OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Enantioselective Copper-Catalyzed Desymmetrization of 1,3-Diketones Involving Borylation of Styrenes

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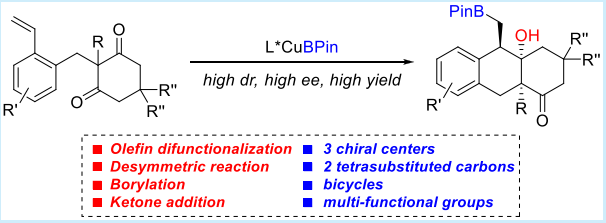
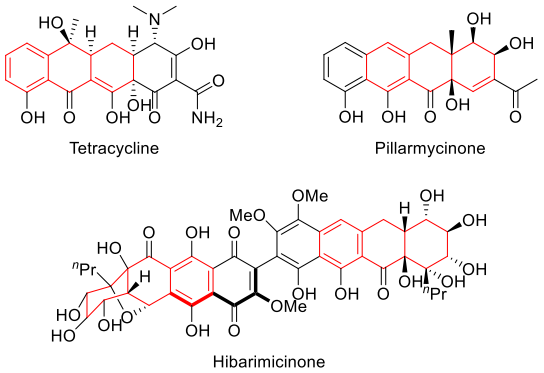
Supporting Information

ABSTRACT: A copper-catalyzed intramolecular enantioselective and diastereoselective borylative coupling of styrenes and ketones was achieved by merging desymmetrization strategy and olefin difunctionalization. The reaction proceeds through an initial enantioselective borylcupration of styrenes, followed by a highly selective direct addition to 1,3-diketones. The bicyclic scaffolds with three chiral carbon centers, including two tetrasubstituted carbons, were generated in excellent yields, diastereoselectivities, and enantioselectivities. This catalytic tandem reaction has great potential for further synthetic application of the chiral polycyclic compounds, because of the versatility of the functional groups in the products.



The benzocyclic framework, including octahydroanthracene, widely exists in natural products, bioactive molecules, and drugs (see Scheme 1).[1] The challenges associated with constructing these skeletons can be fully understood by considering the many popular named reactions for their synthesis (for instance, Diels−Alder reaction, Karus annulation, and Michael−Dieckmann cyclization).[2] In comparison with those methods, catalytic enantioselective desymmetrization of prochiral compounds or *meso*-compounds has many advantages for the synthesis of cyclic scaffolds, especially for the construction of chiral quaternary stereocenters.[3] Among them, desymmetrization of 1,3-diketones with two different substituents at the prochiral carbon are highly attractive, because of the ease of installing various types of functionalities at the α-methylene group of 1,3-diketones.[4] Therefore, these approaches have been explored extensively, including aldol-type,[5] reduction reactions,[6] and others[7] to deliver bicyclic [m,n,o] products.

Scheme 1. Selected Molecules with Benzocyclic Framework



Given the convenience of difunctionalization of unsaturated bonds to synthesize various vicinal carbon−carbon or carbon−heteroatom bonds in a single step from simple precursors, it has been extensively studied over recent decades, particularly in relation to transition-metal catalysis.[8] However, studies on additional tandem transformations with the carbon−metal intermediate after the alkene insertion step are much less common. Therefore, we hypothesized that such tandem transformation may provide a convenient method to construct polycyclic compounds with multichiral centers by merging alkene difunctionalization and desymmetric strategy. To the best of our knowledge, no examples of enantioselective desymmetrizations involving the difunctionalization of styrenes have been described in the literature.

Since the discovery of stoichiometric borylcupration of alkenes by Sadighi and co-workers,[9] copper-catalyzed asymmetric borylative difunctionalization of olefins has drawn increasing attention, because of the robustness and versatility of organoboron compounds.[10] Although this chiral CuBPin species, initiated from copper catalyst with B_2Pin_2 (bis(pinacolato)diboron), has been widely used in the difunctionalizations,[11−13] only a few enantioselective examples have been reported for tandem desymmetrization reactions.[14] In 2012, the Lam group reported a conjugate boration/aldol cyclization of enone diones (Scheme 2a).[14a] However, α,β-unsaturated carbonyl compounds were necessary to form the copper enolate intermediate to facilitate high selectivities in this transformation and poor diastereoselectivities were observed in

Received: June 25, 2019

DOI: 10.1021/acs.orglett.9b02199
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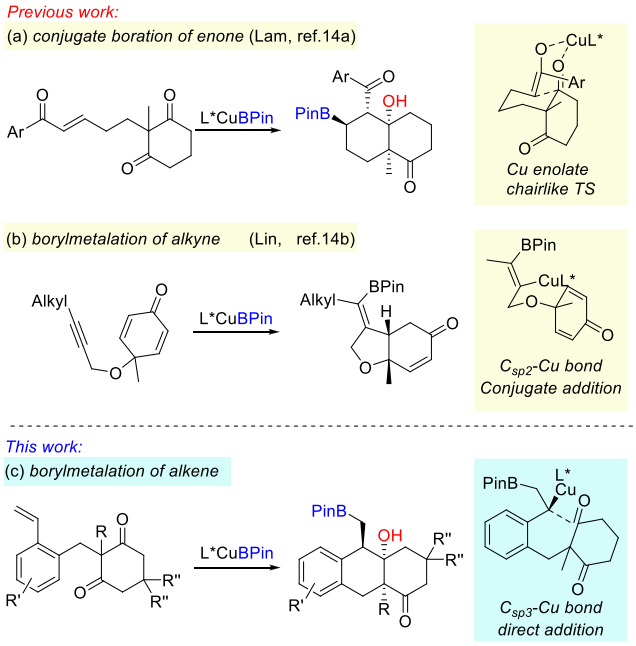
Scheme 2. Enantioselective Desymmetric Addition Initiated with CuBPin and Unsaturated Bonds

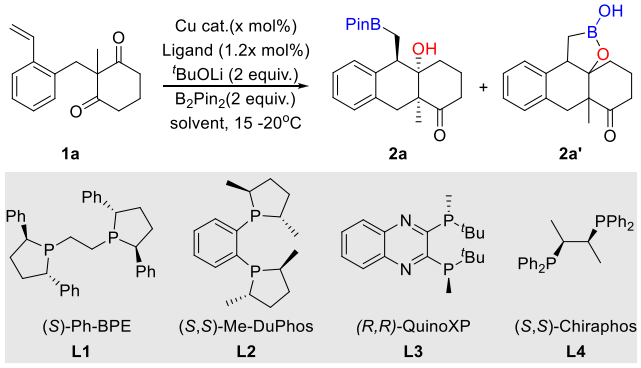


the presence of enones bearing electron-withdrawing substituents (for instance, the trifluoromethyl group). Meanwhile, the Lin group disclosed an asymmetric borylative cyclization of cyclohexadienone-containing 1,6-enynes where a conjugate addition of an alkenyl-Cu species to an enone was proposed but only alkyne compounds were used (Scheme 2b).[14b] Besides these very active substrates, this type of reaction with styrenes is much more challenging and remains an unresolved matter. A well-fixed chairlike [6,6] bicyclic ring system and metal enolate can be formed in the transition state for the α,β-unsaturated carbonyl substrates, but not for styrenes. In addition, the highly enantioselective direct addition of the C_{sp3}−Cu bond to ketones rather than an aldol or Michael-type addition is challenging and suffers from many issues, such as poor enantioselectivity, low diastereoselectivity, or the required use of very specific substrates.[15,16] Therefore, development of a novel method suitable for the styrenes is still in high demand. Herein, we report the enantioselective Cu-catalyzed desymmetrization reaction of 1,3-diketones through the borylcupration of styrenes, which provides access to three optically active carbon centers, including one chiral quaternary and one chiral tetrasubstituted carbon, as well as the polycyclic skeleton in excellent enantioselectivities and high yields (Scheme 2c).

Initial investigations into this process focused on employing compound **1a** as the model substrate to react with B_2Pin_2 under the reaction conditions with CuCl as the catalyst and a chiral biphosphine ligand in the presence of ^{t}BuOLi as the base. An evaluation of ligands revealed (*S*)-Ph-BPE (**L1**) to be superior to all others tested, such as (*S*,*S*)-Me-DuPhos, (*R*,*R*)-QuinoXP, (*S*,*S*)-Chiraphos (Table 1, entries 1−4). The use of **L1** as the ligand afforded the desired product **2a** with high enantioselectivity but in moderate yield, as well as a significant quantity of a side product **2a′**. To minimize this undesired product, a range of solvents were studied (Table 1, entries 5−8). Although varying the solvent has minimal impact on enantioselectivity, 2-MeTHF was shown to give the highest ratio of **2a**/**2a′** and a high yield of target product (Table 1, entry 8). More importantly, only one single *syn* diastereoisomer of product **2a** was detected under these conditions.

With suitable conditions identified, we next explored the scopes of this transformation with a variety of substrates bearing different functional groups on the aryl skeletons, and representative examples are summarized in Table 2. Generally,

Table 1. Optimization of Reaction Conditions[a]

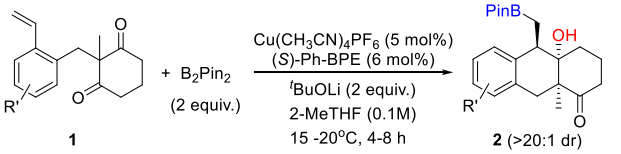


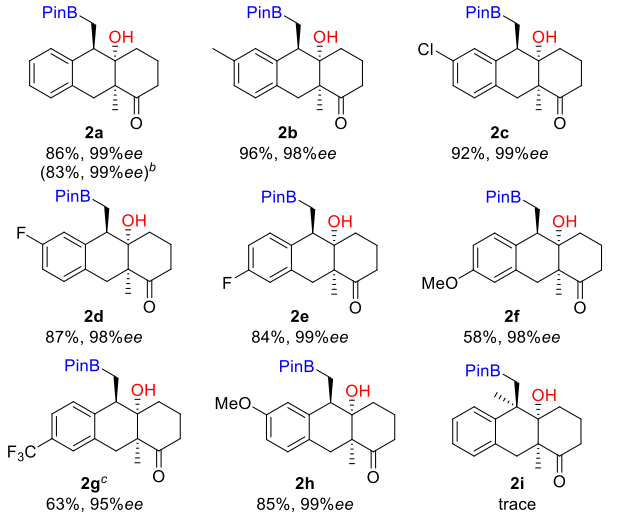
entry	Cu cat. (*x*)	ligand	solvent	**2a** (%)	enantiomeric excess, ee[b] (%)	**2a**/**2a′**
1	CuCl (10)	**L1**	THF	58	94	3.4/1
2	CuCl (10)	**L2**	THF	39	23	3/1
3	CuCl (10)	**L3**	THF	28	26	1/1
4	CuCl (10)	**L4**	THF	37	94	3/1
5[c]	$Cu(CH_3CN)_4PF_6$ (5)	**L1**	THF	85	98	4/1
6	$Cu(CH_3CN)_4PF_6$ (5)	**L1**	TBME	23	n.d.[d]	2.5/1
7	$Cu(CH_3CN)_4PF_6$ (5)	**L1**	Et_2O	52	97	>13/1
8	$Cu(CH_3CN)_4PF_6$ (5)	**L1**	2-MeTHF	94	99	13/1

[a]The reaction was conducted in 0.1 mmol scale. For the details on the experiment procedure, see the Supporting Information. Yields and the ratios of **2a**/**2a′** were determined by ^{1}H NMR with CH_2Br_2 as an internal standard. [b]The ee values were determined by chiral HPLC analysis. [c]At 0 °C. [d]Not determined.

DOI: 10.1021/acs.orglett.9b02199
Org. Lett. XXXX, XXX, XXX−XXX

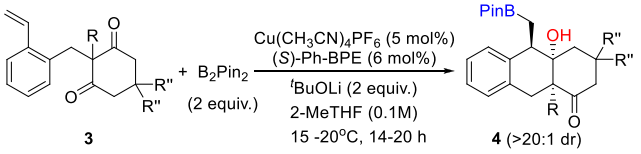
Table 2. Scopes with Respect to the Substituents on the Styrenes[a]

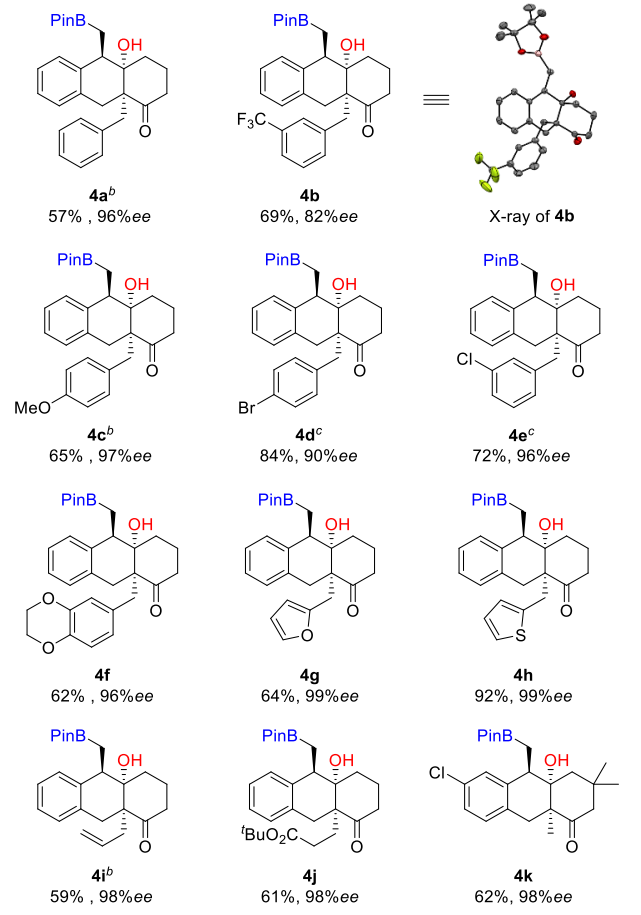




[a]The reaction was conducted in 0.2 mmol scale under the standard conditions, and isolated yields were given. The ee values were determined by chiral HPLC analysis. For all tested samples, the products with a diastereomeric ratio (dr) of >20:1 were found. [b]On 1 mmol scale. [c]The ee value was determined on the corresponding alcohol, which was obtained by oxidation of BPin.

Table 3. Scopes with Respect to the Substituents on the Diketones[a]





[a]The reaction was conducted in 0.2 mmol scale under the standard conditions, and isolated yields were given. The ee values were determined by chiral HPLC analysis. For all tested samples, the products with a diastereomeric ratio (dr) of >20:1 were found. [b]The ee value was determined on the corresponding alcohol, which was obtained by oxidation of BPin. [c]CuCl (5 mol %) was used as the catalyst.

the compounds with electron-neutral, electron-donating, or electron-withdrawing substituents, as well as groups on various positions, reacted smoothly to give the corresponding products in high yields and excellent enantioselectivities. For instance, alkyl group (**2b**) and halide groups (**2c**−**2e**) were well-tolerated under these conditions to afford the desired targets in high yields. The CF_3 (**2g**) and ether group (**2f**, **2h**) remained intact. For all the tested samples, only one single *syn* diastereoisomer of products **2** was isolated. However, if a 1,1-disubstituted aryl alkene was used (**2i**), the corresponding product was not obtained under these conditions.

In the meantime, alternative substituents on the 1,3-diketone part were studied. From Table 3, we can see that the prochiral carbon of the 1,3-diketones can tolerate a wide variety of functionalities. In addition to substrates bearing a methyl group, a benzyl group (**3a**) can also be attached at this position. Those with different electronic properties, such as a CF_3 (**3b**) or a methoxy (**3c**) group on the benzyl substituent, were successfully converted to the borylation products in similar yields, with moderate to high levels of enantioselectivities. Meanwhile, the absolute stereochemistry was determined for compound **4b** by X-ray crystallography, and the configuration of all other products is assigned by analogy. Halide substituents at various positions (**3d**, **3e**) also afforded desired products with good yields and ee values in the presence of CuCl as the catalyst. The substrate with benzodioxan (**3f**) was well-tolerated, and compounds containing heterocyclic skeletons such as furan (**3g**) and thiophene (**3h**) were all readily transformed under the current conditions. Other substituents, including allylic (**3i**) and ester (**3j**), were also investigated and the desired addition products were formed in high yields with excellent enantioselectivities. This desymmetrization conditions could also be applied to compounds with substituents on the cycle of 1,3-diketone ring. As demonstrated with substrate **3k**, a good yield and enantioselectivity was achieved within this protocol. And again, only one single *syn* diastereoisomer of product **4** was isolated. Unfortunately, the reaction with diketones bearing 5-membered rings cannot work well under these conditions.

In an effort to investigate the borylation process in the presence of a variety of additives, we further studied the functional group tolerance of this transformation further (see Figure 1).[17] We found that an aryl ester, aryl amide, thioether, dimethylaniline, protected phenol, alkyl ether, protected alkyl

DOI: 10.1021/acs.orglett.9b02199
Org. Lett. XXXX, XXX, XXX−XXX

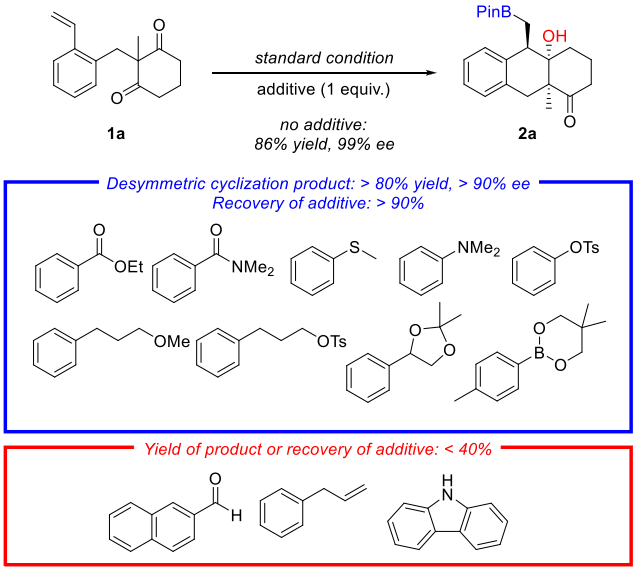
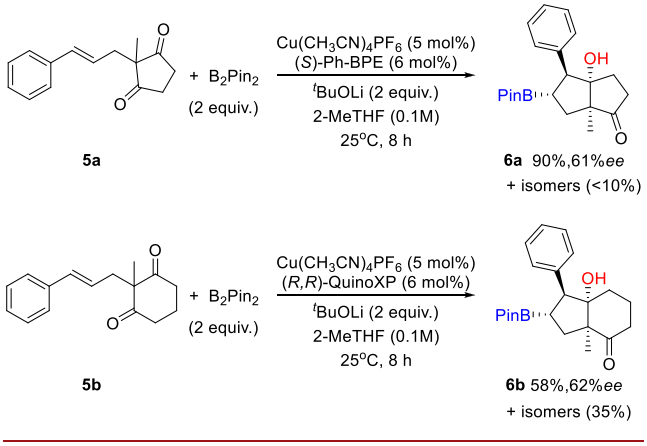


Figure 1. Compatibility of functional groups (each additive was examined individually).

alcohol, ketal, and aryl boronic acid neopentyl ester were all tolerated and had little or no impact on the yield and enantioselectivity of the product. Meanwhile, the additive can be recovered almost quantitatively. However, the reaction was suppressed in the presence of aldehyde, allylbenzene, or carbazole.

The scope of this enantioselective desymmetrization reaction was extended to the internal styrenes (see Scheme 3). When substrate **5a** was used under these conditions,

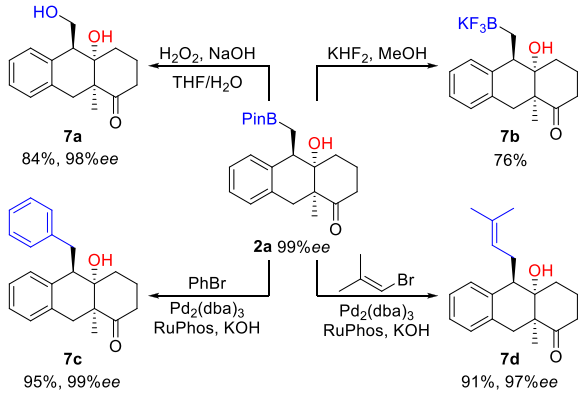
Scheme 3. Transformation of Internal Styrene



compound **6a** was isolated as the main isomer in high yield with moderate ee value.[18] However, the corresponding product for **5b** was only obtained in acceptable yield accompanied by some other unidentified isomers. It is notable that a higher diastereromeric ratio (>10:1) of **6b** to other isomers was detected when the achiral ligand 1,2-bis(diphenylphosphino)-benzene was used, suggesting that the diastereroselectivity is predominantly governed by the reaction conditions rather than the substrate, which is different from enolate-aldol cyclization reported in the previous work.[14a]

To further illustrate the utility of this transformation, the products were shown to be versatile intermediates by conversion to several useful compounds (see Scheme 4). 1,3-

Scheme 4. Representative Transformations of the Enantioenriched Cyclic Boronic Ester Products



Diols (**7a**) were obtained with high enantioselectivity via a simple oxidation process. The cyclization product can also be transformed to the potassium trifluoroborate salt (**7b**) in high yield. In addition, a cross-coupling reaction can be performed to introduce aryl (**7c**) or alkenyl (**7d**) groups into the skeletons.

In summary, we have reported a copper-catalyzed desymmetrization reaction of 1,3-diketones merged with difunctionalization of styrenes, where the α,β-unsaturated carbonyl structure was not necessary and highly selective direct addition process was supposed to be involved. The chiral polycyclic products with several functional groups showed good versatility and could be converted to many other products with C−O or C−C bond formations. This novel tandem asymmetric addition of a C−Cu bond to a ketone initiated with a CuBPin species exhibits excellent step economy and huge potential synthetic utility. Further investigations using this method in more-complex molecular synthesis is ongoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02199.

Experimental procedures and spectroscopic data for new compounds (PDF)

Accession Codes

CCDC 1920286 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.

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DOI: 10.1021/acs.orglett.9b02199
Org. Lett. XXXX, XXX, XXX−XXX

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the "1000 Yonth Talents Plan", Shanghai Pujiang Program, NFS of China (Grant No. 21801188), and Tongji University for financial support. Many thanks to Prof. G. Yin (Wuhan University) and Prof. Q. Cai (Fudan University) for their helpful discussion. We thank Ms. Alison McGonagle for polishing the manuscript.

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Org. Lett. XXXX, XXX, XXX−XXX