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Copper-Catalyzed Asymmetric Propargylic Alkylation with Oxindoles: Diastereo- and Enantioselective Construction of Vicinal Tertiary and All-Carbon Quaternary Stereocenters

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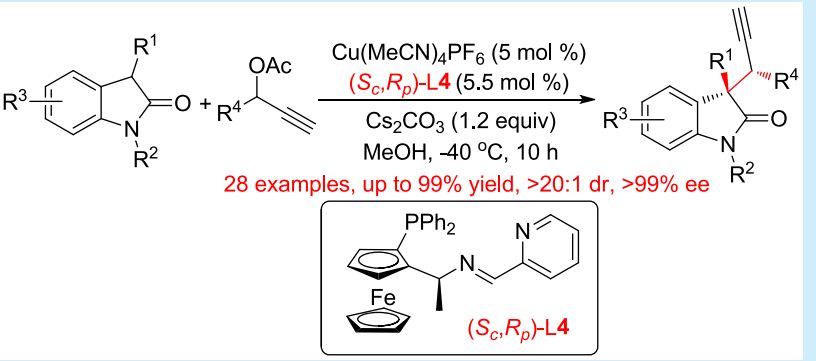

ABSTRACT: A copper-catalyzed asymmetric propargylic alkylation of propargylic acetates with 3-substituted oxindoles for the stereoselective construction of vicinal tertiary and all-carbon quaternary stereocenters in a 3,3-disubstituted oxindole skeleton has been realized. The reaction proceeded smoothly under the catalysis of $Cu(MeCN)_4PF_6$ combined with a chiral tridentate ferrocenyl P,N,N ligand, leading to a broad range of optically active 3,3-disubstituted oxindoles in high yields and with excellent diastereo- and enantioselectivities.

The 3,3-disubstituted oxindoles are synthetically important targets because they widely exist in natural products, pharmaceuticals, and drug candidates.[1] One major strategy for the construction of these structural motifs should be the application of prochiral 3-substituted oxindoles as nucleophiles for various catalytic reactions. Successful examples include the aldol reaction,[2] alkylation and arylation,[3] the Michael reaction,[4] the Mannich reaction,[5] fluorination,[6] and so on.[7] Despite these achievements, the development of an efficient and general method for the preparation of optically active 3,3-disubstituted oxindoles remains challenging due to the inherent difficulty in the installation of a quaternary carbon stereocenter in these structural motifs.

Catalytic asymmetric propargylic substitution has witnessed remarkable progress in the past decade,[8] in which the development of a chiral Cu-catalytic system as the catalyst has significantly expanded the scope of the reaction.[9] Recent advances allowed a variety of C-, N-, and O-nucleophiles for the Cu-catalyzed asymmetric propargylic substitution to synthesize structurally diverse chiral propargylic compounds, mostly constructing a single stereocenter located at the propargylic position.[10−12] In contrast, few propargylic alkylation reactions could realize the simultaneous stereocontrol at both the propargylic electrophile and the nucleophile, especially when an all-carbon quaternary stereocenter is also generated in the process.[13] Due to its demonstrated nucleophilic ability in various catalytic reactions, we envisioned that 3-substituted oxindole should also be a suitable nucleophile for Cu-catalyzed asymmetric propargylic substitution, thus constructing a challenging quaternary−tertiary stereogenic arrangement in a 3,3-disubstituted oxindole. As a result, herein we report a highly diastereo- and enantioselective Cu-catalyzed asymmetric propargylic substitution of propargylic acetates with 3-substituted oxindoles, leading to structurally diverse chiral all-carbon quaternary 3,3-disubstituted oxindoles with a pendant chiral tertiary propargyl moiety.

Our preliminary study commenced with the reaction of *N*-methyl-3-phenylindolin-2-one (**1a**) and 1-phenylprop-2-yn-1-yl acetate (**2a**) with a copper catalyst prepared *in situ* from $Cu(MeCN)_4PF_6$ (5 mol %) and the commercial available (*S*)-BINAP (**L1**) (5.5 mol %) as the ligand. Unfortunately, no

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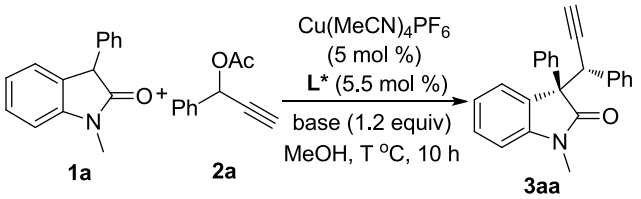
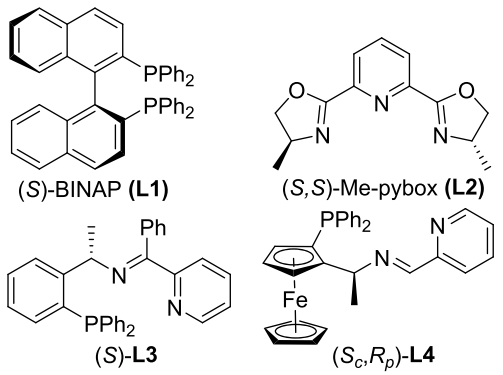
reaction was detected (Table 1, entry 1). By use of the tridentate N-ligand (*S*,*S*)-Me-pybox (**L2**), the reaction

Table 1. Optimization of the Reaction Conditions[a]



entry	L*	base	*T* (°C)	yield[b] (%)	dr[c]	ee[d] (%)
1	**L1**	$^{i}Pr_2NEt$	0			
2	**L2**	$^{i}Pr_2NEt$	0	92	1:1	91
3	**L3**	$^{i}Pr_2NEt$	0	92	2:1	95
4	**L4**	$^{i}Pr_2NEt$	0	63	19:1	92
5	**L4**	$^{i}Pr_2NEt$	−20	60	19:1	97
6	**L4**	$^{i}Pr_2NEt$	−40	58	>20:1	>99
7	**L4**	NEt_3	−40	43	>20:1	>99
8	**L4**	K_3PO_4	−40	63	>20:1	>99
9	**L4**	$KO^{t}Bu$	−40	79	>20:1	>99
10	**L4**	K_2CO_3	−40	79	>20:1	>99
11	**L4**	Cs_2CO_3	−40	99	>20:1	>99

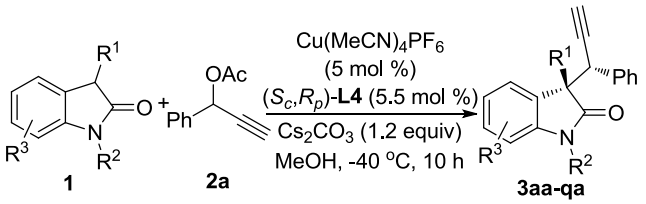
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), base (0.36 mmol), $Cu(MeCN)_4PF_6$ (5 mol %), **L*** (5.5 mol %) in MeOH (3 mL) at indicated temperature for 10 h. [b]Isolated yields. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC analysis.

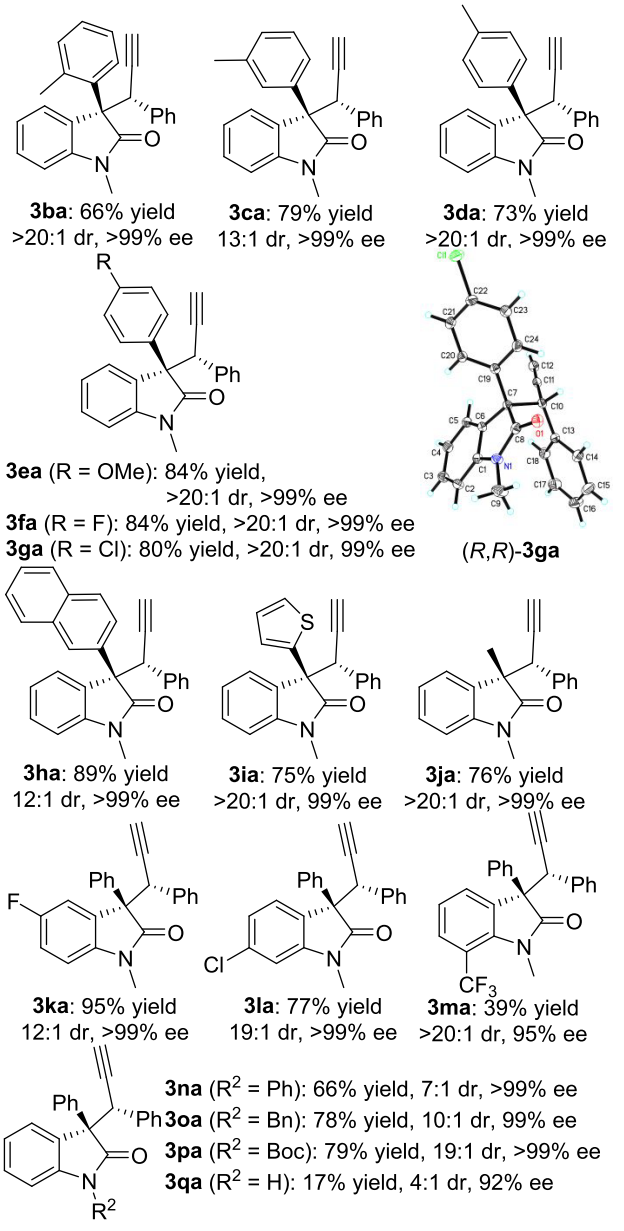


delivered the target product **3aa** in 92% yield and with 90% ee albeit in low diastereoselectivity (entry 2). The tridentate P,N,N-ligand (*S*)-**L3** also led to the satisfactory enantioselectivity but did not improve the diastereoselectivity (entry 3). To our delight, chiral ferrocene-based tridentate P,N,N-ligand (S_cR_p)-**L4** led to a promising result with a diastereoselectivity up to 19:1 dr although the yield was not so satisfactory (entry 4). Lowering the reaction temperature could further enhance the diastereo- and enantioselectivity but less affected the reactivity (entries 4−6). The base additive showed a significant effect in the reactivity (entries 6−11). The use of inorganic bases could greatly improve the reaction yield. Among them, Cs_2CO_3 proved to be the best choice, with which a 99% yield and a dr of >20:1 with >99% ee for the major diastereoisomer were achieved (entry 11).

With optimized conditions in hand, we first investigated the reaction scope of 3-substituted oxindoles **1**, and the results are summarized in Scheme 1. Initially, the effect of the substituent at the 3-position of oxindoles was examined. The results indicated that the substitution pattern on the phenyl ring slightly affected the reactivity, and all substrates **1b−d** bearing

Scheme 1. Scope of 3-Substituted Oxindoles 1[a]





[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), Cs_2CO_3 (0.36 mmol), $Cu(MeCN)_4PF_6$ (5 mol %), (S_cR_p)-**L4** (5.5 mol %) in MeOH (3 mL) at −40 °C for 10 h. Isolated yield was provided. The dr value was determined by ^{1}H NMR. The ee value was determined by chiral HPLC analysis.

a methyl group at the *ortho*, *meta*, or *para* position gave similar good results. 3-Phenyloxindoles **1e−g** with different electron-withdrawing or electron-donating groups at the *para*-position of the phenyl ring reacted smoothly with **2a** to afford the

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desired products **3ea**−**ga** in high yields with excellent diastereo- and enantioselectivities.

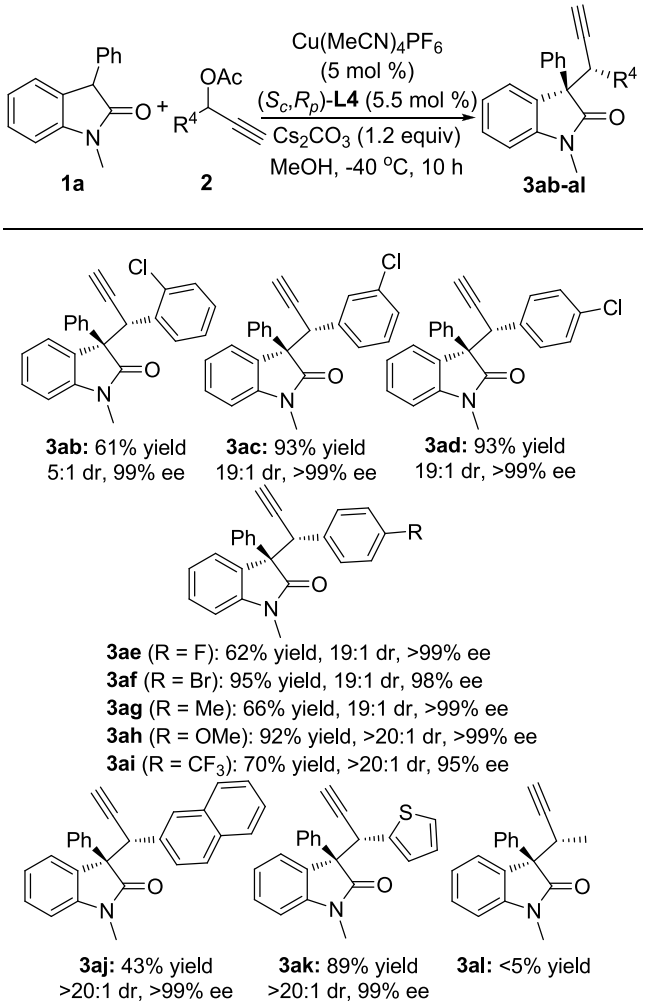
2-Naphthyl substrate **1h** was also suitable to the reaction, giving **3ha** in 89% yield and a dr of 12:1 with >99% ee. Heteroaromatic substrate **1i** served well for the reaction, leading to the corresponding 3,3-disubstituted oxindole **3ia** in high yield, and excellent diastereo- and enantioselectivity. The aliphatic substituent was well tolerated in this reaction. Thus, the product **3ja** bearing a 3-methyl group was obtained in 76% yield and a dr of >20:1 with >99% ee. The substituent at the phenyl ring of the oxindole skeleton was also examined. The results revealed that the substituent at the 5- or 6-position displayed little effect on the reaction performance. In contrast, the substituent at the 7-position resulted in the dramatically reduced reactivity. Thus, 7-CF_3-substituted substrate **1m** gave the desired product **3ma** in only 39% yield albeit in >20:1 dr with 95% ee. Besides the methyl group, other substituents (**1n**−**q**) at the *N*-position of oxindoles were also tolerated in the reaction but did not improve the reaction performance. The absolute configuration of 3,3-disubstituted oxindoles was unambiguously determined by X-ray structure analysis of **3ga**, to which a (*R*,*R*)-configuration was assigned (CCDC 1972452).

Next, the substrate scope with respect to propargylic acetates was investigated, and the results are listed in Scheme 2. The results revealed that all aromatic substrates tested gave rise to perfect enantioselectivity, regardless of the substitution pattern and electronic property of the substituent. The reaction was somewhat sensitive to the substitution pattern on the phenyl ring. Thus, both 3- and 4-chloro-substituted substrates **2c** and **2d** gave similar perfect results; in contrast, the 2-chloro-substituted substrate **2b** led to a significant decrease in the yield and diastereoselectivity presumably due to the steric hindrance. The substituent at the *para* position of the phenyl ring showed an observed effect on the reactivity but less affected the diastereo- and enantioselectivity. 1-(Naphth-2-yl)prop-2-yn-1-yl acetate **2j** was not so compatible with the present catalytic system in terms of yield, in which **3aj** was obtained in only 43% yield but with perfect diastereo- and enantioselectivity. 2-Thienyl substrate **2k** proceeded smoothly, giving the product **3ak** in 89% yield and a dr of >20:1 with >99% ee. However, aliphatic substrate **2l** was not tolerated in the reaction.

To demonstrate the utility of this type of product, some synthetic transformations of **3aa** were carried out as shown in Scheme 3. The scalability of this process was verified by performing the reaction of **1a** and **2a** on a gram-scale, in which **3aa** was isolated in 90% yield and >20:1 dr with >99% ee even at a reduced catalyst loading of 2.5 mol %. The hydrogenation of **3aa** with Lindlar catalyst selectively reduced the alkyne moiety to the alkene **5** in 94% yield without any loss in the diastereo- and enantioselectivity. A click reaction of **3aa** with tosyl azide via the copper-catalysis resulted in 1,2,3-triazole **4** in 81% yield with fully maintained diastereo- and enantioselectivities.

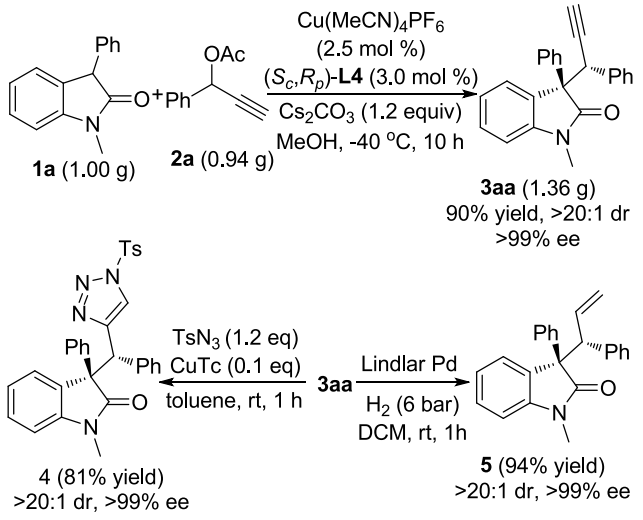
A transition state of Cu−allenylidene complex with chiral ligand (S_c,R_p)-**L4** is proposed to explain the observed stereoselectivities as shown in Scheme 4. Due to the edge-to-face aromatic interaction and the steric hindrance, the nucleophilic attack of oxindoles from the S_i face at the S_i face of the γ-carbon atom of the Cu−allenylidene complex is favored, thus leading to the propargylic alkylation product with a (*R*,*R*)-configuration.

Scheme 2. Scope of Propargylic Acetates 2[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.36 mmol), Cs_2CO_3 (0.36 mmol), $Cu(MeCN)_4PF_6$ (5 mol %), (S_c,R_p)-**L4** (5.5 mol %) in MeOH (3 mL) at −40 °C for 10 h. Isolated yield was provided. The dr value was determined by ^{1}H NMR. The ee value was determined by chiral HPLC analysis.

Scheme 3. Synthetic Applications



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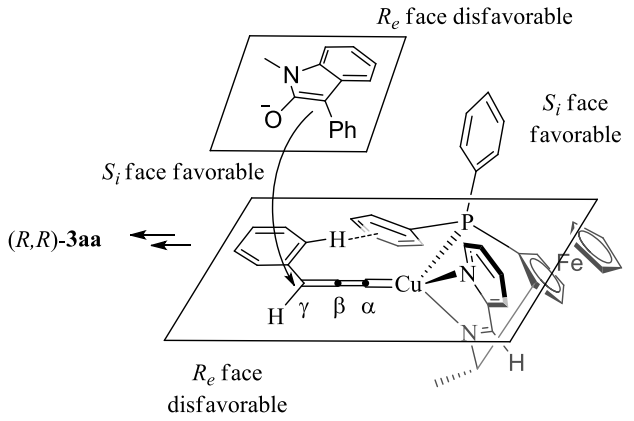
Scheme 4. Model for Stereoselective Induction



In conclusion, we have developed a highly diastereo- and enantioselective Cu-catalyzed propargylic substitution of propargylic acetates with 3-substituted oxindoles enabled by a chiral ferrocene-based tridentate P,N,N-ligand. The reaction displayed wide functional group tolerance, thus generating a variety of optically active 3,3-disubstituted oxindoles bearing vicinal tertiary and all-carbon quaternary stereocenters in high yields, and excellent diastereo- and enantioselectivities. The utility of the present method could be further demonstrated by a gram-scale synthesis and the transformation of the alkyne moiety into other functional groups.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04621.

Experimental details and characterization data including NMR data (PDF)

Accession Codes

CCDC 1972452 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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