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.

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).1 As a result, tremendous efforts have been devoted to achieving these motifs.2 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).3 Despite these impressive numerous works, the efficient construction of contiguous tertiary and all-carbon quaternary stereocenters is still a difficult problem for this methodology.4 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.5 Recently, the stereodivergent synthesis of natural product frameworks via asymmetric catalytic transformations using simple starting materials has aroused widely concern and development.6 To the best of our knowledge, the stereoselective synthesis of chiral C3-

![Fig. 1](https://doi.org/10.1039/d2ra04603b)

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

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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 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 °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

![Scheme 1](image)

Table 1  Optimization of the reaction conditions

| Entry | Ligand | Time (h) | Yield (%) | ee (%) | dr [(R,R)/(S,R)] (%) |
|-------|--------|----------|-----------|--------|----------------------|
| 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     | L6     | 5        | 92        | 90/94  | 1 : 1.5              |
| 9     | L6     | 5        | 95        | 86/92  | 1 : 1.3              |
| 10    | L6     | 5        | 40        | 54/75  | 1.5 : 1              |
| 11    | L6     | 20       | 95(92)    | 91/95  | 1 : 1.6              |

*Unless noted, reactions were performed with 1a (0.20 mmol), 2a (0.3 mmol), CuI (0.02 mmol), L (0.022 mmol) and iPr₂NEt (0.44 mmol) in anhydrous MeOH (3 mL) at r.t. for 1 h. Determined by ¹H NMR of the reaction mixture containing 1,3,5-trimethoxybenzene as an internal standard. ee and dr [(R,R)/(S,R)], determined by chiral HPLC. Reaction performed at 0 °C. Using Et₃N instead of iPr₂NEt. Using K₂CO₃ instead of iPr₂NEt. Reaction performed at –15 °C.

Scheme 1  Substrate scope

| Entry | Ligand | Time (h) | Yield (%) | ee (%) | dr [(R,R)/(S,R)] (%) |
|-------|--------|----------|-----------|--------|----------------------|
| 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     | L6     | 5        | 92        | 90/94  | 1 : 1.5              |
| 9     | L6     | 5        | 95        | 86/92  | 1 : 1.3              |
| 10    | L6     | 5        | 40        | 54/75  | 1.5 : 1              |
| 11    | L6     | 20       | 95(92)    | 91/95  | 1 : 1.6              |

*Unless noted, reactions were performed with 1 (0.20 mmol), 2 (0.3 mmol), CuI (0.02 mmol), L6 (0.022 mmol) and iPr₂NEt (0.44 mmol) in anhydrous MeOH (3 mL) at –15 °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 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).†

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).
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. On the basis of prior studies,7a,7b,9 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 iPr2NEt 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.

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Notes and references

1 For selected examples, see: (a) T. Matsuura, L. E. Overman and D. J. Poon, J. Am. Chem. Soc., 1998, 120, 6500–6503; (b) S. Edmondson, S. J. Danishefsky, L. Sepp-Lorenzino and N. Rosen, J. Am. Chem. Soc., 1999, 121, 2147–2155; (c) L. E. Overman and M. D. Rosen, Angew. Chem., Int. Ed., 2000, 39, 4596–4599; (d) P. R. Sebahar and R. M. Williams, J. Am. Chem. Soc., 2000, 122, 5666–5667; (e) A. Lerchner and E. M. Carreira, J. Am. Chem. Soc., 2002, 124, 14826–14827; (f) C. Marti and E. M. Carreira, Eur. J. Org. Chem., 2003, 2003, 2209–2219; (g) H. Lin and S. J. Danishefsky, Angew. Chem., Int. Ed., 2003, 42, 36–51; (h) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao and D. W. C. MacMillan, Proc. Natl. Acad. Sci. U. S. A., 2004, 101, 5482–5487; (i) A. Huang, J. J. Kodanko and L. E. Overman, J. Am. Chem. Soc., 2004, 126, 14043–14053; (j) F. Y. Miyake, K. Yakushijin and D. A. Horne, Angew. Chem., Int. Ed., 2004, 43, 5357–5360; (k) M. M.-C. Lo, C. S. Neumann, N. Nagayama, E. O. Perlstein and S. L. Schreiber, J. Am. Chem. Soc., 2004, 126, 16077–16086; (l) C. Marti and E. M. Carreira, J. Am. Chem. Soc., 2005, 127, 11505–11515; (m) J. A. May and B. Stoltz, Tetrahedron, 2006, 62, 5262–5271; (n) T. Kawasaki, M. Shinada, D. Kamimura, M. Ohzono and A. Ogawa, Chem. Commun., 2006, 420–422; (o) B. M. Trost and Y. Zhang, J. Am. Chem. Soc., 2006, 128, 4590–4591; (p) B. M. Trost and D. T. Stiles, Org. Lett., 2007, 9, 2763–2766; (q) C. V. Galliford and K. A. Scheidt, Angew. Chem., Int. Ed., 2007, 46, 8748–8758; (r) J. T. Mohr, M. R. Krout and B. M. Stoltz, Nature, 2008, 455, 323–332; (s) P. Siengalewicz, T. Gaich and J. Mulzer, Angew. Chem., Int. Ed., 2008, 47, 8170–8176.

2 For selected reviews see: (a) M. Bandini and A. Eichholzer, Angew. Chem., Int. Ed., 2009, 48, 9608–9644; (b) F. Zhou, Y.-L. Liu and J. Zhou, Adv. Synth. Catal., 2010, 352, 1381–1407; (c) Z.-Y. Cao, Y.-H. Wang, X.-P. Zeng and J. Zhou, Tetrahedron Lett., 2014, 55, 2571–2584; (d) R. Dalpozzo, Adv. Synth. Catal., 2017, 359, 1772–1810; (e) Z.-Y. Cao, F. Zhou and J. Zhou, Acc. Chem. Res., 2018, 51, 1443–1454.

3 For selected examples, see: (a) T. B. K. Lee and G. S. K. Wong, J. Org. Chem., 1991, 56, 872–875; (b) B. M. Trost and M. U. Frederiksen, Angew. Chem., Int. Ed., 2005, 44, 308–310; (c) B. M. Trost and Y. Zhang, J. Am. Chem. Soc., 2006, 128, 4590–4591; (d) B. M. Trost and Y. Zhang, J. Am. Chem. Soc., 2007, 129, 14548–14549; (e) S. Ogawa, N. Shibata, J. Inagaki, S. Nakamura, T. Toru and M. Shiro, Angew. Chem., Int. Ed., 2007, 46, 8666–8669; (f) X. Tian, K. Jiang, J. Peng, W. Du and Y.-C. Chen, Org. Lett., 2008, 10, 3583–3586; (g) K. Jiang, J. Peng, H.-L. Cui and Y.-C. Chen, Chem. Commun., 2009, 3955–3957; (h) A. M. Taylor, R. A. Altman and S. L. Buchwald, J. Am. Chem. Soc., 2009, 131, 9900–9901; (i) T. Bui, S. Syed and C. F. Barbas III, J. Am. Chem. Soc., 2009, 131, 8758–8759; (j) Y. Kato, M. Furutachi, Z. Chen, H. Mitsunuma, S. Matsunaga and M. Shibasaki, J. Am. Chem. Soc., 2009, 131, 9168–9169; (k) R. He, S. Shirakawa and K. Maruoka, J. Am. Chem. Soc., 2009, 131,
9 (a) X.-J. Chen, W. Zhu, W.-K. Qian, E.-G. Feng, Y. Zhou, J.-F. Wang, H.-L. Jiang, Z.-J. Yao and H. Liu, *Adv. Synth. Catal.*, 2012, **354**, 2151–2156; (b) J. Zhou, L.-N. Jia, L. Peng, Q.-L. Wang, F. Tian, X.-Y. Xu and L.-X. Wang, *Tetrahedron*, 2014, **70**, 3478–3484; (c) J. Gao, J.-R. Chen, S.-W. Duan, T.-R. Li, L.-Q. Lu and W.-J. Xiao, *Asian J. Org. Chem.*, 2014, **3**, 530–535; (d) J.-H. Mao, Y.-B. Wang, L.-M. Yang, S.-H. Xiang, Q.-H. Wu, Y. Cui, Q. Lu, J. Lv, S.-Y. Li and B. Tan, *Nat. Chem.*, 2021, **13**, 982–991.

10 C. Girard and H. B. Kagan, *Angew. Chem., Int. Ed.*, 1998, **37**, 2922–2959.