OL | Organic Letters

pubs.acs.org/OrgLett

Letter

Organocatalytic Atroposelective Construction of Axially Chiral *N*-Aryl Benzimidazoles Involving Carbon−Carbon Bond Cleavage

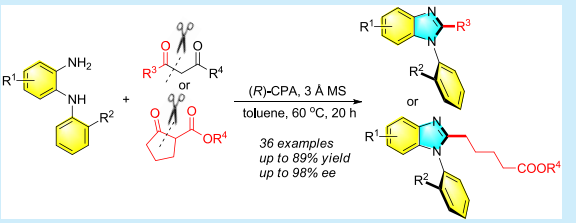
Ningning Man, Zhenbang Lou, Yuming Li, Haijun Yang, Yufen Zhao, and Hua Fu*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02214

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Axially chiral compounds widely occur in natural products, biologically active molecules, ligands, and catalysts, and their efficient and enantioselective synthesis is highly desirable. Herein, we report a novel method for the atroposelective construction of axially chiral *N*-aryl benzimidazoles with chiral phosphoric acid as the organocatalyst via reaction of N^1-(aryl)benzene-1,2-diamines with multicarbonyl compounds. The present method provided the target products in high yields (up to 89%) with excellent enantioselectivity (up to 98% ee).



N-Aryl benzimidazoles are widely found in numerous biologically active molecules. For example, they are applied as the inhibitors of some enzymes such as lymphocyte-specific kinase (Lck),[1] nonpeptide thrombin,[2] 5-lipoxygenase,[3] factor Xa (FXa),[4] and poly(ADP-ribose)polymerase (PRAP).[5] They act as the antagonists of nonpeptide luteinizing hormone-releasing hormone (LHRH),[6] *N*-methyl-D-aspartate (NMDA),[7] and a neuropeptide Y Y1 receptor.[8] *N*-Aryl benzimidazoles are also key core structures of herbicides, fungicides, veterinary medicines,[9] dyes,[10] and high-temperature polymers.[11] Therefore, the synthesis of N-substituted benzimidazoles attracts much attention,[12] in which one of the most common approaches to benzimidazoles is the coupling of substituted 1,2-diaminoarenes with carboxylic acids or their equivalents. Axially chiral compounds are important structures in natural products and biologically active molecules,[13] and they also are privileged cores of chiral ligands and catalysts.[14] Recently, great advances have been achieved in asymmetric synthesis of axially chiral backbones.[15,16] However, to the best of our knowledge, the atroposelective synthesis of *N*-aryl benzimidazoles is very limited thus far. Very recently, Miller and co-workers have developed atroposelective cyclodehydration of 2,2,2-trifluoro-*N*-(2-(arylamino)aryl)-acetamides catalyzed by phosphothreonine-embedded peptidic phosphoric acids and C_2-symmetric chiral phosphoric acids (Scheme 1a).[17]

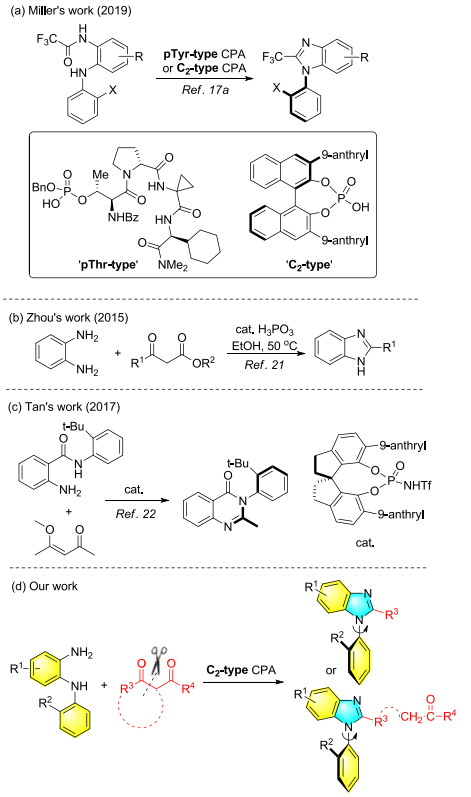
On the other hand, the cleavage of C−C bonds is a topic of significant importance in synthetic organic chemistry. However, acquiring the selective C−C bond cleavage still is a great challenge because of the inherent inert nature and ubiquity of the C−C bonds.[18] In the past decades, various interesting carbon−carbon bond cleavage methods have been developed,[19] in which transition metal catalysis is overwhelming.[20] To realize environmentally friendly and sustainable chemistry, it is highly desirable to develop a transition-metal-free method for carbon−carbon bond cleavage. In 2015, Zhou and co-workers have represented the phosphorous-acid-catalyzed synthesis of benzimidazoles through cyclocondensation of substituted benzene-1,2-diamines and β-ketoesters via the selective C−C bond cleavage (Scheme 1b).[21] In 2017, Tan and co-workers reported the axially chiral *N*-triflylphosphoramide-catalyzed atroposelective synthesis of arylquinazolinones through coupling of *N*-aryl anthranilamides with 4-methoxypentenone (Scheme 1c),[22] but the poor results were observed when the diketone derivatives replaced 4-methoxypentenone as the substrates. Since Akiyama and Terada's initiative discovery in 2004,[23] the axially chiral phosphoric acids (CPAs) have become an important organocatalyst in the asymmetric synthesis.[24] Inspired by the results above, herein, we report an organocatalytic atroposelective construction of axially chiral *N*-aryl benzimidazoles involving carbon−carbon bond cleavage (Scheme 1d).

Initially, reaction of N^1-(naphthalen-1-yl)benzene-1,2-diamine (**1a**) with 2 equiv of acetylacetone (**2a**) was performed in the presence of 10 mol % of CPA ((*R*)-**C1**) and $MgSO_4$ in toluene at 30 °C for 24 h. To our delight, the desired product, (*S*)-**3a**, was obtained in 40% yield (89% ee) as the result of the cleavage of the C−C bond in **2a** (Table 1, entry 1). Subsequently, we commenced screening the optimal reaction conditions to further improve the yield and ee value of (*S*)-**3a**. The results are summarized in Table 1 (see Table S1 in SI for more details).

As shown in Table 1, other chiral phosphoric acids, (*R*)-**C2**∼(*R*)-**C9** (10 mol % relative to the amount of **1a**), were

Received: July 3, 2020

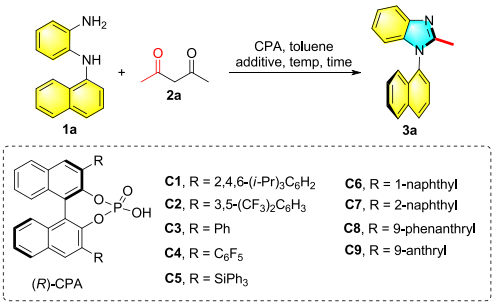
Scheme 1. (a) Atropisomer-Selective Cyclodehydration of Axially Chiral 2,2,2-Trifluoro-*N*-(2-(arylamino)aryl)acetamides, (b) Phosphorous-Acid-Catalyzed Synthesis of Benzimidazoles, (c) Axially Chiral *N*-Triflylphosphoramide-Catalyzed Atroposelective Synthesis of Arylquinazolinones, and (d) Our Protocol for Organocatalytic Atroposelective Construction of Axially Chiral *N*-Aryl Benzimidazoles



first investigated, and the results showed that the BINOL-derived CPAs with various substituents on the 3,3′-position did not improve yield and ee value of (*S*)-**3a** simultaneously (entries 2−9). To promote the cleavage of the C−C bond in **2a**, the temperature was surveyed (entries 10−12). Gratifyingly, we found that 60 °C was a suitable temperature to give (*S*)-**3a** in 86% yield with 88% ee, almost without loss of enantioselectivity (comparing entries 1 and 11). We attempted to shorten the reaction time (entries 13 and 14), and a 20 h reaction was feasible (comparing entries 11 and 13). Another two additives, Na_2SO_4 and 3 Å molecular sieve (MS), were attempted (entries 15 and 16), and 3 Å MS afforded 88% yield and 92% ee (entry 15). It should be pointed out that absolute configuration of product **3a** was determined by comparing the structure of (*S*)-**3t** (the absolute configuration of **3t** was assigned to be (*S*)-form by X-ray diffraction analysis (see SI for details)).

With the optimized conditions in hand, the substrate scope was surveyed for reaction of substituted N^1-(aryl)benzene-1,2-diamines (**1**) with multicarbonyl compounds (**2**) under catalysis of (*R*)-**C1**. As shown in Scheme 2, we first investigated reaction of N^1-(naphthalen-1-yl)benzene-1,2-diamine (**1a**) with three *β*-dicarbonyl compounds, acetylacetone (**2a**), ethyl acetoacetate (**2b**), and 1-phenylbutane-1,3-dione (**2c**), and **2a**−**2c** provided higher reactivity (78−88% yields) and excellent enantioselectivity (91 or 92% ee) (see (*S*)-**3a**), in

Table 1. Optimization of the Reaction Conditions[a]



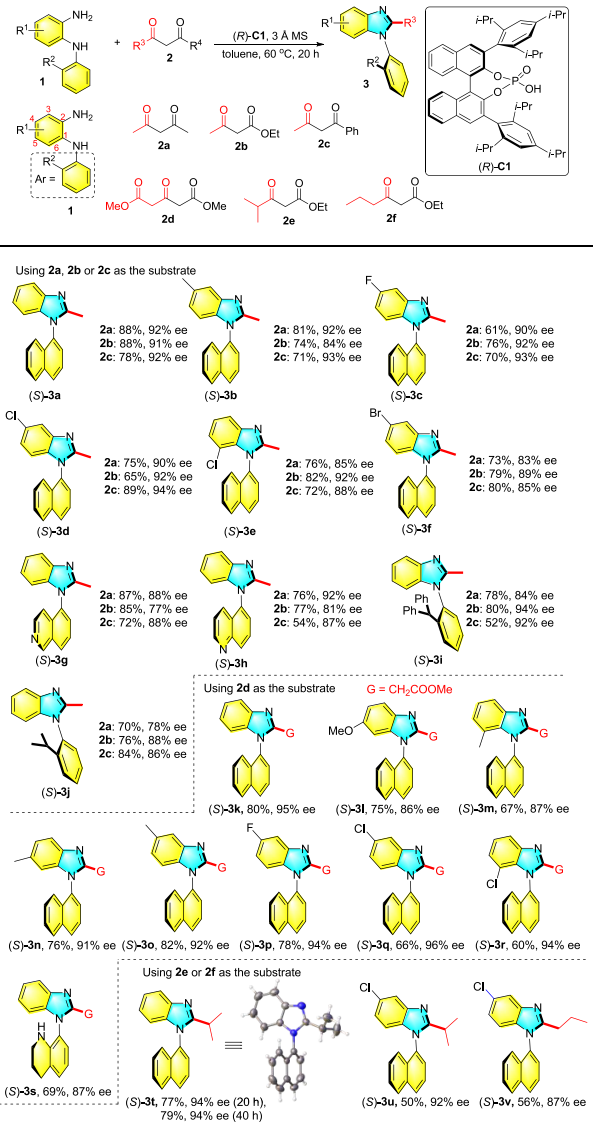
entry	CPA	*T* (°C)	time (h)	yield of **3a** (%)[b]	ee of **3a** (%)[c]
1	**C1**	30	24	40	89
2	**C2**	30	24	35	21
3	**C3**	30	24	33	21
4	**C4**	30	24	41	5
5	**C5**	30	24	55	82
6	**C6**	30	24	41	44
7	**C7**	30	24	44	31
8	**C8**	30	24	53	67
9	**C9**	30	24	45	66
10	**C1**	50	24	75	88
11	**C1**	60	24	86	88
12	**C1**	70	24	82	88
13	**C1**	60	20	86	88
14	**C1**	60	16	74	88
15[d]	**C1**	60	20	76	88
16[e]	**C1**	**60**	**20**	**88**	**92**

[a]Reaction conditions: N^1-(naphthalen-1-yl)benzene-1,2-diamine (**1a**) (0.1 mmol, 1.0 equiv), acetylacetone (**2a**) (0.2 mmol, 2.0 equiv), CPA ((*R*)-**C1**∼(*R*)-**C9**) (10 *μ*mol, 10 mol %), $MgSO_4$ (50 mg), toluene (2.0 mL), temperature (oil bath, 30−70 °C), time (16−24 h) in a sealed Schlenk tube without extrusion of air. [b]Isolated yield. [c]The ee values were determined by HPLC analysis on a chiral stationary phase using a Daicel Chiralpak AD-H column. [d]Na_2SO_4 as the additive. [e]3 Å molecular sieve (MS) as the additive.

which **2c** gave the lowest yield. Subsequently, different substituted N^1-(aryl)benzene-1,2-diamines (**1**) were used as the partners of **2a**−**2c**. The substrates containing 4-substituents including methyl (see (*S*)-**3b**), fluoro (see (*S*)-**3c**), chloro (see (*S*)-**3d**), and bromo (see (*S*)-**3f**) in the benzene-1,2-diamine part of **1** afforded the satisfactory ee values (84−94% ee), but some yields (61−89%) were slightly lower relative to **1a**. Reactions of the substrate containing 6-chloro with **2a**−**2c** were smoothly performed, and 72−76% yields and 85−92% ee values were obtained (see (*S*)-**3e**). Next, we inspected variation of the aryl part in **1**. When two N-heterocyclic groups, isoquinolyl-5-yl and quinolin-5-yl, in **1** were used as the aryl substituents, the chiral phosphoric-acid-catalyzed reactions with **2a** and **2c** were not obviously affected by the nitrogen atoms, but **2b** exhibited lower enantioselectivity (77 or 81% ee) (see (*S*)-**3g** and (*S*)-**3h**). When the aryl part in **1** was 2-benzhydrylphenyl (see (*S*)-**3i**) or isopropylphenyl (see (*S*)-**3j**), the former with bigger steric hindrance provided higher ee values. Furthermore, dimethyl 1,3-acetonedicarboxylate (**2d**) was applied as the partner of **1** (Scheme 2). To our delight, the corresponding products ((*S*)-**3k**∼(*S*)-**3s**) were obtained in 60−82% yields with 86−96% ee. Finally, methyl isobutyrylacetate (**2e**) and methyl butyrylacetate (**2f**) were attempted as the substrates, and they afforded moderate yields (50−77%) and excellent ee values (87−94%

https://dx.doi.org/10.1021/acs.orglett.0c02214
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope of N^1-(Aryl)benzene-1,2-diamines (1) and Multicarbonyl Compounds (2) in the Reactions[a]

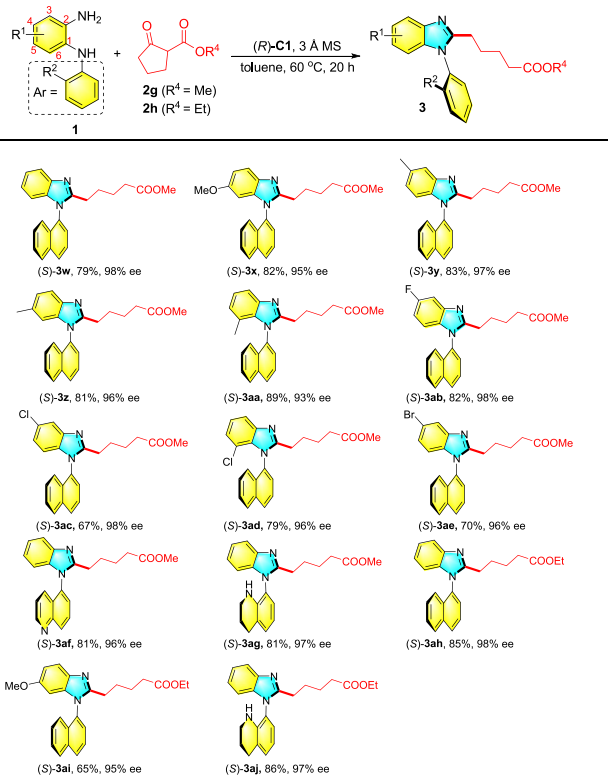


[a]Reaction conditions: N^1-(aryl)benzene-1,2-diamine (**1**) (0.1 mmol, 1.0 equiv, 0.05 M), multicarbonyl compound (**2**) (0.2 mmol, 2.0 equiv, 0.1 M), (*R*)-**C1** (10 μmol, 10 mol %), 3 Å MS (~50 mg), toluene (2.0 mL), temperature (oil bath, 60 °C), time (20 h) in a sealed Schlenk tube. Isolated yield and the ee values were determined by HPLC analysis with chiral columns. Absolute configurations of products **3a**~**3s**, **3u**, and **3v** were determined by comparing the structure of (*S*)-**3t**.

ee). The present reactions could tolerate some functional groups including C−F, C−Cl, and C−Br bonds, ether and ester groups, and N-heterocycles.

Inspired by the results above, we attempted two cyclic β-dicarbonyl compounds, methyl 2-oxocyclopentanecarboxylate (**2g**) and ethyl 2-oxocyclopentanecarboxylate (**2h**), as the partners of **1** (Scheme 3). We first investigated variation of substituents in the benzene-1,2-diamine part of **1**. Reaction of **1a** with **2g** led to (*S*)-**3w** in 79% yield with 98% ee. Other substrates containing different substituents including 5-methoxy, 4-methyl, 5-methyl, 6-methyl, 4-fluoro, 4-chloro, 6-chloro, and 4-bromo showed high reactivity (67−89% yields)

Scheme 3. Substrate Scope of N^1-(Aryl)benzene-1,2-diamines (1) and Alkyl 2-Oxocyclopentanecarboxylate (2) in the Reactions[a]



[a]Reaction conditions: N^1-(aryl)benzene-1,2-diamine (**1**) (0.1 mmol, 1.0 equiv, 0.05 M), alkyl 2-oxocyclopentanecarboxylate (**2**) (0.2 mmol, 2.0 equiv, 0.1 M), (*R*)-**C1** (10 μmol, 10 mol %), 3 Å MS (~50 mg), toluene (2.0 mL), temperature (oil bath, 60 °C), time (20 h) in a sealed Schlenk tube. Isolated yield, and the ee values were determined by HPLC analysis with chiral columns. Absolute configurations of products **3w**−**3aj** were determined by comparing the structure of (*S*)-**3t**.

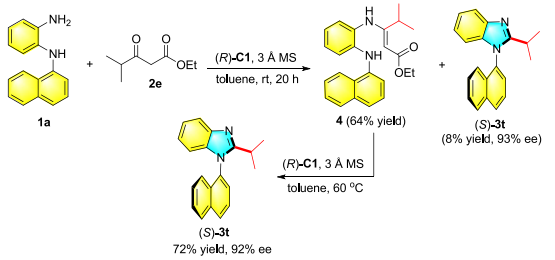
and excellent enantioselectivity (93−98% ee) (see (*S*)-**3x**~(*S*)-**3ae**). When the aryl part in **1** was changed into quinolyl-5-yl or 1,2,3,4-tetrahydroquinolin-8-yl, products (*S*)-**3af** and (*S*)-**3ag** were obtained in high yield (two 81%) and excellent ee values (96% and 97% ee, respectively). Next, **2h** was used as the substrate, and three desired target products, (*S*)-**3ah**, (*S*)-**3ai**, and (*S*)-**3aj**, were provided in 65−86% yields with 95−98% ee. These reactions could tolerate similar functional groups to those in Scheme 2.

To explore the mechanism of the reaction above, reaction of **1a** with **2e** was performed in the presence of (*R*)-**C1** at room temperature for 20 h, and enamine **4** was obtained in 64% isolated yield with a small amount (8% yield) of (*S*)-**3t** appearing (Scheme 4). Subsequently, enamine **4** was treated under the standard conditions, and the reaction provided (*S*)-**3t** in 72% yield with 92% ee (see Scheme S6 in SI for more details). The results above indicated that reaction of **1** with **2** leading to **3** in Schemes 2 and 3 could undergo an enamine intermediate. Therefore, a reaction pathway of this organocatalytic atroposelective construction of axially chiral *N*-aryl benzimidazoles is proposed.

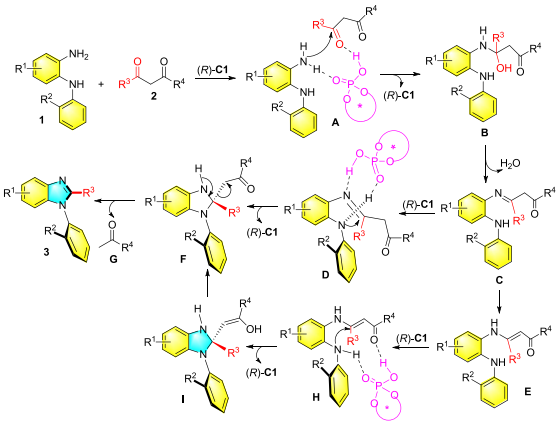
As shown in Scheme 5, treatment of chiral phosphoric acid (*R*)-**C1** with two substrates **1** and **2** through hydrogen bonds forms complex **A**. Then nucleophilic attack of amino in **1** to

https://dx.doi.org/10.1021/acs.orglett.0c02214
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Investigation on the Reaction Mechanism



Scheme 5. Possible Mechanism for the Organocatalytic Atroposelective Construction of Axially Chiral *N*-Aryl Benzimidazoles

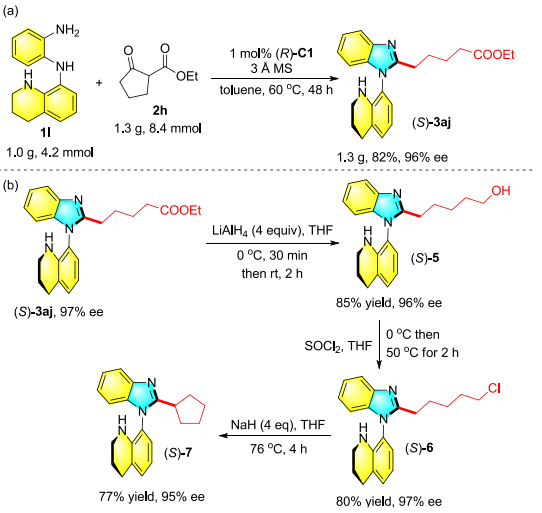


carbonyl in **2** gives **B**, regenerating (*R*)-**C1**, and dehydration of **B** leads to **C**. Recombination of **C** with the catalyst provides **D**, and then intramolecular nucleophilic attack of the imino group to carbon of imine in **D** affords **F**, freeing the catalyst. Elimination of **G** from **F** via C−C bond cleavage gives the target product (**3**). Meanwhile, isomerization of **C** leads to enamine **E**, and then recombination of **E** with the catalyst forms **H**. Intramolecular Michael addition of the imino group to the enamine in **H** leads to **I**, freeing the catalyst. Isomerization of **I** provides **F**, and the C−C bond cleavage in **F** gives **3**.

We investigated applications of our method (Scheme 6). At first, we attempted the gram-scale synthesis of (*S*)-**3aj** under the standard conditions with a lower catalyst loading (1 mol %) and longer reaction time (48 h) (Scheme 6a), and the product was obtained in 82% yield and 96% ee almost without loss of enantioselectivity compared with the small-scale reaction in Scheme 3, which indicated that the present method was a very effective and practical approach to the axially chiral *N*-aryl benzimidazoles. Subsequently, further modification of (*S*)-**3aj** was performed as follows: reduction of (*S*)-**3aj** with $LiAlH_4$ led to (*S*)-**5**, and chlorination of (*S*)-**5** with $SOCl_2$ provided (*S*)-**6**. Reaction of (*S*)-**6** in the presence of NaH (4 equiv) gave cyclic product (*S*)-**7** in 77% yield with 95% ee (Scheme 6b).

Furthermore, we investigated the stability of (*S*)-**3a** in three solvents, toluene, isopropanol, and 1,2-dichloroethane, at different temperatures (Figure 1a), and the progress of racemization was traced by chiral HPLC. We found that almost no racemization occurred below 90 °C for 24 h, but the obvious racemization was observed above 90 °C. Based on the results above, we also calculated the rotation barriers of *N*-aryl

Scheme 6. Applications of Our Method



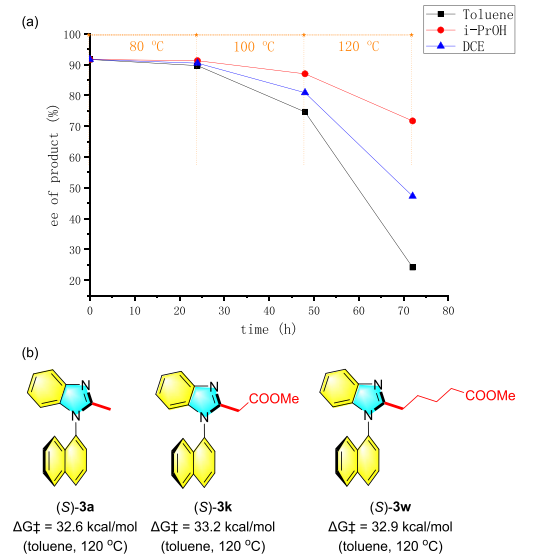


Figure 1. (a) Investigation on the stability of the axial chirality in (*S*)-**3a** at different temperatures. (b) Rotational barrier studies of (*S*)-**3a**, (*S*)-**3k**, and (*S*)-**3w**.

benzimidazoles (see SI for details). As shown in Figure 1b, (*S*)-**3a** containing 2-methyl with smaller steric hindrance at the 2-site shows a lower rotational barrier. When 2-substituents of the *N*-aryl benzimidazoles are bigger groups such as 2-methoxy-2-oxoethyl (see (*S*)-**3k**) and 5-methoxy-5-oxopentyl (see (*S*)-**3w**), the corresponding rotational barriers increase.

In summary, we have developed a novel organocatalytic method for the atroposelective construction of axially chiral *N*-aryl benzimidazoles via reactions of N^1-(aryl)benzene-1,2-diamines with multicarbonyl compounds, and the target products were obtained in high reactivity with excellent enantioselectivity. The method shows some obvious advantages including environmentally friendly chiral phosphoric acid as the organocatalyst, easy carbon−carbon bond cleavage of the multicarbonyl compounds, high efficiency and enantioselectivity, broad substrate scope and functional group tolerance, and gram-scale reaction without loss of reactivity and enantioselectivity.

https://dx.doi.org/10.1021/acs.orglett.0c02214
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02214.

Full experiments and characterization data including ^{1}H and ^{13}C NMR spectra and HPLC for the synthesized products ((*S*)-**3a**−**3aj** and (*S*)-**4**−**7**) (PDF)

Accession Codes

CCDC 1963357 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 Author

Hua Fu − *Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China;* orcid.org/0000-0001-7250-0053; Email: fuhua@mail.tsinghua.edu.cn

Authors

Ningning Man − *Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China;* orcid.org/0000-0003-2872-5970

Zhenbang Lou − *Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China*

Yuming Li − *Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China*

Haijun Yang − *Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China*

Yufen Zhao − *Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02214

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the National Natural Science Foundation of China (Grant No. 21772108) and National Key R&D Program of China (2016YFD0201207) for financial support.

■ REFERENCES

(1) Sabat, M.; Vanrens, J. C.; Laufersweiler, M. J.; Brugel, T. A.; Maier, J.; Golebiowski, A.; De, B.; Easwaran, V.; Hsieh, L. C.; Walter, R. L.; Mekel, M. J.; Evdokimov, A.; Janusz, M. J. The Development of 2-Benzimidazole Substituted Pyrimidine Based Inhibitors of Lymphocyte Specific Kinase (Lck). *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5973−5977.

(2) Hauel, N. H.; Nar, H.; Priepke, H.; Ries, U.; Stassen, J.; Wienen, W. Structure-Based Design of Novel Potent Nonpeptide Thrombin Inhibitors. *J. Med. Chem.* **2002**, *45*, 1757−1766.

(3) Nakano, H.; Inoue, T.; Kawasaki, N.; Miyataka, H.; Matsumoto, H.; Taguchi, T.; Inagaki, N.; Nagai, H.; Satoh, T. Synthesis and Biological Activities of Novel Antiallergic Agents with 5-Lipoxygenase Inhibiting Action. *Bioorg. Med. Chem.* **2000**, *8*, 373−380.

(4) Ueno, H.; Katoh, S.; Yokota, K.; Hoshi, J.; Hayashi, M.; Uchida, I.; Aisaka, K.; Hase, Y.; Cho, H. Structure−Activity Relationships of Potent and Selective Factor Xa Inhibitors: Benzimidazole Derivatives with the Side Chain Oriented to the Prime Site of Factor Xa. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4281−4286.

(5) White, A. W.; Almassy, R.; Calvert, A. H.; Curtin, N. J.; Griffin, R. J.; Hostomsky, Z.; Maegley, K.; Newell, D. R.; Srinivasan, S.; Golding, B. T. Resistance-Modifying Agents. 9.[1] Synthesis and Biological Properties of Benzimidazole Inhibitors of the DNA Repair Enzyme Poly (ADP-ribose) Polymerase. *J. Med. Chem.* **2000**, *43*, 4084−4097.

(6) Li, Y.; Kataoka, M.; Tatsuta, M.; Yasoshima, K.; Yura, T.; Urbahns, K.; Kiba, A.; Yamamoto, N.; Gupta, J. B.; Hashimoto, K. Benzimidazole Derivatives as Novel Nonpeptide Luteinizing Hormone-Releasing Hormone (LHRH) Antagonists. Part 2: Benzimidazole-5-Sulfonamides. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 805−807.

(7) Baudy, R. B.; Fletcher, H., III; Yardley, J. P.; Zaleska, M. M.; Bramlett, D. R.; Tasse, R. P.; Kowal, D. M.; Katz, A. H.; Moyer, J. A.; Abou-Gharbia, M. Design, Synthesis, SAR, and Biological Evaluation of Highly Potent Benzimidazole-Spaced Phosphono-α-Amino Acid Competitive NMDA Antagonists of the AP-6 Type. *J. Med. Chem.* **2001**, *44*, 1516−1529.

(8) Zarrinmayeh, H.; Nunes, A. M.; Ornstein, P. L.; Zimmerman, D. M.; Arnold, M. B.; Schober, D. A.; Gackenheimer, S. L.; Bruns, R. F.; Hipskind, P. A.; Britton, T. C.; Cantrell, B. E.; Gehlert, D. R. Synthesis and Evaluation of a Series of Novel 2-[(4-Chlorophenoxy)-methyl]- benzimidazoles as Selective Neuropeptide Y Y1 Receptor Antagonists. *J. Med. Chem.* **1998**, *41*, 2709−2719.

(9) VelIk, J.; Baliharova, V.; Fink-Gremmels, J.; Bull, S.; Lamka, J.; Skalova, L. Benzimidazole Drugs and Modulation of Biotransformation Enzymes. *Res. Vet. Sci.* **2004**, *76*, 95−108.

(10) Schwartz, G.; Fehse, K.; Pfeiffer, M.; Walzer, K.; Leo, K. Highly Efficient White Organic Light Emitting Diodes Comprising an Interlayer to Separate Fluorescent and Phosphorescent Regions. *Appl. Phys. Lett.* **2006**, *89*, 083509.

(11) Asensio, J. A.; Gomez-Romero, P. Recent Developments on Proton Conducting Poly(2,5-benzimidazole) (ABPBI) Membranes for High Temperature Polymer Electrolyte Membrane Fuel Cells. *Fuel Cells* **2005**, *5*, 336−343.

(12) Grimmett, M. R. In *Imidazole and benzimidazole synthesis, best synthetic methods*; Meth-Cohn, O., Ed.; Academic: London, 1997.

(13) (a) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. Atroposelective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384−5427. (b) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. Atroposelective Total Synthesis of Axially Chiral Biaryl Natural Products. *Chem. Rev.* **2011**, *111*, 563−639. (c) Glunz, P. W. Recent Encounters with Atropisomerism in Drug Discovery. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 53−60. (d) Toenjes, S. T.; Gustafson, J. L. Atropisomerism in Medicinal Chemistry: Challenges and Opportunities. *Future Med. Chem.* **2018**, *10*, 409−422.

(14) For a book: (a) *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, Germany, 2011. For a recent review: (b) Ma, Y.-N.; Li, S.-X.; Yang, S.-D. New Approaches for Biaryl-Based Phosphine Ligand Synthesis via P = O Directed C-H Functionalizations. *Acc. Chem. Res.* **2017**, *50*, 1480−1492.

(15) For selected reviews, see: (a) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. Recent Advances and New Concepts for the Synthesis of Axially Stereoenriched Biaryls. *Chem. Soc. Rev.* **2015**,

44, 3418−3430. (b) Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J. Nonbiaryl and Heterobiaryl Atropisomers: Molecular Templates with Promise for Atropselective Chemical Transformations. *Chem. Rev.* **2015**, *115*, 11239−11300. (c) Loxq, P.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. Synthesis of Axially Chiral Biaryl Compounds by Asymmetric Catalytic Reactions with Transition Metals. *Coord. Chem. Rev.* **2016**, *308*, 131−190. (d) Wang, Y.-B.; Tan, B. Construction of Axially Chiral Compounds via Asymmetric Organocatalysis. *Acc. Chem. Res.* **2018**, *51*, 534−547.

(16) For selected papers, see: (a) Gustafson, J. L.; Lim, D.; Miller, S. J. Dynamic Kinetic Resolution of Biaryl Atropisomers via Peptide-Catalysed Asymmetric Bromination. *Science* **2010**, *328*, 1251−1255. (b) Barrett, K. T.; Miller, S. J. Enantioselective Synthesis of Atropisomeric Benzamides through Peptide-Catalyzed Bromination. *J. Am. Chem. Soc.* **2013**, *135*, 2963−2966. (c) Mori, K.; Ichikawa, Y.; Kobayashi, M.; Shibata, Y.; Yamanaka, M.; Akiyama, T. Enantioselective Synthesis of Multisubstituted Biaryl Skeleton by Chiral Phosphoric Acid Catalyzed Desymmetrization/Kinetic Resolution Sequence. *J. Am. Chem. Soc.* **2013**, *135*, 3964−3970. (d) Miyaji, R.; Asano, K.; Matsubara, S. Bifunctional Organocatalysts for the Enantioselective Synthesis of Axially Chiral Isoquinoline *N*-Oxides. *J. Am. Chem. Soc.* **2015**, *137*, 6766−6769. (e) Diener, M. E.; Metrano, A. J.; Kusano, S.; Miller, S. J. Enantioselective Synthesis of 3-Arylquinazolin-4-(3*H*)-ones via Peptide-Catalysed Atroposelective Bromination. *J. Am. Chem. Soc.* **2015**, *137*, 12369−12377. (f) Chen, Y.-H.; Cheng, D.-J.; Zhang, J.; Wang, Y.; Liu, X.-Y.; Tan, B. Atroposelective Synthesis of Axially Chiral Biaryldiols via Organocatalytic Arylation of 2-Naphthols. *J. Am. Chem. Soc.* **2015**, *137*, 15062−15065. (g) Wang, J.-Z.; Zhou, J.; Xu, C.; Sun, H.; Kürti, L.; Xu, Q.-L. Symmetry in Cascade Chirality-Transfer Processes: A Catalytic Atroposelective Direct Arylation Approach to BINOL Derivatives. *J. Am. Chem. Soc.* **2016**, *138*, 5202−5205. (h) Moliterno, M.; Cari, R.; Puglisi, A.; Antenucci, A.; Sperandio, C.; Moretti, E.; Di Sabato, A.; Salvio, R.; Bella, M. Quinine-Catalyzed Asymmetric Synthesis of 2,2′-Binaphthol-Type Biaryls under Mild Reaction Conditions. *Angew. Chem., Int. Ed.* **2016**, *55*, 6525−6529. (i) Yu, C.; Huang, H.; Li, X.; Zhang, Y.; Wang, W. Dynamic Kinetic Resolution of Biaryl Lactones via a Chiral Bifunctional Amine Thiourea Catalysed Highly Atropoenantioselective Transesterification. *J. Am. Chem. Soc.* **2016**, *138*, 6956−6959. (j) Chen, Y.-H.; Qi, L.-W.; Fang, F.; Tan, B. Organocatalytic Atroposelective Arylation of 2-Naphthylamines as a Practical Approach to Axially Chiral Biaryl Amino Alcohols. *Angew. Chem., Int. Ed.* **2017**, *56*, 16308−16312. (k) Zhang, H.-H.; Wang, C.-S.; Li, C.; Mei, G.-J.; Li, Y.; Shi, F. Design and Enantioselective Construction of Axially Chiral Naphthyl-Indole Skeletons. *Angew. Chem., Int. Ed.* **2017**, *56*, 116−121. (l) Metrano, A. J.; Abascal, N. C.; Mercado, B. Q.; Paulson, E. K.; Hurtley, A. E.; Miller, S. J. Diversity of Secondary Structure in Catalytic Peptides with β-Turn-Biased Sequences. *J. Am. Chem. Soc.* **2017**, *139*, 492−516. (m) Jolliffe, J. D.; Armstrong, R. J.; Smith, M. D. Catalytic Enantioselective Synthesis of Atropisomeric Biaryls by a Cation-Directed *O*-Alkylation. *Nat. Chem.* **2017**, *9*, 558−562.

(17) (a) Kwon, Y.; Li, J.; Reid, J. P.; Crawford, J. M.; Jacob, R.; Sigman, M. S.; Toste, F. D.; Miller, S. J. Disparate Catalytic Scaffolds for Atroposelective Cyclodehydration. *J. Am. Chem. Soc.* **2019**, *141*, 6698−6705. (b) Kwon, Y.; Chinn, A. J.; Kim, B.; Miller, S. J. Divergent Control of Point and Axial Stereogenicity: Catalytic Enantioselective C-N Bond-Forming Cross-Coupling and Catalyst-Controlled Atroposelective Cyclodehydration. *Angew. Chem., Int. Ed.* **2018**, *57*, 6251−6255.

(18) For some reviews, see: (a) Crabtree, R. H. The Organometallic Chemistry of Alkanes. *Chem. Rev.* **1985**, *85*, 245−269. (b) Rybtchinski, B.; Milstein, D. Metal Insertion into C-C Bonds in Solution. *Angew. Chem., Int. Ed.* **1999**, *38*, 870−883. (c) Murakami, M.; Ito, Y. Activation of Unreactive Bonds and Organic Synthesis. *Topics in Organometallic Chemistry*; Murai, S., Alper, H., Gossage, R. A., Eds.; Springer: Berlin, 1999; Vol. 3, p 97.

(19) (a) Jun, C.-H. Transition Metal-Catalyzed Carbon−Carbon Bond Activation. *Chem. Soc. Rev.* **2004**, *33*, 610−618. (b) Jun, C.-H.; Park, J.-W. Directed C − C Bond Activation by Transition Metal Complexes. *Top. Organomet. Chem.* **2007**, *24*, 117−143. (c) Chen, F.; Wang, T.; Jiao, N. Recent Advances in Transition-Metal-Catalyzed Functionalization of Unstrained Carbon−Carbon Bonds. *Chem. Rev.* **2014**, *114*, 8613−8661. (d) Tobisu, M.; Chatani, N. Catalytic Reactions Involving the Cleavage of Carbon−Cyano and Carbon−Carbon Triple Bonds. *Chem. Soc. Rev.* **2008**, *37*, 300−307. (e) Dermenci, A.; Coe, J. W.; Dong, G. Direct Activation of Relatively Unstrained Carbon−Carbon Bonds in Homogeneous Systems. *Org. Chem. Front.* **2014**, *1*, 567−581.

(20) (a) Sattler, A.; Parkin, G. Cleaving Carbon−Carbon Bonds by Inserting Tungsten into Unstrained Aromatic Rings. *Nature* **2010**, *463*, 523−526. (b) Travis, B. R.; Narayan, R. S.; Borhan, B. J. Osmium Tetroxide-Promoted Catalytic Oxidative Cleavage of Olefins: An Organometallic Ozonolysis. *J. Am. Chem. Soc.* **2002**, *124*, 3824−3825. (c) de Boer, J. W.; Brinksma, J.; Browne, W. R.; Meetsma, A.; Alsters, P. L.; Hage, R.; Feringa, B. L. *cis*-Dihydroxylation and Epoxidation of Alkenes by $[Mn_2O(RCO_2)_2(tmtacn)_2]$: Tailoring the Selectivity of a Highly H2O2-Efficient Catalyst. *J. Am. Chem. Soc.* **2005**, *127*, 7990−7791. (d) Trost, B. M.; Morris, P. J. Palladium-Catalyzed Diastereo- and Enantioselective Synthesis of Substituted Cyclopentanes through a Dynamic Kinetic Asymmetric Formal [3 + 2]-Cycloaddition of Vinyl Cyclopropanes and Alkylidene Azlactones. *Angew. Chem., Int. Ed.* **2011**, *50*, 6167−6170. (e) Qin, C.; Zhou, W.; Chen, F.; Ou, Y.; Jiao, N. Iron-Catalyzed C−H and C−C Bond Cleavage: A Direct Approach to Amides from Simple Hydrocarbons. *Angew. Chem., Int. Ed.* **2011**, *50*, 12595−12599. (f) Wang, A.; Jiang, H. Palladium-Catalyzed Cleavage Reaction of Carbon−Carbon Triple Bond with Molecular Oxygen Promoted by Lewis Acid. *J. Am. Chem. Soc.* **2008**, *130*, 5030−5031. (g) He, C.; Guo, S.; Huang, L.; Lei, A. Copper Catalyzed Arylation/C−C Bond Activation: An Approach toward α-Aryl Ketones. *J. Am. Chem. Soc.* **2010**, *132*, 8273−8275. (h) Dieskau, A. P.; Holzwarth, M. S.; Plietker, B. Fe-Catalyzed Allylic C−C-Bond Activation: Vinylcyclopropanes As Versatile a1,a3,d5-Synthons in Traceless Allylic Substitutions and [3 + 2]-Cycloadditions. *J. Am. Chem. Soc.* **2012**, *134*, 5048−5051.

(21) Li, Z.; Dong, J.; Chen, X.; Li, Q.; Zhou, Y.; Yin, S.-F. Metal- and Oxidant-Free Synthesis of Quinazolinones from β-Ketoesters with *o*-Aminobenzamides via Phosphorous acid-Catalyzed Cyclocondensation and Selective C−C Bond Cleavage. *J. Org. Chem.* **2015**, *80*, 9392−9400.

(22) Wang, Y.-B.; Zheng, S.-C.; Hu, Y.-M.; Tan, B. Brønsted Acid-Catalysed Enantioselective Construction of Axially Chiral Arylquinazolinones. *Nat. Commun.* **2017**, *8*, 15489pp.

(23) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566−1568. (b) Uraguchi, D.; Terada, M. Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation. *J. Am. Chem. Soc.* **2004**, *126*, 5356−5357.

(24) Selected examples, see: (a) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. Chiral Brønsted Acid Catalyzed Enantioselective Mannich-Type Reaction. *J. Am. Chem. Soc.* **2007**, *129*, 6756−6764. (b) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. Chiral Brønsted Acid Catalyzed Enantioselective Friedel−Crafts Reaction of Indoles and α-Aryl Enamides: Construction of Quaternary Carbon Atoms. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565−5567. (c) Itoh, J.; Fuchibe, K.; Akiyama, T. Chiral Phosphoric Acid Catalyzed Enantioselective Friedel−Crafts Alkylation of Indoles with Nitroalkenes: Cooperative Effect of 3 Å Molecular Sieve. *Angew. Chem., Int. Ed.* **2008**, *47*, 4016−4018.

https://dx.doi.org/10.1021/acs.orglett.0c02214
Org. Lett. XXXX, XXX, XXX−XXX