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# Enantioselective Synthesis of Axially Chiral Biaryls by Diels–Alder/Retro-Diels–Alder Reaction of 2-Pyrones with Alkynes

Meng-Meng Xu, Xin-Yu You, Yu-Zhen Zhang, Yang Lu, Kui Tan, Limin Yang,* and Quan Cai*

Cite This: J. Am. Chem. Soc. 2021, 143, 8993–9001



**ABSTRACT:** The enantioselective synthesis of axially chiral biaryls by a copper-catalyzed Diels–Alder/retro-Diels–Alder reaction of 2-pyrones with alkynes is reported herein. Using electron-deficient 2-pyrones and electron-rich 1-naphthyl acetylenes as the reaction partners, a broad range of axially chiral biaryl esters are obtained in excellent yields (up to 97% yield) and enantioselectivities (up to >99% ee). DFT calculations reveal the reaction mechanism and provide insights into the origins of the stereoselectivities. The practicality and robustness of this reaction are showcased by gram-scale synthesis. The synthetic utilizations are demonstrated by the amenable transformations of the products.

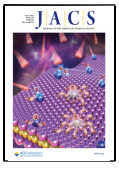


Axially chiral biaryls are highly important structural motifs in natural products,[1] pharmaceuticals,[2] privileged chiral ligands,[3] and catalysts.[4] Therefore, extensive efforts have been made over the past decade for the synthesis of atropisomeric biaryls by asymmetric catalysis.[5−10] Among those reported examples, the atroposelective construction of aryl rings from readily available starting materials has emerged as a straightforward and versatile approach.[11−14] One of the earliest and most successful methods is the transition-metal-catalyzed enantioselective [2+2+2] cyclotrimerization of alkynes.[11] By mimicking the aromatic polyketide biosynthesis, Sparr et al. developed an innovative method for the synthesis of axially chiral biaryls by organocatalytic aldol condensation.[12] Very recently, the *N*-heterocyclic carbene (NHC)-catalyzed arene formation has been demonstrated as a powerful method for the construction of axially chiral biaryls by Lupton,[13a] Zhu,[13b] and Ye.[13c] Despite these achievements, due to the challenges in atroposelective formation of inert arenes, the reaction types of current methods are still limited,[11−14] especially when considering the functionality compatibilities and substitution patterns on aromatic rings. Thus, the development of new methods for atroposelective arene formation is highly desirable.

The sequential Diels–Alder reaction of 2-pyrones with alkenes or alkynes followed by retro-Diels–Alder extrusion of $CO_2$ under thermal reaction conditions has been proved an efficient method for the synthesis of substituted benzenes (Scheme 1a).[15] In general, owing to the semi-aromaticity of 2-pyrones, these reactions are often conducted at high temperatures. Thus, the catalytic asymmetric Diels–Alder/retro-Diels–Alder reaction of 2-pyrones is scarcely utilized for the atroposelective synthesis of chiral arenes. To the best of our knowledge, only one case has been reported to date. In 2014, in the total synthesis of (+)-cavicularin, Beaudry et al. developed a thiourea-catalyzed sequential intramolecular normal-electron-demand Diels–Alder reaction/elimination/retro-Diels–Alder reaction of 2-pyrone with vinylsulfone to construct the distorted phenyl ring atroposelectively (Scheme 1b, 45% yield, 78% ee).[16] Despite this great achievement, a direct catalytic asymmetric Diels–Alder/retro-Diels–Alder reaction of 2-pyrones with alkynes has yet to be realized. As part of our continuous interest in the development of enantioselective inverse-electron-demand Diels–Alder reactions of 2-pyrones,[17−20] we now report the first examples of Diels–Alder/retro-Diels–Alder reaction of 2-pyrones with alkynes by copper catalysis (Scheme 1c). By changing the electron-deficient 2-pyrone and electron-rich naphthylalkyne substrates, this method provides a general platform for the stereoselective synthesis of diverse, axially chiral naphthyl aryl esters with multiple substituents. DFT calculations reveal an intriguing mechanism, involving a vinylidene-quinone methide (VQM)-like intermediate[21] with allene-axial chirality and a lactone intermediate with alkene-axial chirality. The details of this study are reported herein.

Initially, 3-carbomethoxyl-2-pyrone **1a** and 2-methoxy-1-(pent-1-yn-1-yl)naphthalene **2a** were selected as model substrates to evaluate the Diels–Alder/retro-Diels–Alder reaction. To our delight, in the presence of 10 mol% $Cu(OTf)_2$ and 12 mol% bis(oxazoline) (BOX) ligand **L1**, the reaction did occur to afford the desired chiral biaryl **3a** with moderate yield and enantioselectivity (Table 1, entry 1, 37% yield, 66% ee). Further evaluation of various Lewis acids (Table S1) revealed that the utilization of $Cu(ClO_4)_2·6H_2O$ increased the yield to 61% (Table 1, entry 2, 64% ee). Recently, the group of Tang has proved that the side arms of BOX ligands played a pivotal role in tuning both the reactivity and stereocontrol.[22] Consequently, a series of BOX ligands with different substituents and side arms were explored. After

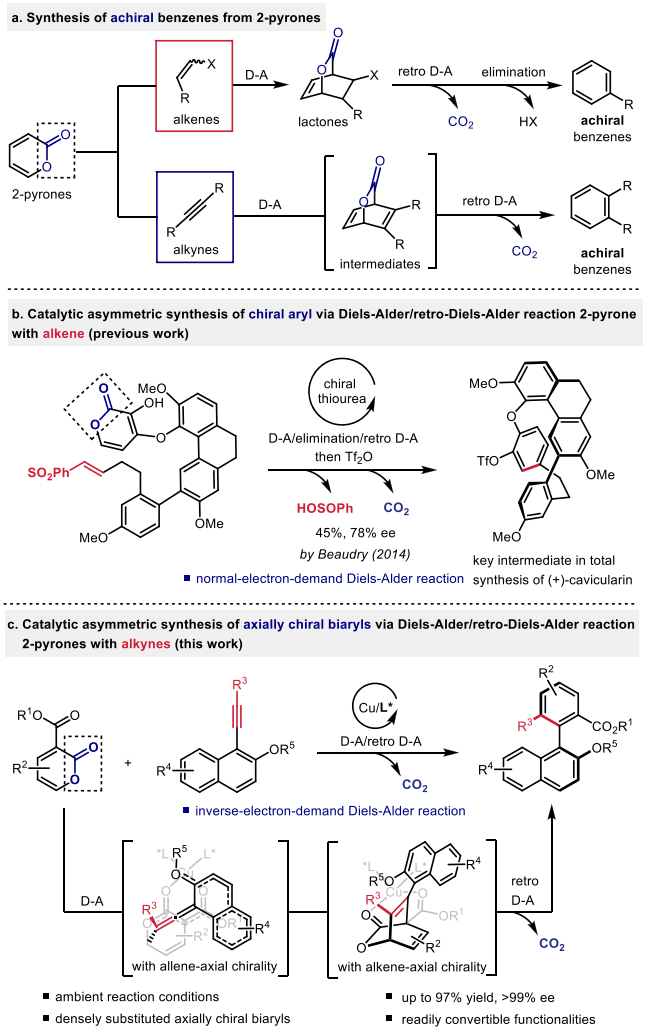
Received: May 7, 2021
Published: June 9, 2021






https://doi.org/10.1021/jacs.1c04759
J. Am. Chem. Soc. 2021, 143, 8993–9001

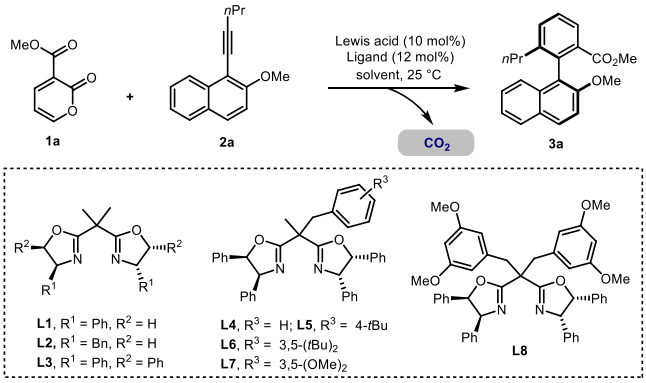
**Scheme 1. Enantioselective Synthesis of Axially Chiral Biaryls by Diels–Alder/Retro-Diels–Alder Reaction of 2-Pyrones**




considerable experimentation (Table 1, entries 3–9, see the Supporting Information for details), it was found that ligand **L7** bearing a 3,5-dimethoxybenzyl side arm group dramatically enhanced the yield and enantioselectivity (Table 1, entry 8, 72% yield, 89% ee). The introduction of two 3,5-dimethoxybenzyl side arm groups on the ligand (**L8**) further improved the enantioselectivity but with slightly decreased yield (Table 1, entry 9, 61% yield, 93% ee). Further reaction optimization revealed significant solvent effects (Table S3 in the Supporting Information), and dichloroethane was optimal, affording **3a** in 88% yield and 95% ee (Table 1, entry 10). Then, the effect of additives was investigated. The addition of 5 Å molecular sieves gave better results (Table 1, entry 11, 91% yield, 96% ee). Of particular note, lower catalyst loading [5 mol% $Cu(ClO_4)_2·6H_2O$ and 6 mol% **L8**] was also compatible, giving **3a** in 97% yield and 96% ee (Table 1, entry 12).

After the optimized reaction conditions were established, the reaction scope was investigated. A variety of 2-pyrones were evaluated (Table 2). The reaction was applicable to 2-pyrones with different ester groups, including methyl (**3a**), ethyl (**3b**), phenylethyl (**3c**), and benzyl (**3d**) examples (73%–97% yields, 94%–96% ee). Notably, various C4-alkyl- and C4-aryl-substituted 2-pyrones underwent the reaction smoothly to

**Table 1. Optimization of the Reaction Conditions**




| entry[a] | Lewis acid | ligand | solvent | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ | **L1** | DCM | 37 | 66 |
| 2 | $Cu(ClO_4)_2·6H_2O$ | **L1** | DCM | 61 | 64 |
| 3 | $Cu(ClO_4)_2·6H_2O$ | **L2** | DCM | 47 | −34 |
| 4 | $Cu(ClO_4)_2·6H_2O$ | **L3** | DCM | 47 | 79 |
| 5 | $Cu(ClO_4)_2·6H_2O$ | **L4** | DCM | 35 | 74 |
| 6 | $Cu(ClO_4)_2·6H_2O$ | **L5** | DCM | 40 | 75 |
| 7 | $Cu(ClO_4)_2·6H_2O$ | **L6** | DCM | 46 | 82 |
| 8 | $Cu(ClO_4)_2·6H_2O$ | **L7** | DCM | 72 | 89 |
| 9 | $Cu(ClO_4)_2·6H_2O$ | **L8** | DCM | 61 | 93 |
| 10 | $Cu(ClO_4)_2·6H_2O$ | **L8** | DCE | 88 | 95 |
| 11[d] | $Cu(ClO_4)_2·6H_2O$ | **L8** | DCE | 91 | 96 |
| 12[e] | $Cu(ClO_4)_2·6H_2O$ | **L8** | DCE | 97 | 96 |

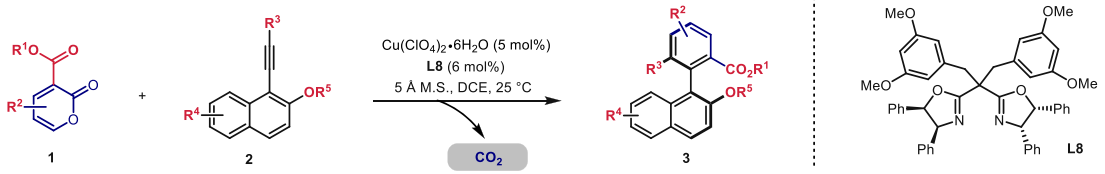
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Lewis acid (10 mol%), and ligand (12 mol%) in solvent (1.0 mL) at 25 °C. [b]Isolated yield of **3a**. [c]Determined by HPLC analysis. [d]5 Å MS (25 mg) was added. [e]**1a** (0.2 mmol), **2a** (0.3 mmol), $Cu(ClO_4)_2·6H_2O$ (5 mol%), **L8** (6 mol%), and 5 Å MS (50 mg) in DCE (1.0 mL). Abbreviations: DCM, dichloromethane; DCE, 1,2-dichloroethane; MS, molecular sieves.

afford the corresponding biaryls **3e–3h** in good yields and enantioselectivities (72%–96% yields, 92%–95% ee). Moreover, 2-pyrones bearing a methyl, phenyl, or bromide group on the C5 position were also tolerated, giving biaryls **3i–3k** in good yields but with slightly decreased enantioselectivities (66%–82% yields, 72%–82% ee). This is probably due to the steric effect caused by the C5-substituent of 2-pyrone and the arylalkyne. Furthermore, when 6-phenyl-substituted 2-pyrone **1l** was used as the substrate, no desired product was obtained.

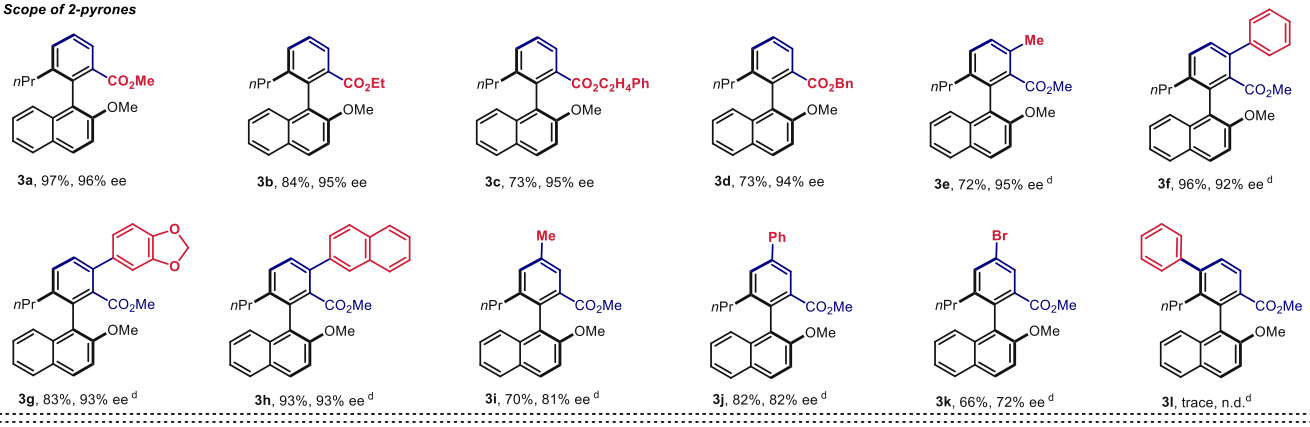
Next, the scope with respect to arylalkynes was investigated. As shown in Table 2, an array of arylalkynes bearing various primary alkyl groups on the terminus of alkynes, including methyl, ethyl, *n*-butyl, and benzyl groups, were investigated, giving **3m–3p** in excellent yields and ee (75%–92% yields, 95%–96% ee). Furthermore, alkynes bearing secondary alkyl groups with significant steric effects, such as cyclopropyl, cyclopentyl, cyclohexyl, and isopropyl groups, were well tolerated in this reaction (**3q–3t**, 81%–95% yields, 95%–96% ee). The arylalkyne with a more sterically hindered *tert*-butyl group showed relatively low reactivity but afforded **3u** with 37% yield and 94% ee. However, when a phenyl group was installed on the terminus of alkyne **2k**, the reactivity was decreased distinctly, and the corresponding product **3v** was obtained in only 16% yield. It is worth mentioning that bromoarylacetylene **2l** and silylarylacetylene **2m** worked very well in this reaction, affording products **3w** and **3x** with excellent yields and ee (84% yield and 94% ee, 89% yield and


https://doi.org/10.1021/jacs.1c04759
J. Am. Chem. Soc. 2021, 143, 8993–9001

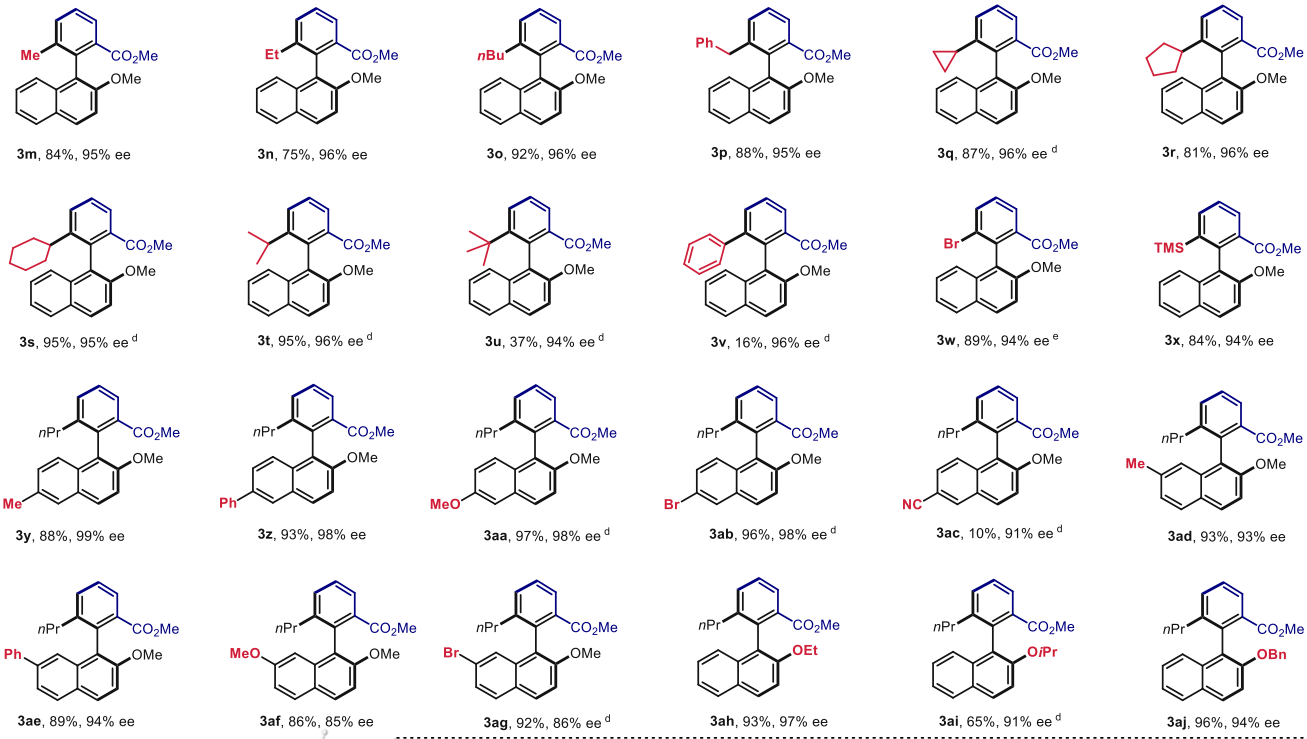
**Table 2. Substrate Scope**[a,b,c]



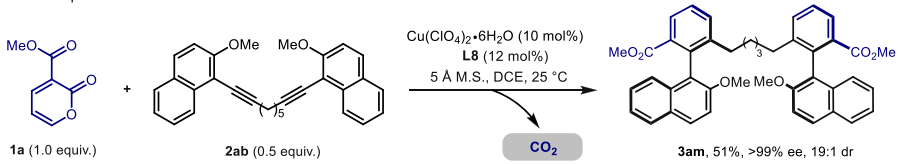

*Scope of 2-pyrones*




*Scope of 1-naphthyl acetylenes*




Double atroposelective Diels-Alder/retro-Diels-Alder reactions of **1a** and **2ab**




[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (5 mol%), **L8** (6 mol%), and 5 Å MS (50 mg) in DCE (1.0 mL) at 25 °C. [b]Isolated yields of **3** are given. [c]The ee was determined by HPLC analysis. [d]$Cu(ClO_4)_2 \cdot 6H_2O$ (10 mol%) and **L8** (12 mol%) were used. [e]The absolute configuration of **3w** was determined by X-ray crystallographic analysis (CCDC 2054016).

94% ee, respectively). The bromo and silyl substituents on the biaryl scaffolds could serve as handles for further functionalization, thus dramatically enhancing the synthetic potential of the products. Moreover, naphthalenes substituted with a variety of



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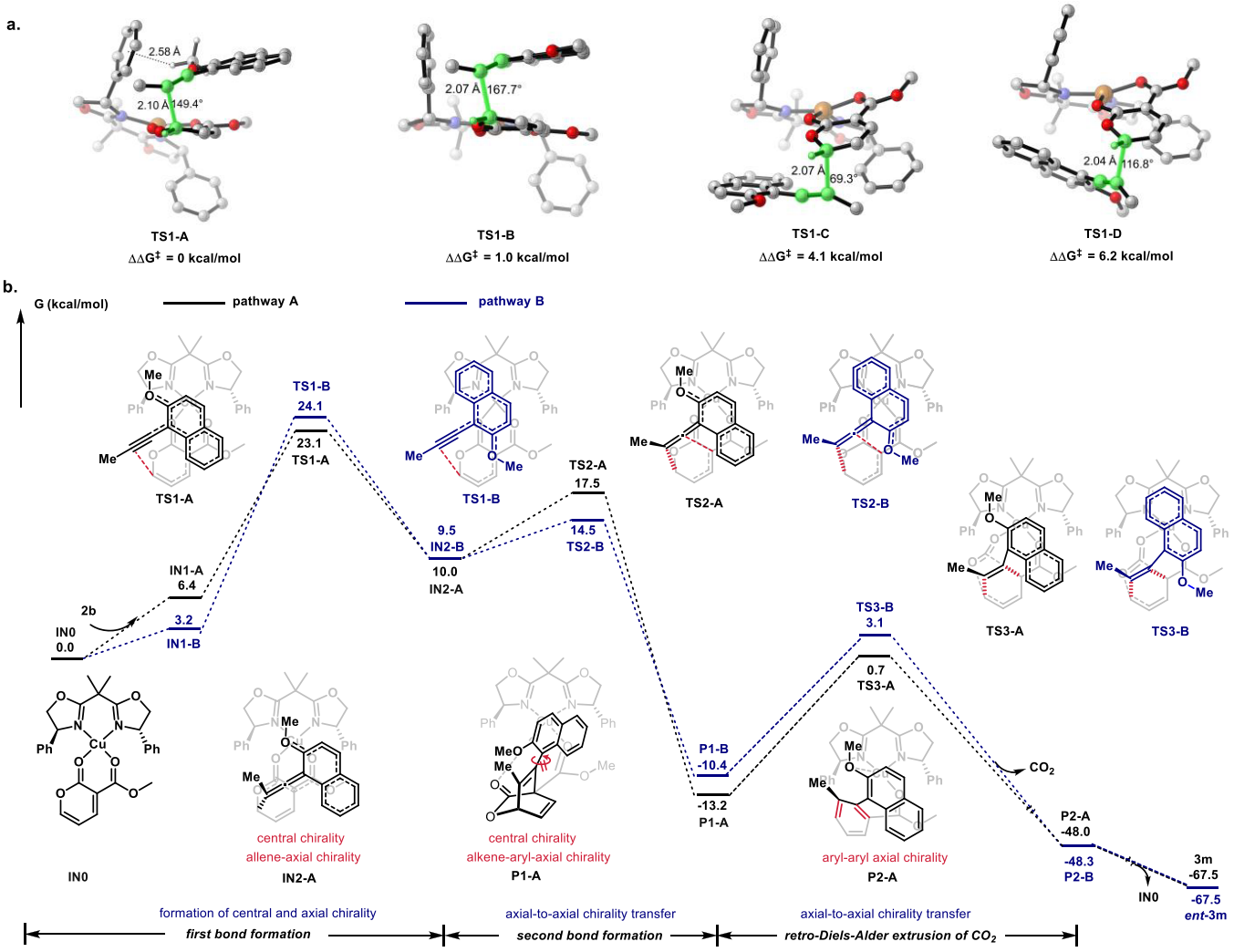



**Figure 1.** DFT calculations. (a) DFT-optimized transition structures and relative free energies. (b) Calculated free energy profile for pathways A and B.

functional groups such as methyl, phenyl, bromo, and alkoxyl groups on various positions were accommodated, affording the products **3y**−**3ag** in good yields and enantioselectivities. Replacement of the 2-methoxyl group with other alkoxyl groups (e.g., EtO-, *i*PrO-, and BnO-) gave the corresponding products **3ah**−**3aj** with comparable yields and ee. To demonstrate the key role of the 2-alkoxyl group on naphthalenes, substrates without an alkoxyl group (**2z**) or with a 2-hydroxyl group (**2aa**) were evaluated. The desired product was not observed (**3ak**) or was afforded with diminished yield and enantioselectivity (52% yield and 32% ee for **3al**). Furthermore, the double Diels−Alder/retro-Diels−Alder reactions of 2-pyrone **1a** with diyne **2ab** were also performed (Table 2). Remarkably, the desired product **3am**, possessing two stereogenic axes, was obtained in 51% yield with excellent enantioselectivity (>99% ee) and diastereoselectivity (19:1 dr).

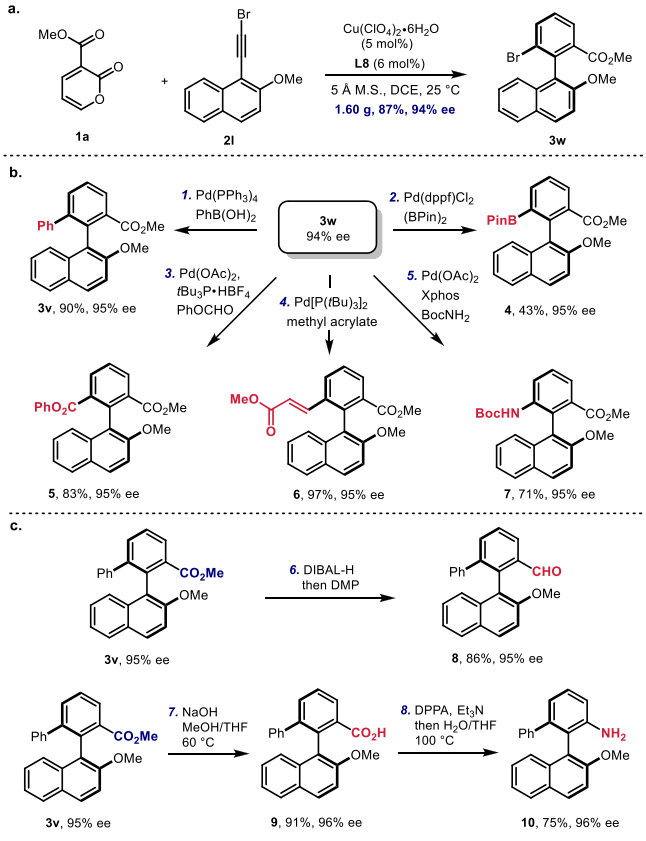
To explore the reaction mechanism and the origins of the stereoselectivities, DFT calculations were conducted on the reaction of 2-pyrones **1a** and arylalkyne **2b** catalyzed by Cu(II)/**L1**. Figure 1 shows the free energy surface starting from the malonate model complex for the BOX ligand used in the experiments. According to the different approaching faces of 2-pyrone and arylalkyne, there should be four possible reaction pathways (**A**, **B**, **C**, and **D**) for the Diels−Alder reaction. We carried out DFT calculations on the corresponding transition states and intermediates, which showed that the Diels−Alder reaction is stepwise, with the first step as the rate-determining step. The four stereoisomeric transition structures are shown in Figure 1a. **TS1-A**, leading to the major axially enantiomeric biaryl product, is energetically more favored than **TS1-B** by 1.0 kcal/mol, leading to the minor axially enantiomeric biaryl product. The enantioselectivity is also determined at this stage in accordance with the experimental observations (68% ee in calculation vs 64% ee in experimental). The major difference between the two transition structures lies in the relative positions of the methoxyl group on the arylalkyne substrate and the phenyl ring on the ligand. In the **TS1-A** structure, the distance between the C−H on the methoxyl group and the center of the phenyl ring is 2.58 Å. In contrast, in the **TS1-B** structure, the methoxyl group on arylalkyne is deviated away from the phenyl ring. These results might suggest that the energy difference between the two transition structures originates from the C−H···$\pi$ interaction and decreasing energy of the favored transition structure **TS1-A**. Similar interactions may also be observed with arylalkynes carrying other alkoxyl groups such as EtO-, *i*PrO-, and BnO-, thus leading to the corresponding products


https://doi.org/10.1021/jacs.1c04759
J. Am. Chem. Soc. 2021, 143, 8993−9001

with comparable yields and ee (**3ah**−**3aj**). In the calculated free energy profile for the reaction (Figure 1b), the catalyst−substrate complex **IN0** associated with arylalkyne **2b** results in an unstabilized complex **IN1** due to the unfavorable entropy of association. In the **TS1** structure, the carbon−carbon triple bond is broken and the naphthyl ring is dearomatized, resulting in a chiral VQM-like[21] transition structure. Meanwhile, a chiral carbon center is formed on pyrone. In the structure of **TS1-A**, the dihedral angle between pyrone and alkyne (highlighted in Figure 1a) is 149° (deviated from 180°); therefore, an intermediate **IN2-A** is formed which is responsible for the stepwise Diels−Alder reaction mechanism. The lower energy transition state **TS1-A**, with the first forming bond length of 2.10 Å, has a barrier of 23.1 kcal/mol compared with **IN0**, while the transition state for the second step of the Diels−Alder reaction (**TS2-A**) has a barrier of 17.5 kcal/mol compared with **IN0**, with the second forming bond length of 2.55 Å. In this step, the naphthyl ring is regenerated, and the axial chirality of the allene intermediate **IN2-A** is transferred to the nascent alkene, affording bridged-lactone cycloadduct **P1-A** with two chiral carbon centers and one stereogenic axis (alkene-aryl axial chirality). The adduct **P1-A** then undergoes retro-Diels−Alder extrusion of $CO_2$ in a concerted mechanism via **TS3-A** with a barrier of 13.9 kcal/mol.

To showcase the practicability of this method, a large-scale reaction was conducted. As illustrated in Scheme 2a, the gram-scale reaction of **1a** and brominated alkyne **2l** proceeded uneventfully to give the product **3w** without loss of yield and enantiopurity (1.60 g, 87% yield, 94% ee). The product **3w** was amenable for further transformations (Scheme 2b). It is worth noting that the bromide of **3w** could be easily converted to various types of functionalities by palladium-catalyzed cross-couplings. For instance, the Suzuki reactions of **3w** gave **3v** (90% yield, 95% ee) and **4** (43% yield, 95% ee); the carbonylation of **3w** gave diester **5** (83% yield, 95% ee); the Heck reaction gave $\alpha,\beta$-unsaturated ester **6** (97% yield, 95% ee); and the Buchwald−Hartwig amination afforded amino-biaryl **7** (71% yield, 95% ee). All of these transformations went on smoothly with high yields and maintained enantioselectivities. Furthermore, the ester group of **3v** was also amenable to be transformed (Scheme 2c): the chiral aldehyde **8** was obtained via sequential reduction and oxidation (86% yield, 95% ee); the chiral carboxylic acid **9** was obtained by hydrolysis (91% yield, 96% ee); and then the chiral amine **10** was obtained by Curtius rearrangement of **9** (75% yield, 96% ee).

**Scheme 2. Gram-Scale Synthesis and Synthetic Transformations**




In summary, we have disclosed the first copper-catalyzed enantioselective sequential Diels−Alder/retro-Diels−Alder reaction of 2-pyrones and alkynes. Under mild reaction conditions, this reaction enables the synthesis of a wide range of axially chiral biaryl esters with excellent yields and enantioselectivities. DFT calculations reveal the Diels−Alder reaction involves a stepwise mechanism, and provide insights into the origins of the stereoselectivities. The obtained products are amenable to being transformed to other valuable axially chiral biaryl scaffolds. It is anticipated that this reaction will become a new strategy for stereoselective arene formation. Further investigations of this strategy are ongoing in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04759.

Experimental procedures and spectra data for all new compounds (PDF)

### Accession Codes

CCDC 2054016 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.

## ■ AUTHOR INFORMATION


### Corresponding Authors

**Quan Cai** − *Department of Chemistry, Fudan University, Shanghai 200433, China;* orcid.org/0000-0002-8493-3267; Email: quan_cai@fudan.edu.cn

**Limin Yang** − *College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China;* orcid.org/0000-0003-1021-3942; Email: myang@hznu.edu.cn

### Authors

**Meng-Meng Xu** − *Department of Chemistry, Fudan University, Shanghai 200433, China*

**Xin-Yu You** − *Department of Chemistry, Fudan University, Shanghai 200433, China*

**Yu-Zhen Zhang** − *Department of Chemistry, Fudan University, Shanghai 200433, China*

**Yang Lu** − *Department of Chemistry, Fudan University, Shanghai 200433, China*
**Kui Tan** − *Department of Chemistry, Fudan University, Shanghai 200433, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c04759

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We acknowledge the National Natural Science Foundation of China (Grant No. 21801043, 22071030), the Natural Science Foundation of Zhejiang Province (ZJNSF) (Grant No. LY20B020010), the "1000-Youth Talents Plan", and Fudan University (start-up grant) for financial support.

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*J. Am. Chem. Soc.* 2021, 143, 8993−9001