




 Cite this: *RSC Adv.*, 2022, 12, 26727

# Stereoselective synthesis of C3-tetrasubstituted oxindoles *via* copper catalyzed asymmetric propargylation†

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Herein, a copper catalyzed asymmetric propargylation of 2-oxindole-3-carboxylate esters with terminal propargylic esters is described. This strategy successfully provides a direct approach to constructing a broad range of chiral C3-tetrasubstituted oxindoles with contiguous tertiary and quaternary carbon stereocenters in high yields and excellent enantioselectivities (16 examples, up to 99% yield and 98% ee). Moreover, the diastereoisomers of the two newly formed stereocenters can be separated by silica gel chromatography, thereby providing a valuable stereoselective access to all four possible stereoisomers of C3-tetrasubstituted oxindoles.

 Received 24th July 2022  
 Accepted 10th September 2022

DOI: 10.1039/d2ra04603b

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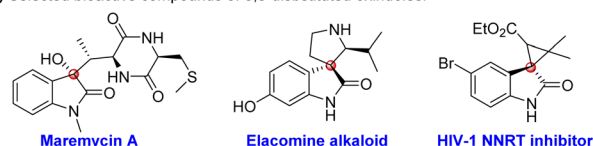
## Introduction

As privileged scaffolds in a large family of natural alkaloid compounds, pharmaceuticals and bioactive products, oxindoles bearing a tetrasubstituted carbon stereocenter at the C3 position widely exist in a range of structural frameworks and architectures owing to their potential biological and pharmacological activities (Fig. 1a).<sup>1</sup> As a result, tremendous efforts have been devoted to achieving these motifs.<sup>2</sup> With the development of asymmetric organocatalysis and transition metal catalysis, catalytic asymmetric protocols to directly construct C3-tetrasubstituted oxindoles with an all-carbon quaternary stereocenter using 3-substituted oxindoles as nucleophiles have received extensive attention in the past decades (Fig. 1b).<sup>3</sup> Despite these impressive numerous works, the efficient synthesis of chiral C3-tetrasubstituted oxindoles bearing contiguous stereocenters remains one of the most difficult issues in asymmetric catalysis.

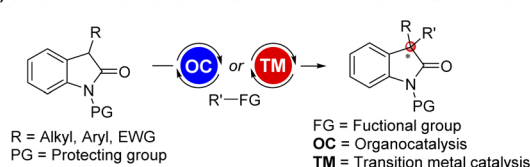
Recently, asymmetric propargylation reactions of readily available racemic terminal propargylic esters catalyzed by non-precious chiral copper complexes have emerged as a promising, fruitful and attractive method to construct useful chiral propargyl compounds.<sup>4</sup> However, although a variety of nucleophiles

can participate in copper catalyzed propargylation substitution,<sup>5</sup> the efficient construction of contiguous tertiary and all-carbon quaternary stereocenters is still a difficult problem for this methodology.<sup>6</sup> In 2020, Hu and co-workers reported a copper catalyzed asymmetric propargylation reaction of 3-aryl substituted oxindoles affording 3,3-disubstituted oxindoles in highly diastereo- and enantioselective results.<sup>7</sup> Recently, the stereodivergent synthesis of natural product frameworks *via* asymmetric catalytic transformations using simple starting materials has aroused widely concern and development.<sup>8</sup> To the best of our knowledge, the stereoselective synthesis of chiral C3-

a) Selected bioactive compounds of 3,3-disubstituted oxindoles:



b) Construction of C3-tetrasubstituted oxindoles with 3-substituted oxindoles:



c) Our strategy:

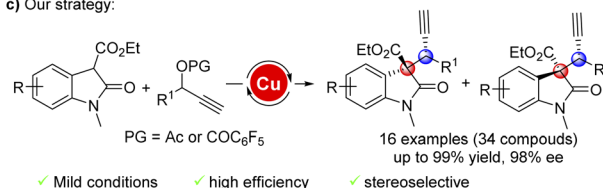


Fig. 1 Representative examples of C3-tetrasubstituted oxindoles and our strategy.

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<sup>†</sup> Electronic supplementary information (ESI) available. CCDC 2181911 and 2181912. For ESI and crystallographic data in CIF or other electronic format see <https://doi.org/10.1039/d2ra04603b>
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tetrasubstituted oxindoles with contiguous tertiary and all-carbon quaternary stereocenters *via* copper catalyzed asymmetric propargylation reaction is still highly desirable. Herein, we report a copper catalyzed asymmetric propargylation substitution of 2-oxindole-3-carboxylate esters<sup>9</sup> with terminal propargylic esters providing a concise strategy for the stereoselective synthesis of chiral C3-tetrasubstituted oxindoles bearing contiguous tertiary and quaternary carbon stereocenters.

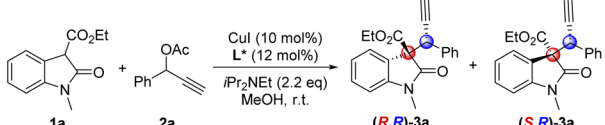
## Results and discussion

To investigate our study, we chose 2-oxindole-3-carboxylate esters **1a** and terminal propargylic acetate **2a** as model substrates in the presence of 10 mol% of copper catalyst in methanol (Table 1). A series of chiral Pybox ligands were first screened, we can successfully get the desired chiral propargylation products **3a** in good yields and moderate enantioselectivities albeit in low diastereoselectivity, in which L(+)-leucinol-derived chiral ligand **L6** is the best choice (Table 1, entries 1–7). Performing the reaction at lower temperature resulted in increased yield and enantioselectivity, but not

diastereoselectivity (Table 1, entry 8). However, changing the base could not improve the reaction results (Table 1, entries 9 and 10). Ultimately, further lowering the reaction temperature to  $-15\text{ }^{\circ}\text{C}$  gave excellent yield and enantioselectivity, but the diastereoselectivity remained unimproved (Table 1, entry 11). Although the diastereoselectivity was not so satisfactory, the two diastereomers (*R,R*)-**3a** and (*S,R*)-**3a** can be separated by silica gel chromatography.

With the optimized reaction conditions in hand, a series of 2-oxindole-3-carboxylate esters **1** were first evaluated, providing

Table 1 Optimization of the reaction conditions<sup>a</sup>

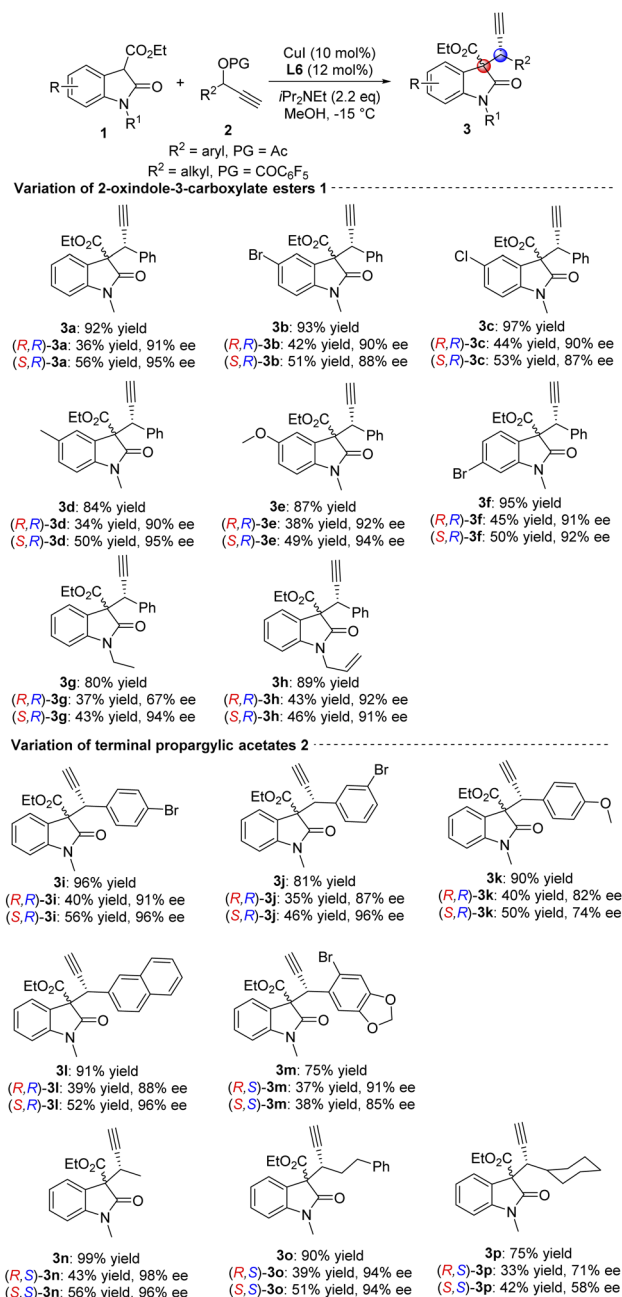


L1: R = Ph  
L2: R = *t*Bu  
L3: R = *i*Pr  
L4: R = Cy

L5, L6, L7 structures are shown as Pybox ligands with various R groups.

Entry	Ligand	Time (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)	dr [( <i>R,R</i> )/( <i>S,R</i> )] <sup>c</sup> (%)
1	L1	1	93	44/60	1 : 1.7
2	L2	1	66	27/4	1.1 : 1
3	L3	1	85	59/48	1.1 : 1
4	L4	1	73	27/4	1 : 1
5	L5	1	60	59/48	1.1 : 1
6	L6	1	90	71/79	1 : 1.2
7	L7	1	80	62/54	1.5 : 1
8 <sup>d</sup>	L6	5	92	90/94	1 : 1.5
9 <sup>d,e</sup>	L6	5	95	86/92	1 : 1.3
10 <sup>d,f</sup>	L6	5	40	54/75	1 : 1.5
11 <sup>g</sup>	L6	20	95(92) <sup>h</sup>	91/95	1 : 1.6

<sup>a</sup> Unless noted, reactions were performed with **1a** (0.20 mmol), **2a** (0.3 mmol), CuI (0.02 mmol), L (0.022 mmol) and *i*Pr<sub>2</sub>NEt (0.44 mmol) in anhydrous MeOH (3 mL) at r.t. for 1 h. <sup>b</sup> Determined by <sup>1</sup>H NMR of the reaction mixture containing 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup> ee and dr [(*R,R*)/(*S,R*)], determined by chiral HPLC. <sup>d</sup> Reaction performed at 0 °C. <sup>e</sup> Using Et<sub>3</sub>N instead of *i*Pr<sub>2</sub>NEt. <sup>f</sup> Using K<sub>2</sub>CO<sub>3</sub> instead of *i*Pr<sub>2</sub>NEt. <sup>g</sup> Reaction performed at  $-15\text{ }^{\circ}\text{C}$ . <sup>h</sup> Isolated yield in parentheses.



Scheme 1 Substrate scope.<sup>a</sup> Unless noted, reactions were performed with **1** (0.20 mmol), **2** (0.3 mmol), CuI (0.02 mmol), L6 (0.022 mmol) and *i*Pr<sub>2</sub>NEt (0.44 mmol) in anhydrous MeOH (3 mL) at  $-15\text{ }^{\circ}\text{C}$  for 20 h. Isolated yields based on **1**, and ee values were determined by chiral HPLC analysis.



the corresponding products in moderate to excellent yields and enantioselectivities, but with low diastereoselectivities (Scheme 1: **3a–3h**, up to 95% yield, 95% ee and 1 : 1.6 dr). As shown in Scheme 1, the reaction has a broad substrate scope and high functional group tolerance. Substituted groups at the 5-position of oxindole such as 5-Br, 5-Cl, 5-Me and 5-MeO reacted smoothly achieving the desired chiral products in high yields and enantioselectivities (**3a–3e**). The results revealed that the electron-withdrawing substituents performed better than the electron-donating substituents. At the same time, the substituent at the 6-position resulted in the same reactivity (**3f**). To further verify the compatibility of this transformation, the protecting group of oxindole was investigated. Ethyl- and allyl-protected 2-oxindole-3-carboxylate esters also proved to be suitable for this reaction (**3g–3h**), but one of the isomers of ethyl-protected chiral product showed lower enantioselectivity (*(R,R)*-**3g**: 67% ee). Next, the substrate scope with respect to terminal propargylic acetates **2** were investigated (Scheme 1: **3i–3p**, up to 99% yield, 98% ee and 1 : 1.4 dr). The substituted groups on the phenyl ring of terminal propargylic acetates were evaluated affording the desired corresponding chiral C3-tetrasubstituted oxindoles in moderate to good yields and enantioselectivities (**3i–3k**). In addition, naphthyl and 2-bromo piperonyl also performed well with good results (**3l–3m**). When adjusting the protecting group of terminal propargylic esters, aliphatic substrates were compatible with the reaction, giving the corresponding chiral products in good to excellent yields and enantioselectivities (**3n–3o**). However, the cyclohexyl substituted substrate only gave moderate results, suggesting a sensitive effect of steric hindrance for this transformation (**3p**). Finally, the absolute configuration of the two isomers can be determined by X-ray structure analysis of *(S,R)*-**3i** (CCDC 2181912) and *(R,S)*-**3m** (CCDC 2181911).<sup>†</sup>

To further demonstrated the utility of this transformation, synthetic transformations were carried out (Fig. 2). Under the standard reaction conditions, using **L6** and its enantiomer *ent*-

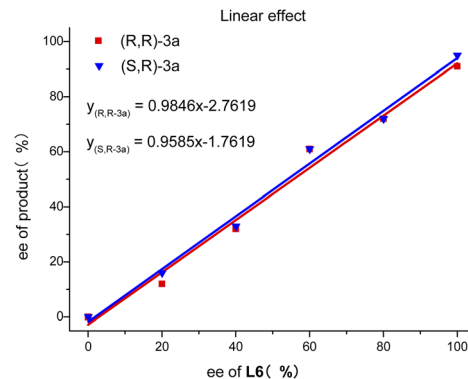


Fig. 3 The linear effect.

**L6** as chiral ligands and **1f** and **2a** as substrates, we were able to obtain all four stereoisomers of chiral product **3f** in moderate yields and excellent enantioselectivities (Fig. 2a). This offered an efficient method for the stereoselective synthesis of chiral C3-tetrasubstituted oxindoles bearing contiguous tertiary and quaternary carbon stereocenters. The click reaction of *(S,R)*-**3f** with anti-HIV drug Zidovudine resulted in chiral triazole product **4** in 90% yield and excellent diastereoselectivity (Fig. 2b).

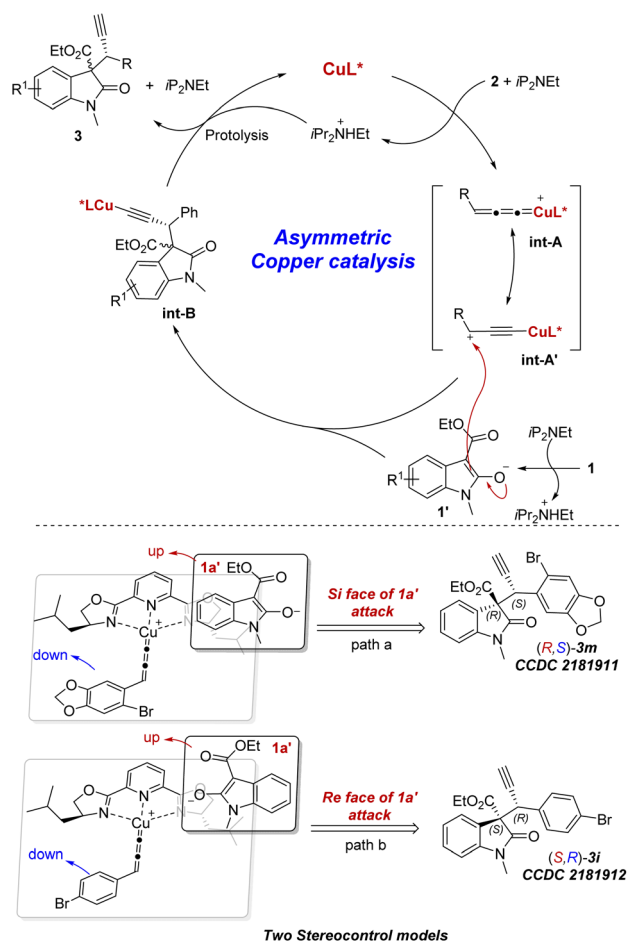
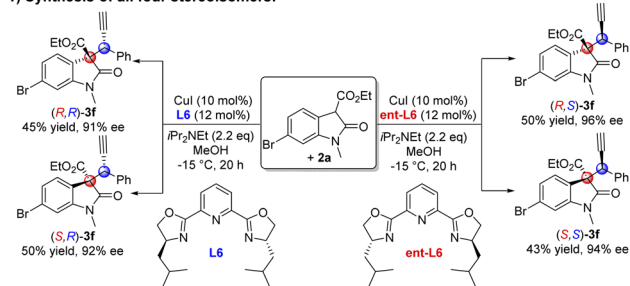


Fig. 4 The proposed mechanism and stereocontrol models.

#### 1) Synthesis of all four stereoisomers:



#### 2) Click reaction:



Fig. 2 Synthetic transformations.



In order to get the insight of this reaction, we performed a set of experiments with ee-varied ligand **L6** under the model reaction. As depicted in Fig. 3, a linear relationship between ee of ligand **L6** and product **3a** was observed, which indicated a mono-copper catalytic process.<sup>10</sup> On the basis of prior studies<sup>6a,7a,9</sup> and our observations, the proposed mechanism and stereocontrol models are depicted in Fig. 4. Firstly, the *in situ* formed chiral copper complex **CuL\*** by **CuI** and **L6** reacted with terminal propargylic acetate **2** with the assistance of *i*Pr<sub>2</sub>NET to generate copper allenylidene intermediate **A** or its resonance intermediate **A'**. In the presence of base, substrate **1** is transformed to its enolate **1'**, followed by nucleophilic attack on the cationic intermediate **A** or **A'** giving the intermediate **B**. Finally, the protolysis of intermediate **B** generates the desired chiral **3a** and release the chiral copper complex. Based on the absolute configurations of the two isomers, rationalized stereocontrol models are proposed in Fig. 4. Owing to the steric hindrance of chiral ligand **L6**, the enolate **1'** favors nucleophilic attack from the top of the face of copper allenylidene intermediate, thus leading to good enantioselectivities. However, the two sides of the enolate **1'** (*Si* face and *Re* face) can attack on the face of copper allenylidene intermediate **A**, respectively, resulting in poor diastereoselectivities (Fig. 4, path a and b).

## Conclusions

In conclusion, we have reported an efficient copper catalyzed asymmetric propargylation substitution of 2-oxindole-3-carboxylate esters with terminal propargylic acetates. This protocol provides a concise and facile synthetic approach to construct a broad range of chiral C3-tetrasubstituted oxindoles bearing contiguous tertiary and quaternary carbon stereocenters. Furthermore, both isomers can be separated by silica gel chromatography. So, this method provides a valuable access for the stereoselective synthesis of four possible C3-tetrasubstituted oxindole stereoisomers. We hope this transformation would inspire the development of new asymmetric and highly practical synthetic methods for the synthesis of chiral C3-tetrasubstituted oxindole derivatives.

## Author contributions

Jiaomei Wang and Yu Zhao contributed equally to this work.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We are grateful for financial support by the National Natural Science Foundation of China (Grants No. 22101102, 22161047), Scientific Research Foundation of Xuzhou Institute of Technology (XKY2019210), Natural Science Foundation of Jiangsu Province (BK20210915).

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