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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Communication

Stereodivergent Synthesis of Enantioenriched 2,3-Disubstituted Dihydrobenzofurans via a One-Pot C−H Functionalization/Oxa-Michael Addition Cascade

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Cite This: J. Am. Chem. Soc. 2021, 143, 8583−8589
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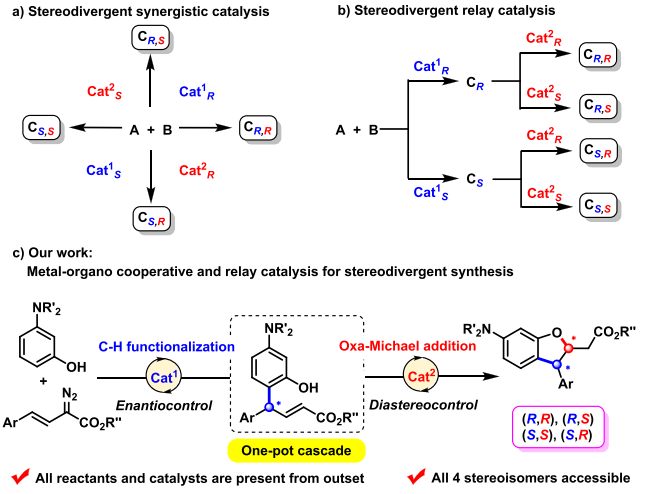
ABSTRACT: A one-pot rhodium-catalyzed C−H functionalization/organocatalyzed oxa-Michael addition cascade reaction has been developed. This methodology enables the stereodivergent synthesis of diverse 2,3-disubstituted dihydrobenzofurans with broad functional group compatibility in good yields with high levels of stereoselectivity under exceptionally mild conditions. The full complement of stereoisomers of chiral 2,3-disubstituted dihydrobenzofurans and 3,4-disubstituted isochromans could be accessed at will by appropriate permutations of the two chiral catalysts. The current work provides a rare example of two chiral catalysts independently controlling two contiguous stereogenic centers subsequently via a two-step reaction in a single operation.

As we all know, bioactive compounds containing n stereogenic centers may have 2^n stereoisomers, while for pharmaceutical molecules, their absolute and relative configurations are often relevant to their biological activities.[1] Consequently, it is meaningful to develop reliable synthetic methodologies for the construction of all stereoisomers using readily available starting materials. However, diastereoselectivity control is a persistent challenge in most current catalytic systems with multiple stereocenters forming, mainly ascribed to one of the diastereomers often being inherently preferred, thus resulting in the prevention of the achievement of all stereoisomers.[2,3] In recent years, merging two or more catalysts in one reaction to realize a transformation unattainable by an individual catalyst alone has emerged as a powerful strategy for creating complex molecular frameworks.[4−6] In this regard, some striking strategies have been developed in the past decade. Since the pioneering work of Carreira and co-workers in 2013,[7] a synergistic dual-catalysis tactic (Scheme 1a) has received intense focus in the area of divergent synthesis. This ingenious design opens up a whole new area and enables an efficient and rapid way to access all four stereoisomers of a target compound containing two chiral centers by the combination of two different chiral catalysts, which simultaneously activate two different substrates, independently. Despite this impressive progress,[8,9] stereodivergent systhesis via relay catalysis (Scheme 1b) is still in its infancy thus far.[10,11] Different from the most synergistic catalysis where only one chemical bond is formed, two or more chemical bonds are formed in series in cascade or tandem reactions via relay catalysis. The previously formed stereocenter would more likely influence the effect of the second catalyst; thus, controlling the overall regio- and stereoselectivity of the reaction becomes rather difficult. The ideal solution to this problem would be that each individual catalysis could proceed in a highly stereospecific manner with no stereochemical interaction.

Scheme 1. (a) Stereodivergent Synergistic Catalysis, (b) Stereodivergent Relay Catalysis, and (c) Our Strategy for Divergent Synthesis of Enantioenriched 2,3-Disubstituted Dihydrobenzofurans



Enantiomerically enriched 2,3-disubstituted dihydrobenzofurans have received considerable attention for their frequent occurrence in numerous biologically active natural products and pharmacologically relevant therapeutic agents.[12] Consequently, a variety of elegant strategies have been developed for their asymmetric synthesis.[13−18] However, a stereo-

Received: April 1, 2021
Published: June 1, 2021

https://doi.org/10.1021/jacs.1c03498
J. Am. Chem. Soc. 2021, 143, 8583−8589

divergent synthesis of this valuable framework that allows for full control over the two vicinal stereogenic centers has not been disclosed.

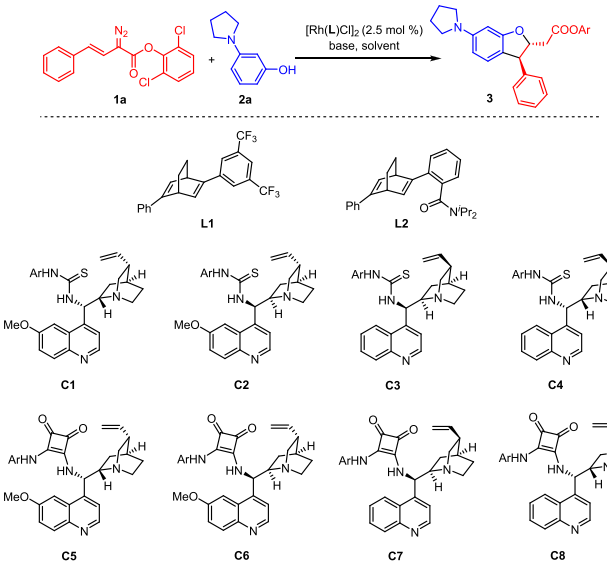
In our prior work on rhodium(I) carbene[19] directed enantioselective C−H functionalization of aniline derivatives,[19g] we realized the potential of accessing enantioenriched 2,3-disubstituted dihydrobenzofurans. Encouraged by this result, we therefore speculated whether stereodivergent systhesis of all four stereoisomers of 2,3-disubstituted dihydrobenzofurans could be achieved through a one-pot cascade C−H functionalization/oxa-Michael addition[20] via relay catalysis in the presence of an appropriate chiral organobase catalyst in combination with the chiral rhodium/diene catalyst (Scheme 1c). However, the development of such a dual-catalytic relay catalysis system is distinctively challenging. One possible challenge associated with the combination of a rhodium complex and organobase catalyst in one pot is the catalysts' incompatibility and inhibition. Therefore, employing a suitable organocatalyst that would enable the oxa-Michael addition with high stereocontrol while maintaining the efficiency of a rhodium catalyst in the initial C−H functionalization step is the key to success. Additionally, an intramolecular asymmetric oxa-Michael addition of *α,β*-unsaturated esters remains less explored probably due to the intrinsic low electrophilicity of *α,β*-unsaturated esters as the Michael acceptor and poor reactivity of oxygen as a nucleophile.[21] Furthermore, for most cyclic compounds with two adjacent stereocenters, one of the diastereomers often can be accessed easily due to its natural preference, while another diastereomer is normally inaccessible, as overriding the natural preference is usually difficult.[2] Herein, we report our development of an efficient method that allows access to the full complement of stereoisomers of chiral 2,3-disubstituted dihydrobenzofurans and 3,4-disubstituted isochromans via a stereodivergent relay catalysis.

To validate the feasibility of our proposed one-pot cascade reaction, we initiated our study by examining the one-pot reaction between **1a** and **2a** in the presence of [Rh((*R,R*)-**L1**)Cl]$_2$ and NEt_3 in CH_2Cl_2 at room temperature. As a result, the *anti* product **3a** with a 2*R*,3*S* configuration was obtained in almost quantitative yield with high relative and absolute stereoselectivity (84:16 dr, 94% ee) (Table 1, entry 1). As the enantioselectivity of the initial C−H functionalization would play a pivotal role in influencing the following stereoselectivity, we carried out further investigations on chiral diene ligands. Pleasingly, (*R,R*)-**L2** was found to show the best performance (entry 2). With **L2** as the optimal ligand, we turned our attention to find suitable organocatalysts for the following oxa-Michael addition in a highly stereospecific manner.

Inspired by the excellent catalytic performance of cinchona alkaloid based organocatalysts[22] in asymmetric oxa-Michael reaction, we first evaluated four commercially available natural cinchona alkaloids (entries 3−6). To our delight, the *anti* product (2*R*,3*S*)-**3a** was delivered in good yield with 96:4 dr and 98% ee when cinchonine (CN) was used, while a reverse of the diastereoselectivity (*anti*:*syn* 48:52) was observed with the use of cinchonidine (CD) (entry 5 vs entry 6). These results demonstrate that the cinchona alkaloid catalysts are able to control the configuration of the newly formed carbon stereocenter likely by the formation of different types of hydrogen bond interactions with the initial C−H functionalization products, which suggested that the combined use of [Rh((*R,R*)-**L2**)Cl]$_2$ and an appropriate cinchona alkaloid based organocatalyst might result in highly diastereoselective formation of the desired product. Encouraged by these promising results, we further evaluated a series of cinchona alkaloid derived bifunctional organocatalysts (**C1**−**C8**, Ar = 3,5-$(CF_3)_2C_6H_3$, entries 7−14). To our delight, quinine-derived thiourea **C1** gave the best result in terms of both diastereoselectivity (*anti*:*syn* 98:2) and enantioselectivity (99% ee) (entry 7). With cinchonine-derived thiourea **C3**, the reaction occurred to give the product in favor of the (2*S*,3*S*)-*syn* diastereomer (*anti*:*syn* 22:78) and with high ees for both isomers (entry 9). Very gratifyingly, a nearly perfect diastereo- and enantiocontrol could be achieved by replacing the solvent CH_2Cl_2 with toluene (entries 16 and 17).

To showcase the stereodivergent synthesis of the complete set of stereoisomeric products, we conducted the one-pot cascade experiments under the above optimized reaction

Table 1. Evaluation of Reaction Conditions[a]



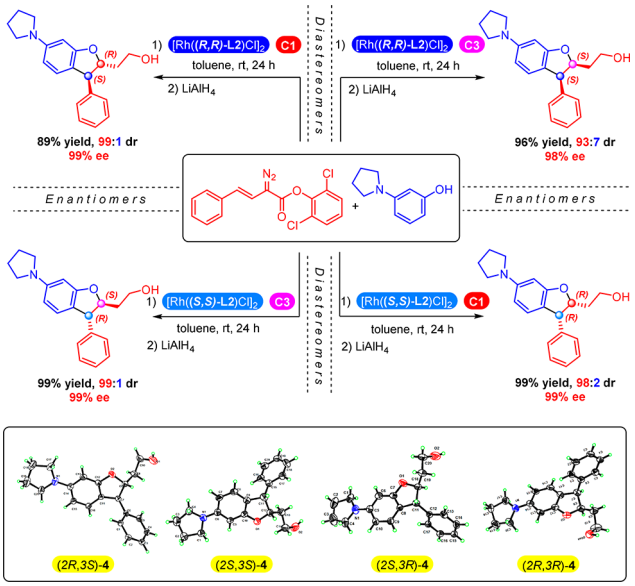
entry	ligand	base	solvent	yield (%)[b]	dr (*anti*:*syn*)[c]	ee (%)[c]
1[d]	(*R,R*)-**L1**	NEt_3	DCM	90	84:16	94, 94
2[d]	(*R,R*)-**L2**	NEt_3	DCM	85	85:15	97, 97
3	(*R,R*)-**L2**	QN	DCM	94	62:38	93, 99
4	(*R,R*)-**L2**	QD	DCM	84	95:5	96, –
5	(*R,R*)-**L2**	CN	DCM	90	96:4	98, –
6	(*R,R*)-**L2**	CD	DCM	88	48:52	91, 99
7	(*R,R*)-**L2**	**C1**	DCM	84	98:2	99, –
8	(*R,R*)-**L2**	**C2**	DCM	76	22:78	78, 99
9	(*R,R*)-**L2**	**C3**	DCM	78	22:78	88, 99
10	(*R,R*)-**L2**	**C4**	DCM	86	98:2	98, -
11	(*R,R*)-**L2**	**C5**	DCM	84	96:4	97, -
12	(*R,R*)-**L2**	**C6**	DCM	87	27:73	68, 99
13	(*R,R*)-**L2**	**C7**	DCM	89	25:75	64, 99
14	(*R,R*)-**L2**	**C8**	DCM	88	96:4	97, –
15	(*R,R*)-**L2**	**C1**	$CHCl_3$	84	99:1	99.7, –
16	(*R,R*)-**L2**	**C1**	toluene	89	99:1	99.9, –
17	(*R,R*)-**L2**	**C3**	toluene	96	7:93	–, 98

[a]Reactions were performed with **1a** (0.1 mmol) and **2a** (0.2 mmol) in the presence of 2.5 mol % of [Rh(**L**)Cl]$_2$ and 5.0 mol % of base in solvent (4.0 mL) for 24 h, unless otherwise noted. Abbreviations: QN, quinine; QD, quinidine; CN, cinchonine; CD, cinchonidine. [b]Isolated yield. [c]Determined by chiral HPLC after reduction with $LiAlH_4$. [d]Et_3N was added after C−H functionalization was finished.

https://doi.org/10.1021/jacs.1c03498
J. Am. Chem. Soc. 2021, 143, 8583−8589

conditions by combining the appropriate enantiomer of the chiral diene ligand **L2** with organothiourea catalyst **C1** or **C3**. Remarkably, the use of four available catalyst permutations allowed a stereodivergent access to the full matrix of stereoisomeric 2,3-disubstituted dihydrobenzofuran products uniformly in a highly diastereo- and enantioselective manner (Scheme 2). It is notable that the stereochemistries of all four stereoisomers were unambiguously confirmed by X-ray crystallography.

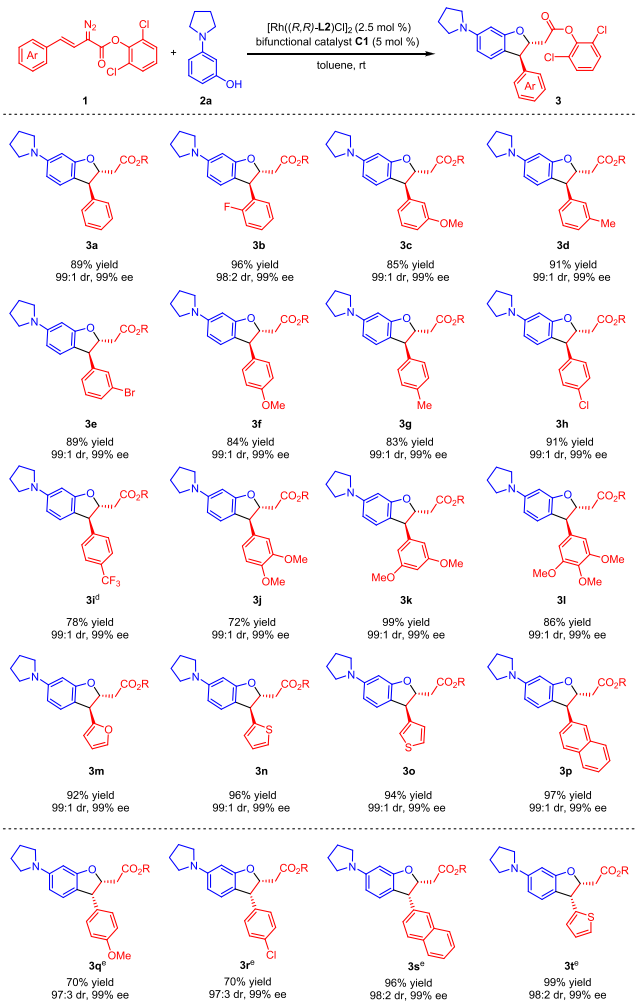
Scheme 2. Divergent Synthesis of All Four Isomers of 2,3-Disubstituted Dihydrobenzofurans



With the optimized conditions in hand, we set out to explore the generality of this one-pot cascade reaction. As shown in Scheme 3, arylvinyldiazoacetates with different electronic properties and different substitution patterns on the benzene ring were all tolerated, delivering the corresponding products in consistently good yields with excellent diastereo- and enantioselectivities. Notably, heteroaryl-substituted vinyldiazoacetate were also well-behaved, furnishing the chiral dihydrobenzofurans in good yields with excellent diastereo- and enantioselectivities (**3m−o,t**). Additionally, it was found that halogen could be retained during the process of LAH reduction, which may provide chances for further derivatization (**3e,h,r**). When [Rh((*R*,*R*)-**L2**)Cl]$_2$ was changed to [Rh((*S*,*S*)-**L2**)Cl]$_2$, a series of *syn* products were successfully obtained in highly enantiomerically enriched form (**3q−t**).

After exploration of the reaction scope of vinyldiazoacetates, the effects of aminophenol were subsequently evaluated (Scheme 4). We were pleased to find that the reaction is highly compatible with dimethyl, diethyl and dibenzyl substitution on the amine (**3aa−ac**). In addition to 3-(pyrrolidin-1-yl)phenol, 3-(piperidin-1-yl)phenol and 3-(azepan-1-yl)phenol are reactive as well, furnishing the nearly optically pure products **3ad,ae** in good yields. Moreover, 3-morpholinophenol and 3-(piperazin-1-yl)phenol were also competent substrates, affording the 2,3-disubstituted dihydrobenzofurans **3af−ah** in excellent diastereo- and enantioselectivities, abeit with slightly low yields. Furthermore, 3-(pyrrolidin-1-yl)phenol-containing substituents on benzenes were also suitable substrates for this transformation, providing

Scheme 3. Scope of Arylvinyldiazoacetates[a−c]



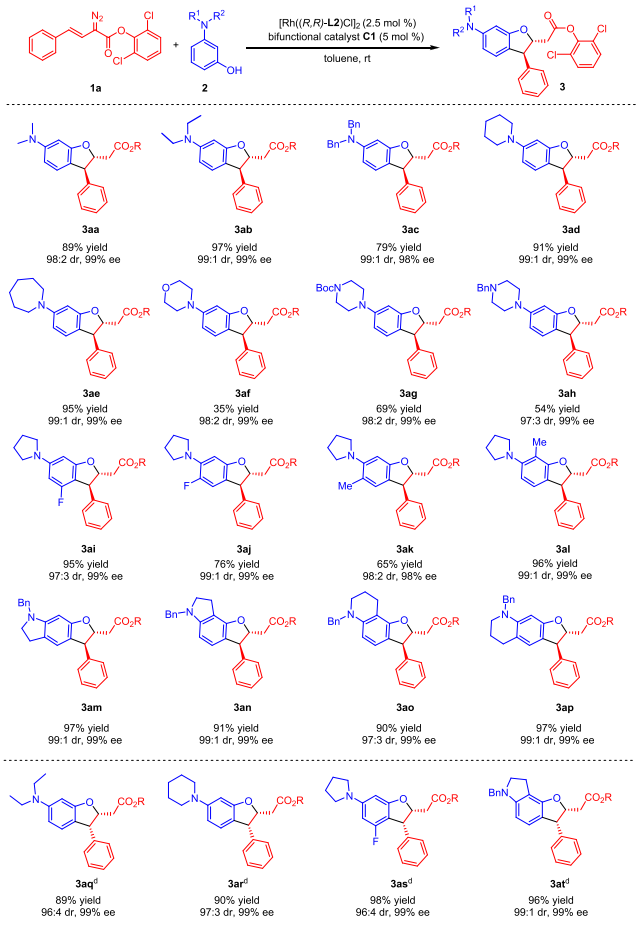
[a]Reactions were performed with **1** (0.1 mmol) and **2** (0.2 mmol) in the presence of 2.5 mol % of [Rh((*R*,*R*)-**L2**)Cl]$_2$ and 5 mol % of **C1** in toluene (4.0 mL) at room temperature for 24 h, unless otherwise noted. [b]Isolated yield. [c]For 3a−p, dr = *anti*:*syn*; for 3q−t, dr = *syn*:*anti*; the dr and ee were determined by chiral HPLC after reduction with $LiAlH_4$. [d]2.5 mol % of **C1** was used. [e][Rh((*S*,*S*)-**L2**)Cl]$_2$ was used instead of [Rh((*R*,*R*)-**L2**)Cl]$_2$.

the products **3ai−al** in good yields with high levels of stereoselectivity. It is quite remarkable that indoline and tetrahydroquinoline substrates were also well-behaved in this cascade reaction, providing a series of highly valuable enantiomerically pure benzo-fused tricyclic heterocycles **3am−ap** in good yields. Similarly, *syn* isomers (e.g., **3aq−at**) could be accessed by a combination of catalysts [Rh((*S*,*S*)-**L2**)Cl]$_2$ and **C1**. These results demonstrated that the current method provides a very reliable and powerful protocol for stereodivergent access to optically pure 2,3-disubstituted dihydrobenzofurans.

Encouraged by the above excellent results, we next wondered whether this one-pot tandem protocol could be further expanded to the stereodivergent synthesis of chiral 3,4-disubstituted isochromans,[23] other pharmaceutically useful frameworks.[24] To our disappointment, the reaction of **1a** with (3-(pyrrolidin-1-yl)phenyl)methanol under the standard conditions led to only a trace amount of the expected product. Fortunately, after careful investigation (see the Supporting

https://doi.org/10.1021/jacs.1c03498
J. Am. Chem. Soc. 2021, 143, 8583−8589

Scheme 4. Scope of Aminophenol[a–c]



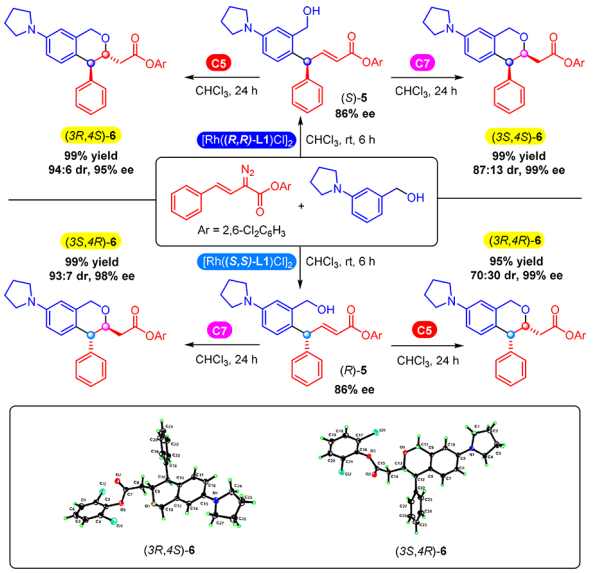
[a]Reactions were performed with **1** (0.1 mmol) and **2** (0.2 mmol) in the presence of 2.5 mol % of $[Rh((R,R)\text{-}\mathbf{L2})Cl]_2$ and 5 mol % of **C1** in toluene (4.0 mL) at room temperature for 24 h, unless otherwise noted. [b]Isolated yield. [c]For 3aa–ap, dr = *anti*:*syn*; for 3aq–at, dr = *syn*:*anti*; the dr and ee were determined by chiral HPLC after reduction with $LiAlH_4$. [d]$[Rh((S,S)\text{-}\mathbf{L2})Cl]_2$ was used instead of $[Rh((R,R)\text{-}\mathbf{L2})Cl]_2$.

Information for details), we were able to establish a stereodivergent process to obtain all four stereoisomers of 3,4-disubstituted isochroman (**6**) in good yields with high levels of stereoselectivities through a two-step sequence by using different catalyst permutations (Scheme 5).

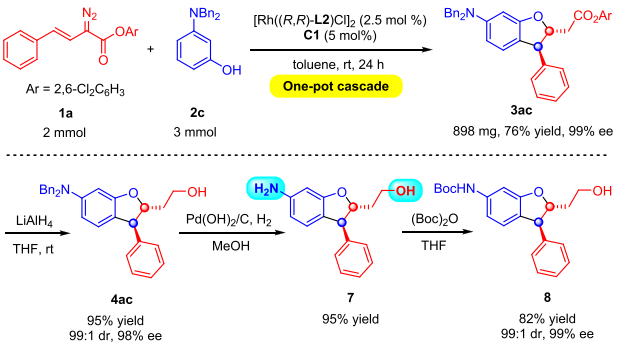
To demonstrate the practicality of this methodology, the one-pot cascade reaction of **1a** and **2c** was carried out on a 2 mmol scale under the standard conditions. As shown in Scheme 6, the product **3ac** was obtained in comparable yield with the same high levels of diastereoselectivity and enantioselectivity. LAH reduction and *N*-debenzylation with $Pd(OH)_2/C$ and H_2 afforded the pharmceutially interesting chiral amino alcohol **8** containing a dihydrobenzofuran-incorporated moiety with no loss of enantiopurity.

In summary, we have developed a stereodivergent relay catalysis strategy for the rapid synthesis of optically active 2,3-disubstituted dihydrobenzofurans. This method successfully combines a rhodium/chiral diene-catalyzed enantioselective C–H functionalization with a cinchona alkaloid derived thiourea catalyst controlled diastereoselective intramolecular oxa-Michael addition in a simple one-pot procedure. By an

Scheme 5. Divergent Synthesis of All Four Isomers of 3,4-Disubstituted Isochromans



Scheme 6. Gram-Scale Synthesis of 3ac and Its Derivatization



appropriate permutation of the chiral rhodium catalyst and organocatalyst, all four stereoisomers of the products could be accessed at will in a highly enantiomerically pure form. Moreover, this dual-catalytic strategy could be extended to the stereodivergent synthesis of enantioenriched 3,4-disubstituted isochromans. We believe that this predictable assembly of chiral dihydrobenzofuran and isochroman structures will provide new opportunities for their application in drug discovery. Of particular note, *this work provides a rare example of two chiral catalysts independently controlling two contiguous stereogenic centers subsequently via a two-step reaction in a single operation.*

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c03498.

Experimental procedures and spectroscopic data of all new compounds (PDF)

Accession Codes

CCDC 1978705, 2073588, 2073593, 2073595–2073596, and 2073599 contain 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_

https://doi.org/10.1021/jacs.1c03498
J. Am. Chem. Soc. 2021, 143, 8583–8589

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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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21971103, 21672229), the Guangdong Provincial Key Laboratory of Catalysis (2020B121201002), and the Shenzhen Science and Technology Innovation Commission (JCYJ20200109141408054) for financial support. We are especially grateful to Dr. Stefan Abele at Idorsia Pharmaceuticals Ltd., Switzerland, for his very generous donation of the key intermediate (1*R*,4*R*)-5-phenylbicyclo[2.2.2]oct-5-en-2-one for diene preparation.

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