CJC Chinese Journal of Chemistry 中国化学 - An International Journal

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Concise Report

Cite this paper: *Chin. J. Chem.* **2024**, *42*, 3006—3012. **DOI: 10.1002/cjoc.202400612**

Palladium-Catalyzed Construction of Phthalides Bearing Two Adjacent Stereocenters through Retro-oxa-Michael Addition

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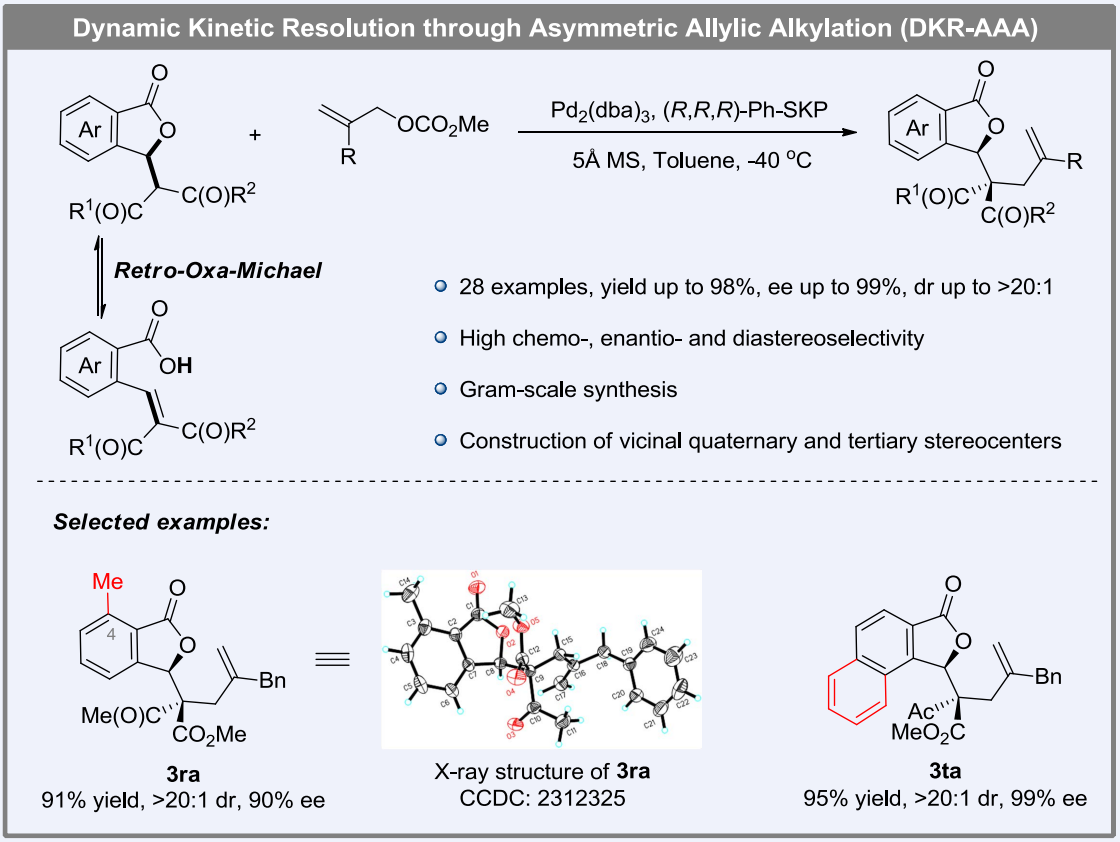
Keywords

Retro-oxa-Michael addition | Dynamic kinetic resolution | Palladium catalysis | Asymmetric allylic alkylation | Chemoselectivity | Stereochemistry | Lactones

Comprehensive Summary



Optically active phthalides are prevalent in many natural and bioactive products. Herein, a novel dynamic kinetic resolution of isobenzofuranone derivatives through palladium-catalyzed asymmetric allylic alkylation has been developed to synthesize phthalide derivatives bearing vicinal quaternary and tertiary stereocenters with high yields, showing excellent chemo-, enantio- and diastereoselectivity. Furthermore, gram-scale experiment underwent smoothly and the transformation of product could build a bridged bicyclic skeleton.

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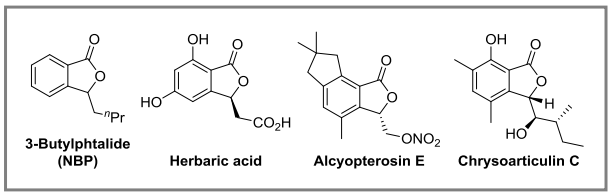
Background and Originality Content

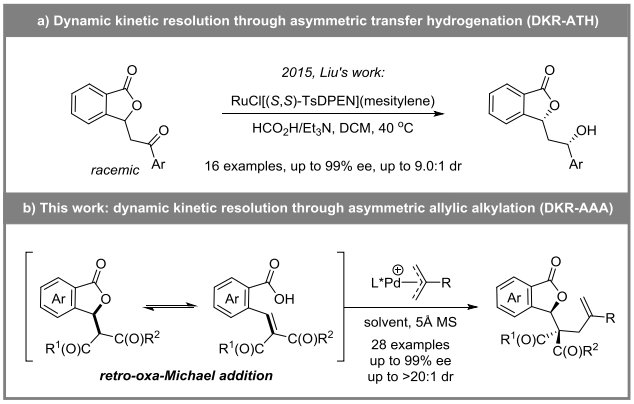
Isobenzofuranones, commonly termed as phthalides, are prevalently found in naturally occurring products and exhibit a myriad of biological activities,[1] which also act as pragmatic building blocks in organic synthesis.[2] For instance, 3-butylphthalide (NBP)[3] is a cardiovascular drug for the treatment of cerebral ischemia. It is also a natural antioxidant and has anticonvulsant activity. Herbaric acid[4] has antibacterial property and alcyopterosin E[5] showed mild cytotoxicity toward human tumor cell lines. Chrysoarticulin C[6] exhibited weak cytotoxicity against the K562 and A549 cancer cell lines and was also moderately active against sortase A (Scheme 1).

Scheme 1 Representative examples of natural phthalides



In recent years, various elegant methods have been developed for the asymmetric catalytic synthesis of phthalides, involving metal,[7] organic[8] and biological catalysis.[9] These reported literatures mainly focused on the enantioselective construction of isobenzofuranone framework. In contrast, it is rare to achieve enantioselective synthesis of phthalide derivatives based on this framework. Indubitably, the dynamic kinetic resolution (DKR)[10] has been demonstrated as a powerful tool. Hence, for the construction of enantiopure phthalides, dynamic kinetic resolution of compounds bearing isobenzofuranone framework is effective. In 2015, Liu and coworkers[7f] developed DKR of phthalides through asymmetric transfer hydrogenation[11] to construct 3-(2-hydroxy-2-arylethyl)isobenzofuran-1(3*H*)-one bearing 1,3-distereocenters with excellent enantioselectivities and acceptable diastereomeric ratios, which utilized the racemization through retro-oxa-Michael addition (Scheme 2a). Previously, our group made efforts in the dynamic kinetic resolution of substrates based on retro-oxa-Michael addition process.[12] Among them, we have realized dynamic kinetic resolution of 2,3-disubstituted flavonoids *via* palladium-catalyzed asymmetric allylic alkylation,[13] and two contiguous stereogenic centers were constructed on the endocyclic structure.[12a] As is well known, it is more difficult to stereoselectively build multiple stereocenters on the acyclic structure. Herein, utilizing retro-oxa-Michael addition process, we reported an efficient dynamic kinetic resolution through asymmetric allylic allylation to provide a wide range of phthalide derivatives bearing two contiguous stereocenters (including an all-carbon quaternary stereocenter) with high yields, excellent enantio- and diastereoselectivities (Scheme 2b).

Scheme 2 Dynamic kinetic resolution of phthalide derivatives



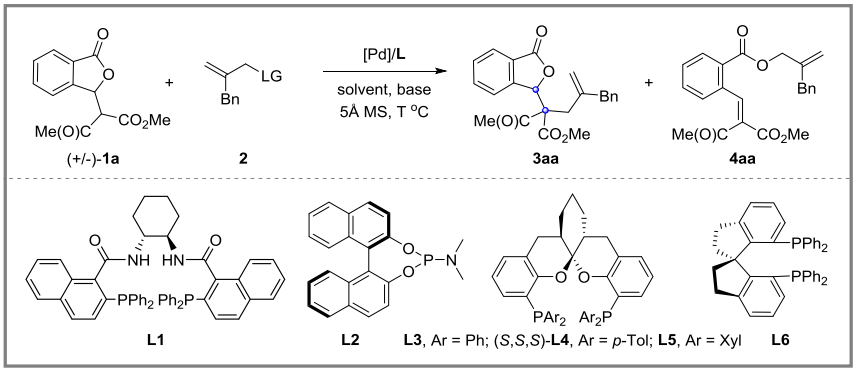
Results and Discussion

Encouraged by our antecedent work on retro-oxa-Michael addition,[12a] we chose $Pd_2(dba)_3$/(*R*,*R*)-DACH-Naphthyl Trost Ligand (**L1**) as catalyst to investigate the asymmetric allylic alkylation between 2-substituted allyl carbonate (**2a**) and isobenzofuranone derivative (**1a**). Under this condition, the target product **3aa** was obtained with only 24% yield and 5.0 : 1 dr. At the same time, there was also the generation of chemoselective sideproduct **4aa** with 10% yield (Table 1, entry 1). We deem that chiral ligands may play a pivotal role in this alkylation reaction. Thus, the chiral ligand effect was initially examined (entries 2—6). Fortunately, the chemo- and diastereoselectivity of asymmetric allylic alkylation were excellent when the chiral spiroketal-based diphosphine SKPs[14] were used, in which (*R*,*R*,*R*)-Ph-SKP **L3** was optimal. Then, the different leaving groups of allyl reagents were investigated, among which allyl carbonate was superior to allyl acetate and allyl chloride (entries 7—8). Subsequently, the different solvents were tested (entries 9—12). It was found that toluene as the solvent afforded the desired product in 93% yield with > 20 : 1 dr and 79% ee. Next, triethylamine was used instead of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as the base and found that the results of alkylation reaction were similar (entries 9 and 13). Inferring the base might not be necessary, asymmetric allylic alkylation without base was attempted, which furnished the desirable product in the identical yield with 80% ee (entry 14). Therefore, we chose not to add the base. Then, the palladium precursors were investigated, showing that $Pd_2(dba)_3$ was still better for the enantioselectivity compared with $Pd(dba)_2$, $[Pd(C_3H_5)Cl]_2$ and $Pd(OAc)_2$ (entries 15—17). Naturally, the temperature was decreased to further improve the stereoselectivity (entries 18—19). Reaction temperature at –40 °C was determined to be the optimal, delivering the desired product with > 20 : 1 dr and 93% ee. Ultimately, the amount of ligand was decreased to 6.0 mol% and the optimal conditions were established in entry 20. In addition, we found that when **4aa** reacted at 50 °C under above conditions, it can be completely converted to **3aa** with 78% ee.

After identifying the optimal conditions, the substrate scope of this methodology was evaluated. First of all, a range of allyl substrates were investigated as shown in Scheme 3. It was found that substituents on the allyl carbonates have a vast effect on the stereoselectivity. With simple allyl methyl carbonate (**2b**) as the electrophile, the alkylation reaction displayed a lower enantioselectivity (42% ee). Cinnamyl methyl carbonate (**2c**) performed very poorly, providing the corresponding product **3ac** in 30% yield with only 4.0 : 1 dr and 24% ee for the major diastereoisomer. When the substituents on the 2-position of allyl methyl carbonate were tested, such as phenyl (**2d**) and methyl (**2e**), the reaction exhibited moderate enantioselectivity. 2-Benzyl substituted allyl substrates played an important role in the stereoselectivity. Accordingly, the different substituents on the aryl group of allyl substrate (**2f—j**) were explored. When electron-withdrawing substituent (F) was introduced, the reactivity and diastereoselectivity was not diminished, but enantioselectivity slightly decreased to 85%. When other substituents, such as methoxy (**2g**) and methyl on different positions (**2h—j**), were introduced, the reactivity would be affected and the reaction needed to be carried out at –30 °C.

Afterwards, the substrate scope was further investigated with a series of isobenzofuranone derivatives, using 2-benzylallyl methyl carbonate (**2a**) as the electrophile (Scheme 3). The effect of electron-withdrawing substituents of isobenzofuranone derivatives was first probed. It was found that isobenzofuranone

Table 1 Optimization of reaction conditions[a]



entry	L	LG	solvent	base	[Pd]	yield (%) of **4aa**[b]	yield (%)of **3aa**[b]	dr of **3aa**[b]	ee (%) of **3aa** (major isomer)[c]
1	**L1**	OCO_2Me	$PhCF_3$	DBU	$Pd_2(dba)_3$	10	24	5.0 : 1	77
2	**L2**	OCO_2Me	$PhCF_3$	DBU	$Pd_2(dba)_3$	9	21	4.3 : 1	17
3	**L3**	OCO_2Me	$PhCF_3$	DBU	$Pd_2(dba)_3$	< 5	89	> 20 : 1	79
4	**L4**	OCO_2Me	$PhCF_3$	DBU	$Pd_2(dba)_3$	< 5	88	~20 : 1	78
5	**L5**	OCO_2Me	$PhCF_3$	DBU	$Pd_2(dba)_3$	< 5	69	7.6 : 1	14
6	**L6**	OCO_2Me	$PhCF_3$	DBU	$Pd_2(dba)_3$	< 5	36	5.0 : 1	16
7	**L6**	OAc	$PhCF_3$	DBU	$Pd_2(dba)_3$	< 5	47	~20 : 1	78
8	**L6**	Cl	$PhCF_3$	DBU	$Pd_2(dba)_3$	< 5	73	~20 : 1	78
9	**L3**	OCO_2Me	toluene	DBU	$Pd_2(dba)_3$	< 5	93	> 20 : 1	79
10	**L3**	OCO_2Me	THF	DBU	$Pd_2(dba)_3$	< 5	> 95	~20 : 1	76
11	**L3**	OCO_2Me	DCM	DBU	$Pd_2(dba)_3$	< 5	79	18.8 : 1	72
12	**L3**	OCO_2Me	CH_3CN	DBU	$Pd_2(dba)_3$	< 5	25	7.3 : 1	52
13	**L3**	OCO_2Me	toluene	Et_3N	$Pd_2(dba)_3$	< 5	> 95	> 20 : 1	78
14	**L3**	OCO_2Me	toluene	—	$Pd_2(dba)_3$	< 5	> 95	> 20 : 1	80
15	**L3**	OCO_2Me	toluene	—	$Pd(dba)_2$	< 5	> 95	> 20 : 1	79
16	**L3**	OCO_2Me	toluene	—	$[Pd(C_3H_5)Cl]_2$	< 5	> 95	> 20 : 1	79
17	**L3**	OCO_2Me	toluene	—	$Pd(OAc)_2$	< 5	> 95	> 20 : 1	79
18[d]	**L3**	OCO_2Me	toluene	—	$Pd_2(dba)_3$	< 5	> 95	> 20 : 1	89
19[e]	**L3**	OCO_2Me	toluene	—	$Pd_2(dba)_3$	< 5	> 95	> 20 : 1	93
20[e,f]	**L3**	OCO_2Me	toluene	—	$Pd_2(dba)_3$	< 5	> 95 (96[g])	> 20 : 1	93

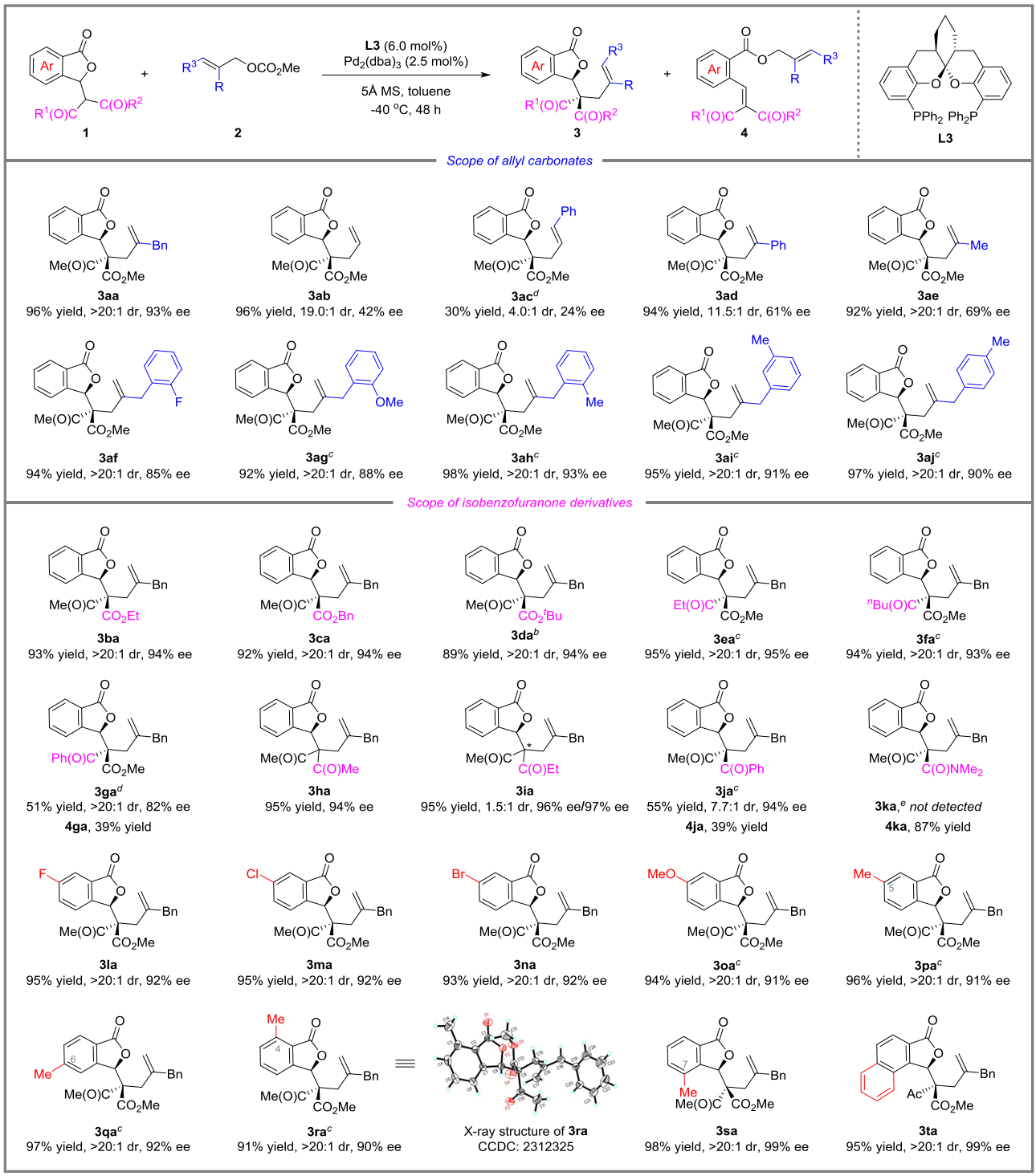
[a] Reactions were carried out with **1a** (0.10 mmol), **2** (1.5 eq.), [Pd] (5.0 mol%), **L** (7.5 mol%), base (1.0 eq.), solvent (1.0 mL), 5 Å MS (50 mg), 30 °C, 1—48 h. [b] Yield and diastereomeric ratio were measured by analysis of ^{1}H NMR spectra using 1,3,5-trimethoxybenzene as the internal standard. [c] Determined by chiral HPLC. [d] –20 °C instead of 30 °C. [e] –40 °C instead of 30 °C. [f] **L3** (6.0 mol%). [g] Isolated yield for the reaction on 0.20 mmol scale and toluene (1.0 mL).

compounds containing β-keto ester structure were better. Various alkoxycarbonyl groups were well tolerated in the reaction, such as ethoxycarbonyl (**1b**), benzyloxycarbonyl (**1c**) and *tert*-butoxycarbonyl (**1d**). When R^1 was changed from methyl to ethyl (**1e**) or *n*-butyl (**1f**), the enantioselectivity was slightly improved, albeit a little lower reactivity resulting in the reaction conducted at –30 °C. When R^1 was phenyl (**1g**), the chemoselectivity of this reaction was profoundly affected, delivering the sideproduct **4ga** in 39% yield and the desired product **3ga** in 51% yield with 82% ee. For isobenzofuranone compounds containing 1,3-dione structure, there was no change in enantioselectivity. However, for nucleophile (**1i**), asymmetric allylic alkylation could only obtain 1.5 : 1 diastereomeric ratio. Additionally, chemo- and diastereoselectivity of the alkylation reduced when R^2 was phenyl (**1j**). When substrate **1k** bearing dimethylamino as R^2 was employed, it was a pity that chemoselective sideproduct **4ka** was generated in 87% yield and the desired **3ka** was not detected. Due to the fact that **4aa** could be converted to **3aa** at 50 °C under standard conditions, we attempted to obtain the desired product **3ka** at higher reaction temperature. However, no **3ka** was also obtained at 50 °C and even at 80 °C.

Furthermore, it was executed to screen substituents on aromatic ring of the isobenzofuranone derivatives **1**. Halogen atoms such as F, Cl and Br on the C5 position of isobenzofuranone derivatives (**1l—n**) were compatible, and the reactivity and stereoselectivity of asymmetric allylic alkylation could be maintained. When electron-donating groups like methoxy and methyl (**1o**,**p**) were introduced, the alkylation reaction proceeded at –30 °C, which was the same as the substrates bearing methyl group on the C4 or C6 position (**1q**,**r**). Gladly, methyl group on the C7 position of isobenzofuranone derivative was advantageous, and the corresponding product **3sa** was obtained with 99% ee. In addition, using substrate bearing naphthalene for asymmetric allylic alkylation, the product **3ta** could also be generated in 95% yield with 99% ee. Besides, to determine the absolute configuration of products, the X-ray crystallographic analysis evidenced that (+)-**3ra** was confirmed as (+)-(*R*,*R*)-**3ra** and the absolute configurations of all other products were assigned by analogy.

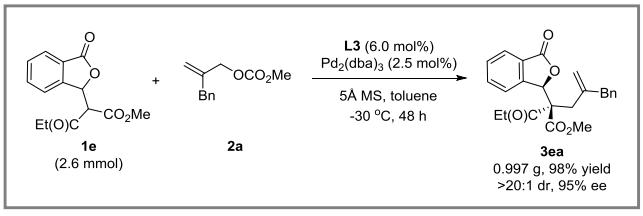
To demonstrate the practicability of the above methodology, gram-scale reaction on **1e** was executed under the corresponding condition, providing the product **3ea** in 98% yield without loss of stereoselectivity (Scheme 4). Meanwhile, further derivatizations of compound **3ea** were performed (Scheme 5). A tandem epoxidation and acid-promoted intramolecular ring-opening reaction of

Scheme 3 Substrate scopes[a]



[a] Reactions were carried out with **1** (0.20 mmol), **2** (0.30 mmol), $Pd_2(dba)_3$ (2.5 mol%), **L3** (6.0 mol%), toluene (1.0 mL), 5 Å MS (50 mg), –40 °C, 48 h. [b] –40 °C, 55 h. [c] –30 °C, 48 h. [d] –30 °C, 72 h. [e] –40 °C, 55 h then –20 °C, 40 h.

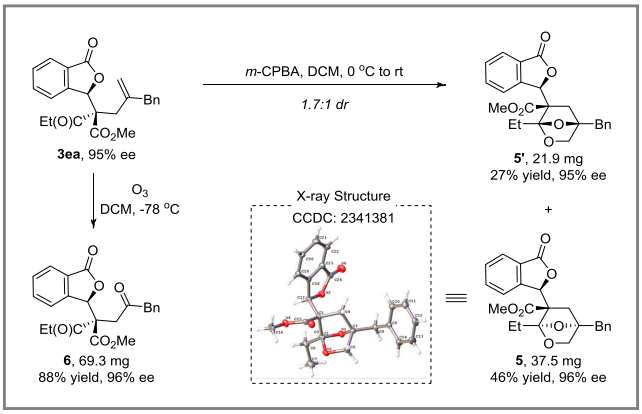
Scheme 4 Gram-scale experiment



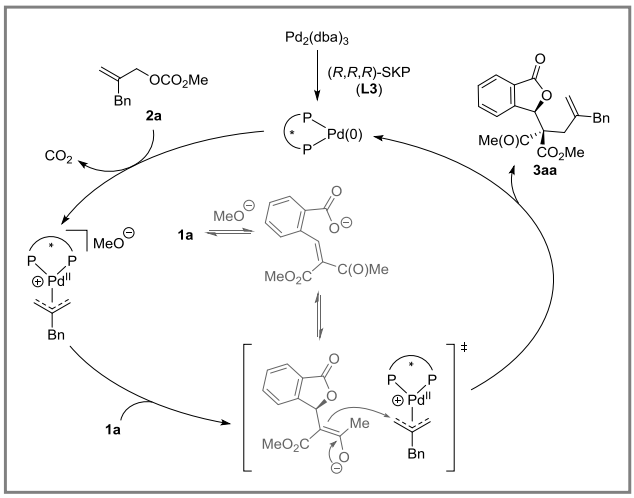
3ea happened in the presence of *m*-chloroperbenzoic acid, delivering the bridged skeleton **5/5'** with 1.7 : 1 dr and maintained optical purity. Finally, oxidative cleavage of the terminal alkene with ozone produced the chiral ketone **6** in 88% yield with 96% ee.

On the basis of the above experimental results and mechanism on palladium-catalyzed allylic alkylation using allyl carbonates,[15] a plausible mechanism was proposed in Scheme 6. For the stereoselective control, the enolate of the nucleophile approaches the (π-allyl)palladium-**L3** complex by its *Si* face.

Scheme 5 Product derivatization



Scheme 6 Plausible mechanism



Conclusions

In summary, we have successfully developed dynamic kinetic resolution of isobenzofuranone derivatives through palladium-catalyzed asymmetric allylic alkylation, based on fast retro-oxa-Michael addition as the racemization step. It is highly efficient to construct a series of enantioenriched phthalide derivatives bearing vicinal tertiary and all-carbon quaternary stereocenters. This strategy has high chemo-, enantio- and diastereoselectivity, showing good functional group tolerance and scale-up reactivity. In addition, the bridged bicyclic skeleton could be built by the transformation of product.

Experimental

General procedure for the palladium-catalyzed asymmetric allylic alkylation

The metal precursor $Pd_2(dba)_3$ (0.005 mmol, 4.6 mg, 2.5 mol%), (*R*,*R*,*R*)-Ph-SKP ligand (**L3**) (0.012 mmol, 7.9 mg, 6.0 mol%) and toluene (0.5 mL) were placed in a dried Schlenk tube under nitrogen atmosphere. The mixture was stirred at 30 °C for 30 min. Then the mixture was cooled to −40 or −30 °C. Thereafter, the isobenzofuranone derivatives **1** (0.20 mmol) and 5 Å MS (50 mg) were added. Sequentially, allyl carbonates **2** (0.30 mmol) and toluene (0.5 mL) were added slowly. The mixture was stirred at −40 or −30 °C for 48—72 h. After the completion of the reaction, without any treatment, the reaction mixture was directly purified by column chromatography on silica gel using hexanes/ethyl acetate (50/1—5/1) as eluent to give the desirable chiral products **3**.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.202400612.

Acknowledgement

Financial support from National Key R&D Program of China (2023YFA1507500), National Natural Science Foundation of China (92356302, 22171260) and Dalian Institute of Chemical Physics (DICP 1202241) is acknowledged.

References

[1] (a) Lin, G.; Chan, S. S.-K.; Chung, H.-S.; Li, S.-L. Chemistry and Biological Activities of Naturally Occurring Phthalides. *Stud. Nat. Prod. Chem.* **2005**, *32*, 611–669; (b) Beck, J. J.; Chou, S. C. The Structural Diversity of Phthalides from the Apiaceae. *J. Nat. Prod.* **2007**, *70*, 891–900; (c) Karmakar, R.; Pahari, P.; Mal, D. Phthalides and Phthalans: Synthetic Methodologies and Their Applications in the Total Synthesis. *Chem. Rev*. **2014**, *114*, 6213–6284; (d) Zhang, L.-B.; Lv, J.-L.; Liu, J.-W. Phthalide Derivatives with Anticoagulation Activities from *Angelica Sinensis*. *J. Nat. Prod.* **2016**, *79*, 1857–1861; (e) León, A.; Del-Ángel, M.; Ávila, J. L.; Delgado, G. Phthalides: Distribution in Nature, Chemical Reactivity, Synthesis, and Biological Activity. In *Progress in the Chemistry of Organic Natural Products. Progress in the Chemistry of Organic Natural Products*, Vol. 104, Eds.: Kinghorn, A. D.; Falk, H.; Gibbons, S.; Kobayashi, J., Springer, **2017**, pp. 127–246.

[2] (a) Snieckus, V. Directed *ortho* Metalation. Tertiary Amide and *O*-Carbamate Directors in Synthetic Strategies for Polysubstituted Aromatics. *Chem. Rev.* **1990**, *90*, 879–933; (b) Cox, C.; Danishefsky, S. J. Synthesis of the Functionalized Tricyclic Core of Lactonamycin by Oxidative Dearomatization. *Org. Lett.* **2000**, *2*, 3493–3496; (c) Napoletano, M.; Norcini, G.; Pellacini, F.; Marchini, F.; Morazzoni, G.; Ferlenga, P.; Pradella, L. Phthalazine PDE4 Inhibitors. Part 2: The Synthesis and Biological Evaluation of 6-Methoxy-1,4-disubstituted Derivatives. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 33–37; (d) Li, Y.; Linden, A.; Hesse, M. Total Synthesis of the Spermidine Alkaloid 13-Hydroxyisocyclocelabenzine. *Helv. Chim. Acta* **2003**, *86*, 579–591; (e) Mal, D.; Pahari, P. Recent Advances in the Hauser Annulation. *Chem. Rev*. **2007**, *107*, 1892–1918; (f) Rathwell, K.; Brimble, M. A. Use of Stabilized Phthalide Anion Annulation Reactions in Synthesis: An Update. *Synthesis* **2007**, 643–662; (g) Hobson, S. J.; Parkin, A.; Marquez, R. Oxidative Rearrangements of Isobenzofurans: Studies toward the Synthesis of the Ajudazols. *Org. Lett*. **2008**, *10*, 2813–2816.

[3] (a) Yu, S.-R.; You, S.-Q.; Chen, H.-Y. The Pharmacological Actions of 3-*n*-Butylphthalioe (AG-1). *Acta Pharm. Sinica* **1984**, *19*, 486–490; (b) Xiong, N.; Huang, J.; Chen, C.; Zhao, Y.; Zhang, Z.; Jia, M.; Zhang, Z.; Hou, L.; Yang, H.; Cao, X.; Liang, Z.; Zhang, Y.; Sun, S.; Lin, Z.; Wang, T. *dl*-3-*n*-Butylphthalide, a Natural Antioxidant, Protects Dopamine Neurons in Rotenone Models for Parkinson's Disease. *Neurobiol. Aging* **2012**, *33*, 1777–1791; (c) Diao, X.; Deng, P.; Xie, C.; Li, X.; Zhong, D.; Zhang, Y.; Chen, X. Metabolism and Pharmacokinetics of 3-*n*-Butylphthalide (NBP) in Humans: The Role of Cytochrome P450s and Alcohol Dehydrogenase in Biotransformation. *Drug Metab. Dispos.* **2013**, *41*, 430–444.

[4] Jadulco, R.; Brauers, G.; Edrada, R. A.; Ebel, R.; Wray, V.; Proksch, S.; Proksch, P. New Metabolites from Sponge-Derived Fungi *Curvularia Lunata* and *Cladosporium Herbarum*. *J. Nat. Prod.* **2002**, *65*, 730–733.

[5] Palermo, J. A.; Rodriguez Brasco, M. F.; Spagnuolo, C.; Seldes, A. M. Illudalane Sesquiterpenoids from the Soft Coral *Alcyonium paessleri*: The First Natural Nitrate Esters. *J. Org. Chem*. **2000**, *65*, 4482–4486.

[6] Jeon, J.; Julianti, E.; Oha, H.; Park, W.; Oh, D.-C.; Oh, K.-B.; Shin, J. Stereochemistry of Hydroxy-Bearing Benzolactones: Isolation and Structural Determination of Chrysoarticulins A-C from a Marine-Derived Fungus *Chrysosporium articulatum*. *Tetrahedron Lett*. **2013**, *54*,

3111–3115.

[7] (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. Homogeneous Asymmetric Hydrogenation of Functionalized Ketones. *J. Am. Chem. Soc.* **1988**, *110*, 629–631; (b) Tanaka, K.; Osaka, T.; Noguchi, K.; Hirano, M. Rhodium-Catalyzed Asymmetric One-Pot Transesterification and [2+2+2] Cycloaddition Leading to Enantioenriched 3,3-Disubstituted Phthalides. *Org. Lett*. **2007**, *9*, 1307–1310; (c) Zhang, B.; Xu, M.-H.; Lin, G.-Q. Catalytic Enantioselective Synthesis of Chiral Phthalides by Efficient Reductive Cyclization of 2-Acylarylcarboxylates under Aqueous Transfer Hydrogenation Conditions. *Org. Lett*. **2009**, *11*, 4712–4715; (d) Phan, D. H. T.; Kim, B.; Dong, V. M. Phthalides by Rhodium-Catalyzed Ketone Hydroacylation. *J. Am. Chem. Soc*. **2009**, *131*, 15608–15609; (e) Yang, J.; Yoshikai, N. Cobalt-Catalyzed Enantioselective Intramolecular Hydroacylation of Ketones and Olefins. *J. Am. Chem. Soc*. **2014**, *136*, 16748–16751; (f) Cheng, T.; Ye, Q.; Zhao, Q.; Liu, G. Dynamic Kinetic Resolution of Phthalides *via* Asymmetric Transfer Hydrogenation: A Strategy Constructs 1,3-Distereocentered 3-(2-Hydroxy-2-arylethyl)-isobenzofuran-1(3*H*)-one. *Org. Lett*. **2015**, *17*, 4972–4975; (g) Ge, Y.; Han, Z.; Wang, Z.; Feng, C.-G.; Zhao, Q.; Lin, G.-Q.; Ding, K. Ir-SpinPHOX Catalyzed Enantioselective Hydrogenation of 3-Ylidenephthalides. *Angew. Chem. Int. Ed*. **2018**, *57*, 13140–13144; (h) Chen, W.; Li, J.; Xie, H.; Wang, J. Rhodium(III)-Catalyzed Asymmetric Addition of Inert Arene C-H Bond to Aldehydes to Afford Enantioenriched Phthalides. *Org. Lett*. **2020**, *22*, 3586–3590.

[8] (a) Watanabe, M.; Hashimoto, N.; Araki, S.; Butsugan, Y. A Facile Synthesis of Optically Active 3-Ethyl- and 3-Butylphthalides *via* Catalytic Enantioselective Addition of Dialkylzinc Reagents to *o*-Phthalaldehyde. *J. Org. Chem*. **1992**, *57*, 742–744; (b) Zhong, F.; Luo, J.; Chen, G.-Y.; Dou, X.; Lu, Y. Highly Enantioselective Regiodivergent Allylic Alkylations of MBH Carbonates with Phthalides. *J. Am. Chem. Soc*. **2012**, *134*, 10222–10227; (c) Youn, S. W.; Song, H. S.; Park, J. H. Asymmetric Domino Multicatalysis for the Synthesis of 3-Substituted Phthalides: Cinchonine/NHC Cooperative System. *Org. Lett*. **2014**, *16*, 1028–1031; (d) Pan, Y.-L.; Zheng, H.-L.; Wang, J.; Yang, C.; Li, X.; Cheng. J.-P. Enantioselective Allylation of Oxocarbenium Ions Catalyzed by $Bi(OAc)_3$/Chiral Phosphoric Acid. *ACS Catal*. **2020**, *10*, 8069–8076.

[9] Mangas-Sánchez, J.; Busto, E.; Gotor-Fernández, V.; Gotor, V. Highly Stereoselective Chemoenzymatic Synthesis of the 3*H*-Isobenzofuran Skeleton. Access to Enantiopure 3-Methylphthalides. *Org. Lett*. **2012**, *14*, 1444–1447.

[10] For selected reviews on dynamic kinetic resolution, see: (a) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. Racemisation in Asymmetric Synthesis. Dynamic Kinetic Resolution and Related Processes in Enzyme and Metal Catalysis. *Chem. Soc. Rev.* **2001**, *30*, 321–331; (b) Pàmies, O.; Bäckvall, J.-E. Combination of Enzymes and Metal Catalysts. A Powerful Approach in Asymmetric Catalysis. *Chem. Rev.* **2003**, *103*, 3247–3262; (c) Pellissier, H. Recent Developments in Dynamic Kinetic Resolution. *Tetrahedron* **2008**, *64*, 1563–1601; (d) Pellissier, H. Organocatalyzed Dynamic Kinetic Resolution. *Adv. Synth. Catal.* **2011**, *353*, 659–676; (e) Pellissier, H. Recent Developments in Dynamic Kinetic Resolution. *Tetrahedron* **2011**, *67*, 3769–3802; (f) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. Advances in Stereoconvergent Catalysis from 2005 to 2015: Transition-Metal-Mediated Stereoablative Reactions, Dynamic Kinetic Resolutions, and Dynamic Kinetic Asymmetric Transformations. *Chem. Rev.* **2017**, *117*, 4528–4561.

[11] For selected reviews on asymmetric transfer hydrogenation, see: (a) Noyori, R.; Hashiguchi, S. Asymmetric Transfer Hydrogenation Catalyzed by Chiral Ruthenium Complexes. *Acc. Chem. Res.* **1997**, *30*, 97–102; (b) Ikariya, T.; Blacker, A. J. Asymmetric Transfer Hydrogenation of Ketones with Bifunctional Transition Metal-Based Molecular Catalysts. *Acc. Chem. Res*. **2007**, *40*, 1300–1308; (c) Wang, D.; Astruc, D. The Golden Age of Transfer Hydrogenation. *Chem. Rev*. **2015**, *115*, 6621–6686; (d) *Asymmetric Hydrogenation and Transfer Hydrogenation*, Eds.: Ratovelomanana-Vidal, V.; Phansavath, P., Wiley-VCH, **2021**.

[12] (a) Liu, L.-X.; Huang, W.-J.; Xie, Q.-X.; Wu, B.; Yu, C.-B.; Zhou, Y.-G. Dynamic Kinetic Resolution of Flavonoids *via* Asymmetric Allylic Alkylation: Construction of Two Contiguous Stereogenic Centers on Nucleophiles. *ACS Catal.* **2021**, *11*, 12859–12863; (b) Xie, Q.-X.; Liu, L.-X.; Zhu, Z.-H.; Yu, C.-B.; Zhou, Y.-G. Asymmetric Transfer Hydrogenation of 2,3-Disubstituted Flavanones through Dynamic Kinetic Resolution Enabled by Retro-oxa-Michael Addition: Construction of Three Contiguous Stereogenic Centers. *J. Org. Chem.* **2022**, *87*, 7521–7530; (c) Liu, L.-X.; Huang, W.-J.; Yu, C.-B.; Zhou, Y.-G. Palladium-Catalyzed Stereoselective Construction of Chiral Allenes Bearing Nonadjacent Axial and Two Central Chirality. *Org. Biomol. Chem.* **2023**, *21*, 8516–8520.

[13] For selected articles on asymmetric allylic alkylation, see: (a) Trost, B. M.; Van Vranken, D. L. Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev*. **1996**, *96*, 395–422; (b) Trost, B. M.; Crawley, M. L. Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **2003**, *103*, 2921–2944; (c) Trost, B. M. Asymmetric Allylic Alkylation, an Enabling Methodology. *J. Org. Chem*. **2004**, *69*, 5813–5837; (d) Trost, B. M.; Machacek, M. R.; Aponick, A. Predicting the Stereochemistry of Diphenylphosphino Benzoic Acid (DPPBA)-Based Palladium-Catalyzed Asymmetric Allylic Alkylation Reactions: A Working Model. *Acc. Chem. Res*. **2006**, *39*, 747–760; (e) Lu, Z.; Ma, S. Metal-Catalyzed Enantioselective Allylation in Asymmetric Synthesis. *Angew. Chem. Int. Ed*. **2008**, *47*, 258–297; (f) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev*. **2019**, *119*, 1855–1969; (g) Pàmies, O.; Margalef, J.; Cañellas, S.; James, J.; Judge, E.; Guiry, P. J.; Moberg, C.; Bäckvall, J.-E.; Pfaltz, A.; Pericàs, M. A.; Diéguez, M. Recent Advances in Enantioselective Pd-Catalyzed Allylic Substitution: From Design to Applications. *Chem. Rev*. **2021**, *121*, 4373–4505; (h) Jiang, R.; Ding, L.; Zheng, C.; You, S.-L. Iridium-Catalyzed *Z*-Retentive Asymmetric Allylic Substitution Reactions. *Science* **2021**, *371*, 380–386.

[14] (a) Wang, X.; Guo, P.; Han, Z.; Wang, X.; Wang, Z.; Ding, K. Spiroketal-Based Diphosphine Ligands in Pd-Catalyzed Asymmetric Allylic Amination of Morita-Baylis-Hillman Adducts: Exceptionally High Efficiency and New Mechanism. *J. Am. Chem. Soc*. **2014**, *136*, 405–411; (b) Liu, J.; Han, Z.; Wang, X.; Meng, F.; Wang, Z.; Ding, K. Palladium-Catalyzed Asymmetric Construction of Vicinal Tertiary and All-Carbon Quaternary Stereocenters by Allylation of β-Ketocarbonyls with Morita-Baylis-Hillman Adducts. *Angew. Chem. Int. Ed*. **2017**, *56*, 5050–5054; (c) Wang, X.; Han, Z.; Wang, Z.; Ding, K. A Type of Structurally Adaptable Aromatic Spiroketal Based Chiral Diphosphine Ligands in Asymmetric Catalysis. *Acc. Chem. Res*. **2021**, *54*, 668–684.

[15] (a) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. Allylic Carbonates. Efficient Allylating Agents of Carbonucleophiles in Palladium-Catalyzed Reactions under Neutral Conditions. *J. Org. Chem.* **1985**, *50*, 1523–1529; (b) Tsuji, J.; Minami, I. New Synthetic Reactions of Allyl Alkyl Carbonates, Allyl β-Keto Carboxylates, and Allyl Vinylic Carbonates Catalyzed by Palladium Complexes. *Acc. Chem. Res*. **1987**, *20*, 140–145; (c) Chen, G.; Mo, J.; Jiang, D.; Peng, Y. Synthesis of Chiral 1,1,1-Trifluoro-α,α- disubstituted 2,4-Diketones *via* Palladium-Catalyzed Asymmetric Allylation. *Org. Lett.* **2023**, *25*, 2388–2393.

Manuscript received: June 10, 2024
Manuscript revised: July 30, 2024
Manuscript accepted: August 1, 2024
Version of record online: August 21, 2024

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