Chinese Chemical Letters 33 (2022) 867–870

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

# Copper-catalyzed asymmetric propargylic substitution of anthrones and propargylic esters

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ARTICLE INFO

*Article history:*
Received 19 May 2021
Revised 4 August 2021
Accepted 5 August 2021
Available online 11 August 2021

*Keywords:*
Asymmetric catalysis
Propargylic substitution
Anthrones
Copper catalysis
Tridentate ligand

ABSTRACT

Anthrones are key structural motifs in many natural products, bioactive compounds and pharmaceutical chemicals. Earth-abundant-metal-catalyzed asymmetric functionalization of anthrones has not proved to be viable. Herein, we disclosed a highly enantioselective propargylic substitution of anthrones with propargylic esters using copper salts with chiral *N, N, P*-ligand. This strategy is amenable to a broad range of substrates, uses readily available starting materials, provides excellent yields with remarkable enantioselectivity under mild conditions, and enables attractive products diversification routes.



Anthrones are privileged scaffolds, and their derivatives possess multiple biological activities including anticancer and anti-inflammatory properties (Scheme 1a) [1–6]. For example, Dithranol has been used in the treatment of psoriasis, and Emodin plays an important role in antitumor immunity [4–6]. In recent years, considerable progress has been achieved for the enantioselective synthesis of anthrone derivatives especially by organocatalysts [7–14]. The established protocols mainly limited to 1,4-additions and Diels-Alder reaction of anthrones. For instance, in 2006, Tan and coworkers developed a highly enantioselective Diels-Alder reaction of anthrones with phenylmaleimides by chiral guanidine catalyst [14]. In contract, little attention has been paid on transition-metal catalyzed asymmetric reactions of anthrones. Until 2015, Lautens and coworkers realized the first rhodium(I)-catalyzed benzylic functionalization of anthrones *via* ring opening of oxabicycles (Scheme 1b) [15]. Thereafter, You and Wu *et al.* disclosed a highly enantioselective iridium-catalyzed allylation of anthrones (Scheme 1b) [16]. Despite these indisputable advances, earth-abundant-metal-catalyzed asymmetric functionalization of anthrones continue to be scarce [17]. Therefore, the use of earth-abundant metals to realize asymmetric functionalization of anthrones remains a challenging but highly desirable goal.

In the meantime, enantioselective copper catalyzed transformations have ermerged as powerful protocols in organic synthesis [18–29]. For examples, copper-catalyzed asymmetric propargylic substitution [30–35] is a powerful approach for the construction of C–C [36–47] or C–X [48–53] (X = N, O) bonds. A diverse range of propargylic compounds have been synthesized through the addition of nucleophiles to Cu-allenylidene intermediates [54–61]. However, to our knowledge, the use of anthrones as C-nucleophile for propargylic alkylation has not been realized, which may be attributed to the more challenging site- and enantio-selectivitive control. Within the program on asymmetric propargylic substitutions [62–64], we now report the asymmetric copper-catalyzed propargylic substitution of anthrones and propargylic esters utilizing a chiral *N, N, P*-ligand (Scheme 1c).

We initiated our investigation using phenyl-2-propynyl acetate (**1a**) and anthrone (**2a**) as model substrates to explore the use of various chiral ligands in the presence of diisopropylethylamine (DIPEA) as a base (Table 1 and Tables S1 in Supporting information). The desired product **3aa** was obtained in 27% yield with 66% *ee* using Bn-BOX (**L1**) as ligand at room temperature (entry 1). Other bidentate ligand such as PHOX (**L2**) led to almost completely racemic product (entry 2). Afterwards we turned our attention to use tridentate ligand for turning chirality environment of the copper catalyst. A range of PyBOX analogues were screened, and Ph-PyBOX (**L3**) and $^{i}$Pr-PyBOX (**L4**) catalyzed the reaction smoothly (entries 3 and 4), delivering **3aa** in high yield with lower *ee*. We

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https://doi.org/10.1016/j.cclet.2021.08.009
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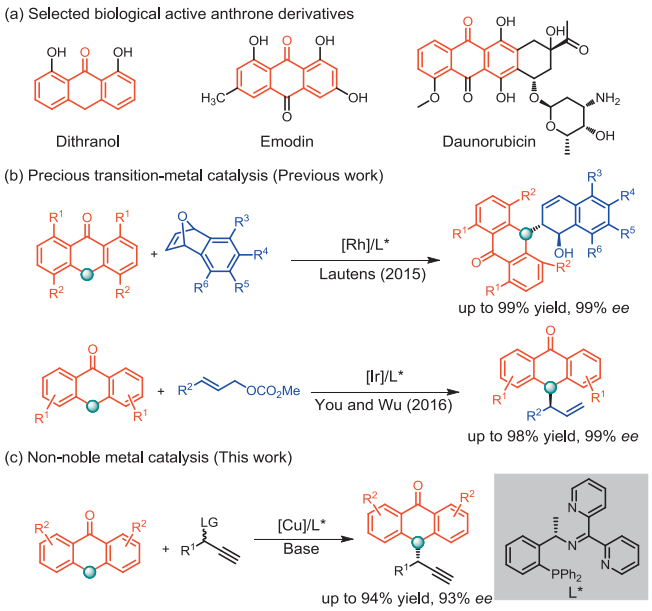
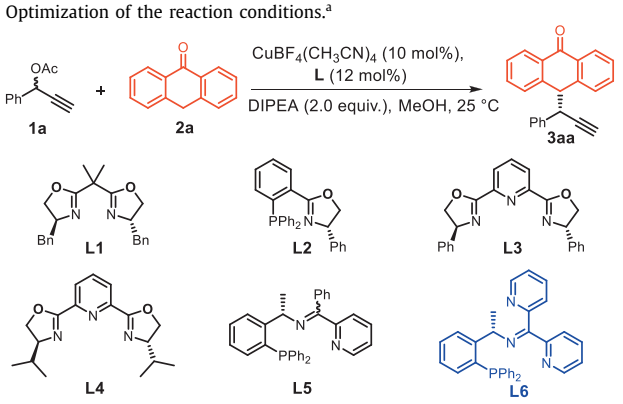



**Scheme 1.** (a) Representative biological anthrone derivatives; (b) Previous studies; (c) This work.

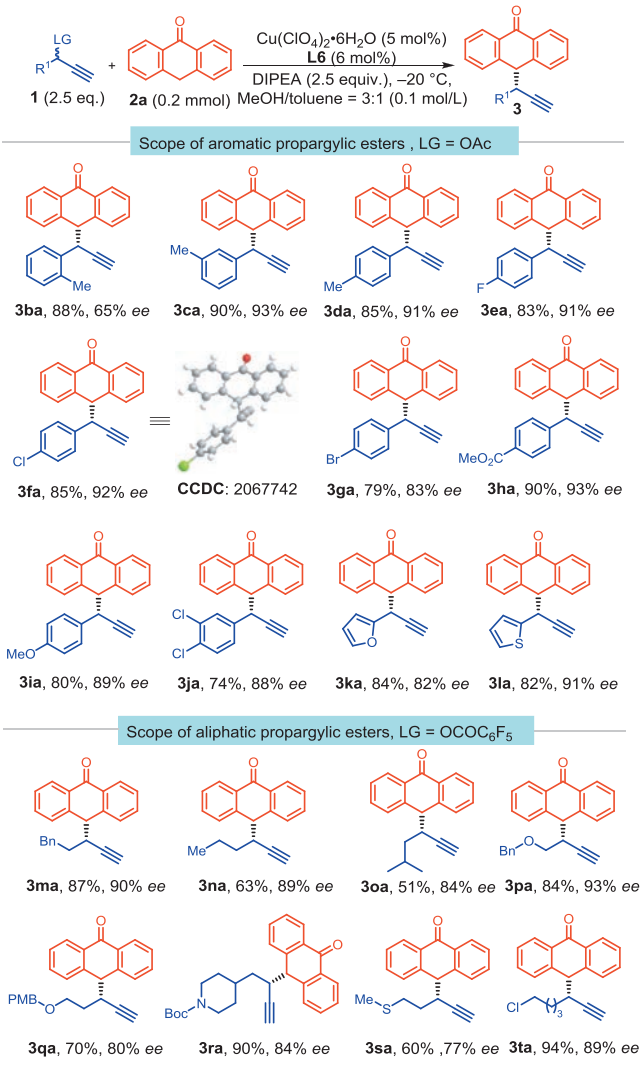
**Table 1**
Optimization of the reaction conditions.[a]




| Entry | L | t (h) | Yield (%)[b] | *ee* (%)[b] |
|---|---|---|---|---|
| 1 | **L1** | 24 | 27 | 66 |
| 2 | **L2** | 24 | 7 | 8 |
| 3 | **L3** | 2 | 82 | 14 |
| 4 | **L4** | 17 | 61 | 39 |
| 5 | **L5** | 4 | 25 | 67 |
| 6 | **L6** | 12 | 50 | 77 |
| 7[c] | **L6** | 14 | 76 | 76 |
| 8[c,d] | **L6** | 2 | 68 | 87 |
| 9[d,e] | **L6** | 2 | 67 | 92 |
| 10[d,e,f] | **L6** | 45 | 82 (80) | 92 |

[a] Reaction conditions: **1a** (1.5 equiv.), **2a** (0.2 mmol), MeOH (0.1 mol/L), DIPEA (2.0 equiv.), $CuBF_4(CH_3CN)_4$ (10 mol%), **L** (12 mol%).
[b] The yield and the *ee* value were determined by HPLC analysis on a chiral stationary phase.
[c] $Cu(ClO_4)_2{\cdot}6H_2O$ (10 mol%) was used instead of $CuBF_4(CH_3CN)_4$.
[d] MeOH/toluene = 3:1.
[e] $Cu(ClO_4)_2{\cdot}6H_2O$ (5 mol%), L6 (6 mol %), –20 °C.
[f] **1a** (2.5 equiv.), DIPEA (2.5 equiv.).

further probed tridentate ligand **L5** developed by Hu group [61], affording the desired product in moderate enantioselectivity (entry 5, 67% *ee*). Notably, the enantioselectivity of the target molecule was increased to 77% and the yield was improved considerably using dipyridyl *N, N, P*-ligand **L6**, which was developed by our group (entry 6). For the copper catalyst, $Cu(ClO_4)_2{\cdot}6H_2O$ gave the best results (entry 7) (For details, see Supporting information). The

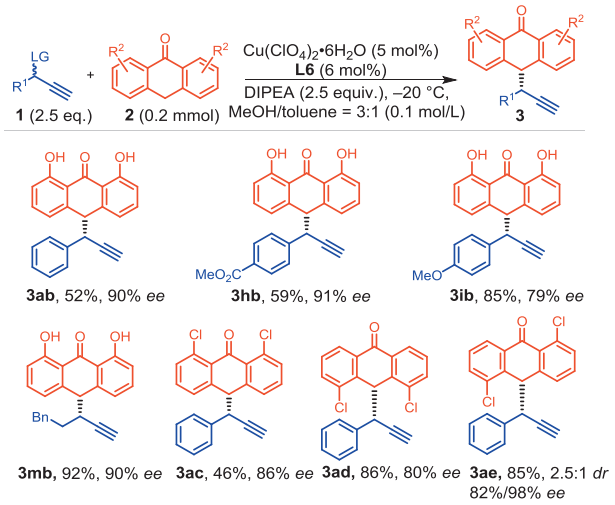



**Scheme 2.** Scope of the reaction with propargylic esters.

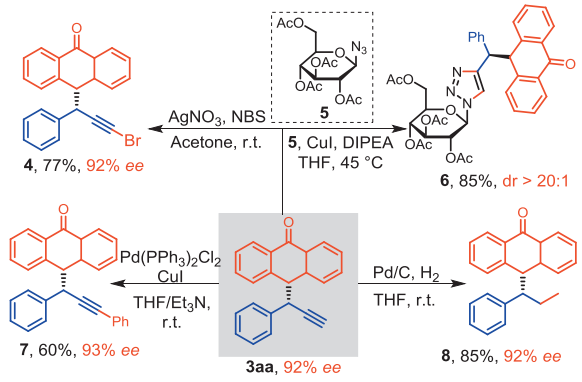
*ee* of the product was increased to 87% with mixture solvents (MeOH/toluene = 3:1) (entry 8).

Interestingly, the asymmetric propargylic substitution occurred efficiently with catalyst loadings as low as 5 mol% (entry 9). Finally, the desired product **3aa** could be isolated in 80% yield with 92% *ee* (entry 10).

With the optimized conditions in hand, we then explored the versatility of the reaction with respect to the propargylic esters (Scheme 2). A variety of aryl propargylic esters were tolerated and participated in the reaction smoothly. For example, substituents on the *meta*- and *ortho*-positions proved to be compatible with this reaction, producing the corresponding products **3ba** and **3ca** with 65% and 93% *ee*, respectively. Similarly, the introduction of either electron-withdrawing or electron-donating groups at the *para*-position of the phenyl group delivered the products **3da**–**3ja** with 83%–93% *ee*. Notably, heteroaromatic esters were also efficiently converted with high selectivity control, providing the desired products **3ka** and **3la** in 84% and 82% yield with 82% and 91% *ee*, respectively. The absolute configuration of chiral 10-propargylanthrone **3fa** was unambiguously confirmed by X-ray analysis, and the configurations of the other products were assigned by analogy (For details, see Supporting information.). Aliphatic-substituted propargylic substrates with perfluorobenzoyl as the leaving group also reacted smoothly with anthrone (**2a**)




**Scheme 3.** Scope of the reaction with anthrones.



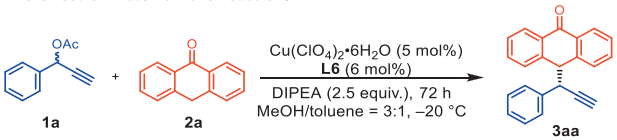

**Scheme 4.** Derivatization of the enantiomerically enriched anthrones.

under our optimized reaction conditions. A variety of secondary propargylic esters reacted well, and excellent enantioselectivities of the products **3ma**–**3pa** was observed. The *ee* values of the compounds **3na** and **3oa** were assigned by Cu-catalyzed azide-alkyne cycloaddition. (For details, see Supporting information). The functional groups, such as ether, amine, thioether, and chloro, were fully tolerated, which is invaluable for further late-stage diversification.

To our delight, anthrones bearing hydroxyl groups (anthralin) and chlorines proceeded smoothly under the standard reaction conditions (Scheme 3). The reactivity of anthralin also favoured carbon over oxygen attack, providing the benzylic functionalization product **3ab** in 52% yields with 90% *ee*. Electron rich and electron deficient aryl propargylic esters proceeded smoothly under the standard reaction conditions, generating the desired products **3hb-3ib** in good yields with good to excellent enantioselectivities. Again, aliphatic propargylic ester was the suitable substrate (**3mb**). Interestingly, the reaction with 1,8-dichloroanthrone and 4,5-dichloroanthrone gave the corresponding products **3ac** and **3ad** in 46% and 86% yield with 86% and 80% *ee*, respectively. Additionally, unsymmetrical anthrone 1,5-dichloroanthrone **2e** was also performed to deliver **3ae** with moderate diastereoselectivity of 2.5:1 d.r. in 85% yield with 82%/98% *ee*.

To demonstrate the potential synthetic power of the present asymmetric copper-catalyzed propargylic substitution in practical organic synthesis, we performed various transformations with substituted anthrone **3aa** (Scheme 4). Bromo-alkyne **4** was easily prepared *via* bromination of terminal alkyne with NBS and

**Table 2**
The effect of water on the reaction.[a]




| Entry | Additive | Amount | Yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|
| 1[d] | - | - | 88 | 92 |
| 2[e] | - | - | 86 | 92 |
| 3 | 4Å MS | 50 mg | 60 | 83 |
| 4 | $H_2O$ | 2.5 equiv. | 90 | 92 |
| 5 | $H_2O$ | 5.0 equiv. | 77 | 92 |

[a] Reaction conditions: **1a** (2.5 equiv.), **2a** (0.2 mmol), MeOH/toluene = 3:1 (0.1 mol/L), DIPEA (2.5 equiv.), $Cu(ClO_4)_2{\cdot}6H_2O$ (5 mol%), **L6** (6 mol%), –20 °C.
[b] Isolated yield.
[c] The *ee* value was determined by HPLC analysis on a chiral stationary phase.
[d] Distilled solvents.
[e] Undistilled solvents.

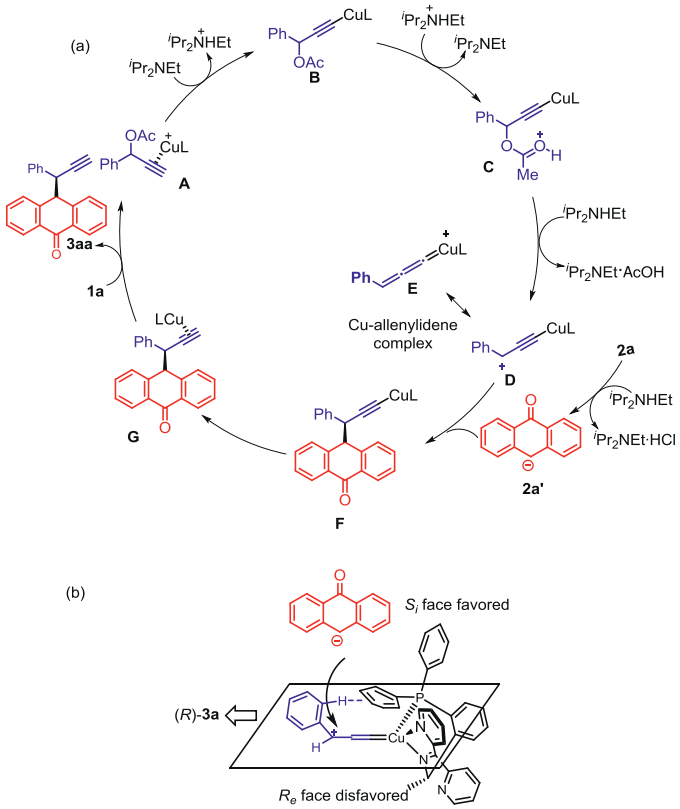
$AgNO_3$. Cu-catalyzed azide-alkyne cycloaddition of **3aa** with optically active 1-azido-1-deoxy-$\beta$-D-flucopyranoside tetraacetate generated cycloadduct **6** with greater than 20:1 diastereoselectivity ratio. Sonagoshira coupling between iodobenzene and **3aa** delivered compound **7** in 60% yield. The terminal alkyne group could be hydrogenated with Pd/C under $H_2$, delivering the target hydrogenation product **8** in 85% yield.

Several control experiments were conducted to test the effect of $H_2O$ on the reaction (Table 2). There was no obvious difference between the results obtained with freshly distilled and undistilled solvents, and the reaction proceeded smoothly to deliver the desired product in 86%–88% yields with 92% *ee*. However, the reactivity and the enantioselectivity of **3aa** decreased when 4Å MS was added as an additive to remove trace amount of water in the system. Furthermore, addition of 2.5–5.0 equiv. of $H_2O$ to the model reaction led to the product **3aa** in 77%–90% yield and 92% *ee*. The trance amount of $H_2O$ in the system is beneficial to both the yield and enantioselectivity of the reaction, which probably enhancing the proton shift in the catalytic cycles. Notably, these findings highlight the water-tolerant nature of the Cu-catalyzed alkylation, which, moreover, is a practical protocol in transition-metal asymmetric synthesis.

Based on previously developed methods and past mechanistic studies [65,66], we anticipate that the reaction mechanism proceeds as depicted below (Scheme 5a). In the presence of base and the copper catalyst, the copper acetylide **B** was generated. Losing the acetate group formed Cu–allenylidene complex **D** which exists a resonance structure of **E** bearing a cationic $\gamma$-carbon. Subsequently, in the presence of DIPEA, anionic **2a′** was released from the anthrone **2a**, which would then undergo a nucleophilic addition reaction with **D**, *via* a hydrogen atom shift, providing the Cu-$\pi$-alkyne complex **G**. After the ligand exchange, the desired product **3aa** was formed, while regenerating the copper catalyst.

Meanwhile, based on the observed absolute stereochemistry of the major enantiomer, we proposed a preliminary model for the enantioinduction (Scheme 5b). An edge-to-face aromatic interaction makes a phenyl group of the substrate close to a phenyl group of the ligand in the copper complex. Therefore, nucleophiles favorably attack $\gamma$-carbon atoms from $S_i$ surface to form (*R*)-products, while $R_e$ surface is hindered by steric hindrance of ligands.

In summary, the highly enantioselective propargylic substitution of propargylic esters with anthrones has been developed by employing a copper–*N, N, P*-ligand complex as catalyst. A series of anthrone derivatives bearing a terminal alkyne moiety were obtained in high yields with good to excellent enantioselectivities.




**Scheme 5.** Proposed mechanism and model for enantioinduction.

The utility of this method has been demonstrated by derivatization on the terminal alkyne functionality of the substituted products.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

Generous financial support from the National Natural Science Foundation of China (No. 21801087), Fundamental Research Funds for the Central Universities CCNU (No. CCNU19QN064), the Ministry of Science and Technology of China (No. 2016YFE0132600), Henan Center for Outstanding Overseas Scientists (No. GZS2020001) and the Key Scientific and Technological Project of Henan Province (No. 212102311068) is gratefully acknowledged.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.08.009.

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