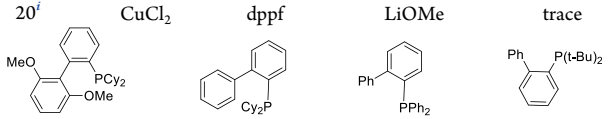
Table 1. Reaction Conditions Optimization[a]



1a 2a

entry	[Cu]	ligand	base	yield[b] (%)
1	CuCl	dppf	LiO*t*-Bu	27
2	CuBr	dppf	LiO*t*-Bu	30
3	CuI	dppf	LiO*t*-Bu	19
4	$CuCl_2$	dppf	LiO*t*-Bu	35
5	CuF_2	dppf	LiO*t*-Bu	18
6	**$CuCl_2$**	**dppf**	**LiOMe**	**62**
7	$CuCl_2$	dppf	NaOMe	19
8	$CuCl_2$	dppf	KO*t*-Bu	trace
9	$CuCl_2$	dppe	LiOMe	17
10	$CuCl_2$	BINAP	LiOMe	15
11	$CuCl_2$	PPh_2Cy	LiOMe	24
12	$CuCl_2$	**L1**	LiOMe	16
13	$CuCl_2$	**L2**	LiOMe	20
14	$CuCl_2$	**L3**	LiOMe	16
15	$CuCl_2$	**L4**	LiOMe	15
16[c]	$CuCl_2$	dppf	LiOMe	NR[d]
17[e]	$CuCl_2$	dppf	LiOMe	trace
18[f]	$CuCl_2$	dppf	LiOMe	ND[g]
19[h]	$CuCl_2$	dppf	LiOMe	26
20[i]	$CuCl_2$	dppf	LiOMe	trace



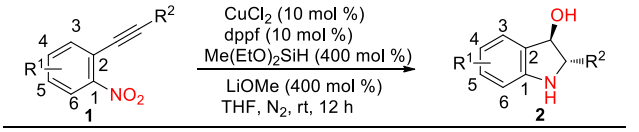
L1 L2 L3 L4

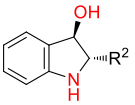
[a]Reaction conditions: **1a** (1 mmol), THF (2 mL), N_2 atmosphere, room temperature (rt). [b]Yields were determined by ^1H NMR using CH_2Br_2 as the internal standard. [c][Si−H] = Et_3SiH. [d]NR = no reaction. [e][Si−H] = $[(CH_3)_3SiO]_2CH_3SiH$. [f][Si−H] = $[(CH_3)_2SiH]_2NH$. [g]ND = not detected. [h][Si−H] = $(EtO)_3SiH$. [i][Si−H] = $(CH_3O)_3SiH$.

Evaluation of hydrosilanes revealed that $Me(EtO)_2SiH$ was superior to all others tested (Table 1, entry 8 vs entry 16). On the basis of the above observations, we concluded that the optimized conditions for this transformation involved the use of $Me(EtO)_2SiH$ as the reductant, $CuCl_2$ as the catalyst, dppf as the ligand, and LiOMe as the base at room temperature (Table 1, entry 6; see the SI for details).

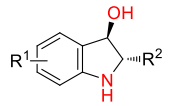
With the optimal reaction conditions in hand, we examined the scope of substrates **1** with variable R^1 and R^2 groups for this transformation (see Scheme 1). For R^1 = H, R^2 can be a phenyl group, or phenyl groups substituted with electron-donating groups of Me, Et, *t*-Bu, MeO, and with electron-withdrawing groups of chlorides, CF_3. The corresponding products were afforded in yields of 40%−63% (**4a**−**4l**). R^2 can also be 1-naphthyl, 2-naphthyl, and thienyl, giving the desired products in yields of 41%, 51%, and 60%, respectively (**2m**−**2o**). Notably alkyl groups of R^2 (**1p** and **1q**) were also suitable to this reaction, producing the corresponding products **2p** and **2q**, albeit in low yields (30% and 25%, respectively). When R^2 was 4-Me-Ph, R^1 was an electron-rich or electron-deficient group, products (**2r**−**2t**) were obtained in yields of 40%−62%. Substrate **1u**, carrying both electron-rich substitutes of R^1 and R^2, was also a good candidate for this transformation,

Scheme 1. Substrate Scope[a]

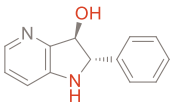




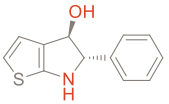
2a, R^2 = 4-Me-C_6H_4, 52%
2b, R^2 = C_6H_4, 62%
2c, R^2 = 4-MeO-C_6H_4, 61%
2d, R^2 = 4-*t*Bu-C_6H_4, 56%
2e, R^2 = 4-Et-C_6H_4, 56%
2f, R^2 = 3-MeO-C_6H_4, 52%
2g, R^2 = 3-Me-C_6H_4, 54%
2h, R^2 = 2-Me-C_6H_4, 52%
2i, R^2 = 4-Br-C_6H_4, 40%
2j, R^2 = 4-F-C_6H_4, 63%
2k, R^2 = 4-Cl-C_6H_4, 54%
2l, R^2 = 4-CF_3-C_6H_4, 58%
2m, R^2 = 1-Np, 41%
2n, R^2 = 2-Np, 51%
2o, R^2 = thienyl, 60%
2p, R^2 = *n*-C_8H_{17}, 30%
2q, R^2 = *t*-Bu, 25%



2r, R^1 = 5-Cl, R^2 = 4-Me-C_6H_4, 49%
2s, R^1 = 5-Me, R^2 = 4-Me-C_6H_4, 40%
2t, R^1 = 4-F, R^2 = 4-Me-C_6H_4, 62%
2u, R^1 = 5-Me, R^2 = 3-MeO-C_6H_4, 52%
2v, R^1 = 5-Cl, R^2 = 4-Cl-C_6H_4, 53%
2w, R^1 = 5-Me, R^2 = 4-Cl-C_6H_4, 70%



2x, ND



2y, ND

[a]All reactions were performed on a 0.5 mmol scale. Yields of isolated products are given.

furnishing reduction product **2u** in 52% yield. When R^2 was 4-Cl-Ph and R^1 was 5-Cl or 5-Me, products **2v** and **2w** were obtained in yields of 53% and 70%, respectively. The failure to obtain **2x** may be due to the strong coordination of pyridine ring with the catalyst, leading to no reaction. When the substrate possessing a thiophene framework was subjected to the standard reaction conditions, the desired product (**2y**) was not observed but a complex mixture was produced.

Encouraged by the above outcomes and, given that 2-aryl-3H-indol-3-ones were widely used in organic and medicinal chemistry, further exploration into the one-pot conversion of *o*-alkynylnitroarenes to 2-aryl-3H-indol-3-ones, which represent a class of important compounds with potent antiplasmodial activities and have application as useful building blocks, was attempted.[12] As shown in Scheme 2, a range of 2-aryl-3H-indol-3-ones **3** were produced in moderate yields (43%−68%) upon treatment of **1** with $Cu(OAc)_2$ (10 mol %), dppf (10 mol %), and $Me(EtO)_2SiH$ (400 mol %) in THF at room temperature overnight, followed by treatment with silica gel at 80 °C for 12 h under O_2. Note that before the treatment with silica gel, the formed product was not stable enough to be isolated by using silica chromatography.

Some control experiments were conducted to gain insight into the mechanism for the formation of **2** (Scheme 3). First, subjecting 1-nitro-2-styrylbenzene (**4**) to the standard conditions did not afford **2b**, indicating that **4** was not the intermediate (see Scheme 3a). Second, the triple bond of diphenylacetylene was not hydrogenated under the standard conditions (Scheme 3b). Third, the isatogen **5b**, prepared via the known method,[13] was transformed to **2b** in 58% yield under the standard conditions, indicating that **5b** was a possible intermediate (Scheme 3c). Fourth, subjecting **3a** to the standard conditions afforded **2a** in 50% yield (Scheme 3d). Fifth, the reaction of **3a** with $Me(EtO)_2SiH$ and LiOMe

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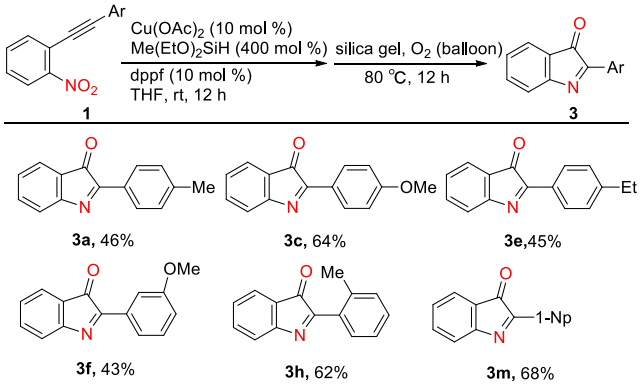
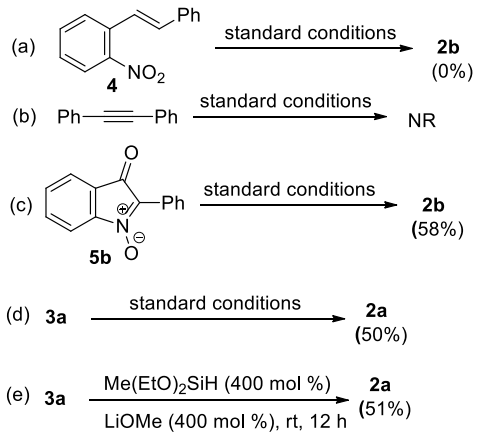
Scheme 2. One-Pot Conversion of Nitroarenes to 2-Aryl-3H-indol-3-ones[a]



[a]All reactions were performed on a 0.5 mmol scale. Silica (0.06 g). Yields of isolated products are given.

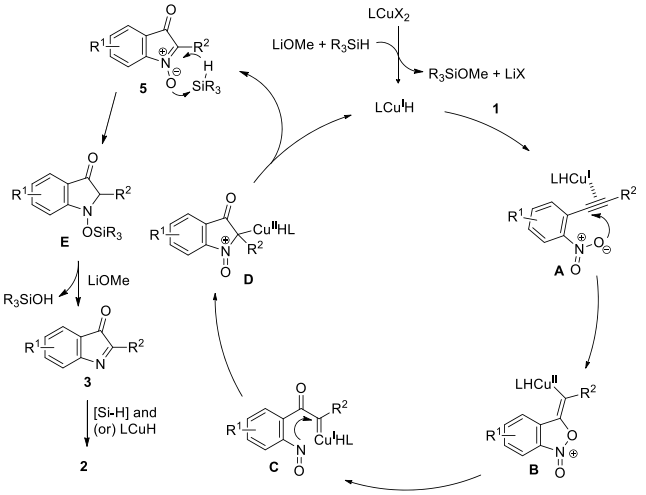
Scheme 3. Control Experiments



afforded **2a** in 51% yield. (Scheme 3e). The two control experiments (Schemes 3d and 3e) indicate that **3a** is likely the intermediate and can be reduced into **2a** using silane and (or) LCuH as the reductant (see the SI for details of the control experiments).

On the basis of the above observations and previous reports on transition-metal-catalyzed cycloisomerizations of *o*-alkynylnitroarene into isatogens,[13,14] and hydrosilylation of imines[15] and carbonyl functionalities,[16] a possible reaction mechanism for the formation of **2** involving the intermediates of isatogens **5** and 2-aryl-3H-indol-3-ones **3** is described in Scheme 4. Specifically, LCuH species is initially formed after the reaction of $CuCl_2$ with a ligand and a stoichiometric amount of hydrosilane.[17] LCuH coordinates with substrate **1** to give species **A**. The addition of nitroxide to the triple bond of **A** led to **B** that isomerizes to copper-carbene **C**, which is then transformed to **D** via intramolecular trapping of the nitroso group in the *5-exo* annulation. The dissociation of **D** delivers isatogen **5**,[14c,f] which is reduced by hydrosilane to generate **E**. Subsequent reductive elimination of **E** with the aid of LiOMe delivers the product **3**. Finally, **3** is diasterospecifically reduced by silane and (or) LCuH to furnish the thermodynamically more stable indoline **2**.[18] According to the control experiments (see control experiments (j) and (k) in the SI),[19] we speculated that **3** might be mainly produced by the elimination of **E** with the assistance of silica gel. The minor way for **3** is

Scheme 4. Possible Mechanism for the Formation of 2



likely by the oxidation of reduced species of **E** in the crude products, using O_2 as the oxidant (for the detailed formation mechansim of **3**, see the SI).

In summary, we have developed a diasterospecific and step-economic method for the synthesis of 3-hydroxyindolines and 2-aryl-3H-indol-3-ones by CuH-catalyzed reductive coupling of readily available *o*-alkynylnitroarene under mild conditions with simple experimental procedure. In this protocol, the nitro group serves as the nitrogen and oxygen source of indolines and 2-aryl-3H-indol-3-ones with the simultaneous formation of C−N and C−O bonds. Further studies on the reaction scope, enantioselectivity control, and its application in synthesizing bioactive products are underway, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01849.

Details about experimental conditions, characterization data, copies of ^{1}H and ^{13}C NMR spectra of all new compounds (PDF)

Accession Codes

CCDC 1878765 contains 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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