ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

Facile Construction of Structurally Diverse Thiazolidinedione-Derived Compounds via Divergent Stereoselective Cascade Organocatalysis and Their Biological Exploratory Studies

Yongqiang Zhang,[†] Shengzheng Wang,[†] Shanchao Wu,[†] Shiping Zhu,[†] Guoqiang Dong,[†] Zhenyuan Miao,[†] Jianzhong Yao,[†] Wannian Zhang,*[,†] Chunquan Sheng,*[,†] and Wei Wang*[,‡,§]

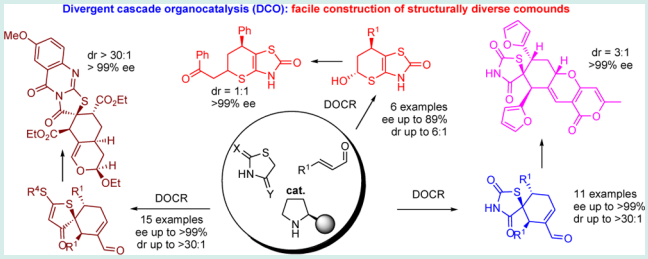
[†]Department of Medicinal Chemistry, School of Pharmacy, Second Military Medical University, 325 Guohe Road, Shanghai 200433, P. R. China

[‡]Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131-0001, United States

[§]School of Pharmacy, East China University of Science and Technology, Shanghai 200237, P. R. China

Supporting Information

ABSTRACT: In this article, we present a new approach by merging two powerful synthetic tactics, divergent synthesis and cascade organocatalysis, to create a divergent cascade organocatalysis strategy for the facile construction of new "privileged" substructure-based DOS (pDOS) library. As demonstrated, notably 5 distinct molecular architectures are produced facilely from readily available simple synthons thiazolidinedione and its analogues and α,β-unsaturated aldehydes in 1−3 steps with the powerful strategy. The beauty of the chemistry is highlighted by the efficient formation of structurally new and diverse products from structurally close reactants under the similar reaction conditions. Notably, structurally diverse spirothiazolidinediones and -rhodanines are produced from organocatalytic enantioselective 3-component Michael−Michael−aldol cascade reactions of respective thiazolidinediones and rhodanines with enals. Nevertheless, under the similar reaction conditions, reactions of isorhodanine via a Michael−cyclization cascade lead to structurally different fused thiopyranoid scaffolds. This strategy significantly minimizes time- and cost-consuming synthetic works. Furthermore, these molecules possess high structural complexity and functional, stereochemical, and skeletal diversity with similarity to natural scaffolds. In the preliminary biological studies of these molecules, compounds **4f**, **8a**, and **10a** exhibit inhibitory activity against the human breast cancer cells, while compounds **8a**, **9a**, and **9b** display good antifungal activities against *Candida albicans* and *Cryptococcus neoformans*. Notably, their structures are different from clinically used triazole antifungal drugs. Therefore, they could serve as good lead compounds for the development of new generation of antifungal agents.



KEYWORDS: *divergent cascade organocatalysis, thiazolidinedione derivatives, structural diversity, anticancer, antifungal*

INTRODUCTION

The diversification of "privileged" structures[1] using diversity-oriented synthesis (DOS),[2] defined as rational DOS or privileged substructure-based DOS (pDOS) strategy,[2c,3] has proven to be a fruitful tool to rapidly discover biologically active lead compounds.[4] However, one of the important challenges in the construction of pDOS libraries is to identify or develop efficient synthetic methods to creatively and facilely construct diverse molecular architectures embedded with privileged substructures.[5]

Organocatalytic cascade reactions have been demonstrated as powerful tools for the facile assembly of diverse and complex frameworks in "one-pot" operations with high enantio- and diastereoselectivity.[6] Moreover, these processes have been utilized in target-oriented synthesis.[7] Nevertheless, their applications in DOS is limited.[8,9] Driven by our research interest in DOS and drug discovery, we recently have initiated a program aimed at incorporating cascade organocatalysis into DOS.[10] A new divergent organocatalytic cascade approach was introduced into DOS[11] by merging two powerful synthetic strategies, divergent synthesis and cascade catalysis.[12] In divergent synthesis, the power of the strategy is fueled by the use of similar reactants under the same reaction conditions or the different reactants under the same/similar reaction conditions to generate different products. It is expected that incorporation of organocatalytic enantioselective cascade reactions into the strategy allows for the generation of compounds with functional, stereochemical, and skeletal diversity. Therefore, this new strategy could significantly save cost and improve synthetic efficiency. Moreover, the use of

Received: February 18, 2013
Revised: April 15, 2013
Published: April 24, 2013

such an approach to building privileged substructure derived libraries with structural diversity can delivers drug like molecules and thereby offers the great possibility of identifying novel modulators for biological targets.

For the construction of pDOS libraries, it is crucial to identify a privileged substructure with the potential for synthetic transformations toward novel skeletons via the proposed divergent organocatalytic cascade approach (DOCA). It is recognized that heterocyclic thiazolidinedione, rhodanine and isorhodanine moieties units are featured in a number of molecules displaying a broad spectrum of biological activities, including antitumor, antibacterial, antiviral effect, etc. (Figure 1).[13] In particular, thiazolidinediones represent an important class of antidiabetic agents, such as rosiglitazone, troglitazone, and epalrestat (Figure 1).[14] In the construction of the privileged substructure based libraries using the DOCA, the reactants should be simple and readily available or easily prepared. Furthermore, they should be able to participate in organocatalytic cascade reactions in a divergent fashion. This is a formidable challenging task. To our knowledge, thiazolidinedione-based diversity oriented synthesis and the constitution of their corresponding DOS libraries with skeletal and stereochemical diversity is a largely untapped field.

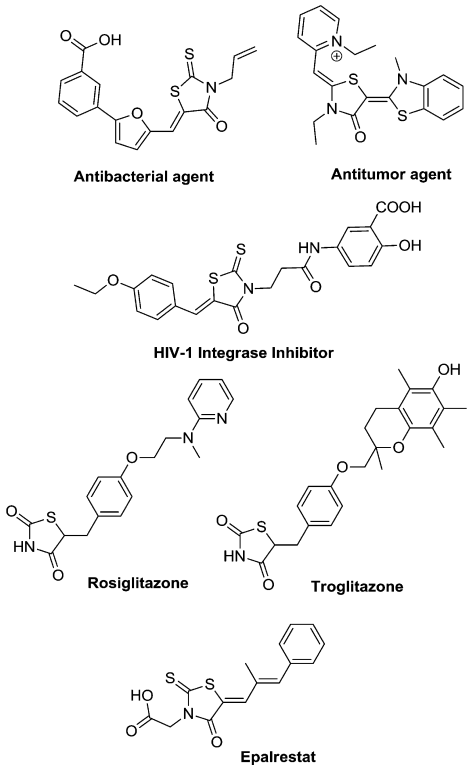
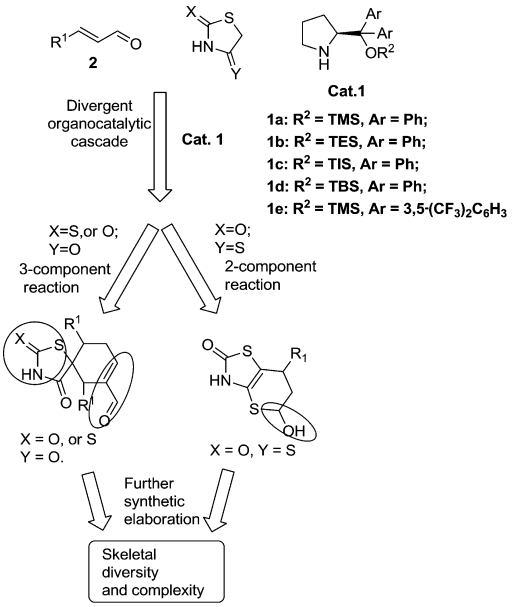


Figure 1. Representative structures of pharmaceutically relevant thiazolidinedione or rhodanine derivatives.

Herein, we wish to report the results of the investigation of the divergent, organocatalytic, enantioselective, cascade reactions between thiazolidinedione analogues and α,β-unsaturated aldehydes to yield diverse polyheterocyclic scaffolds with excellent stereoselectivity and to illustrate their efficiency in the generation of structural complexity and diversity of libraries (Scheme 1). Remarkably, by manipulation of the functional group reactivities in thiazolidinedione and rhodanine, and isorhodanine, respective organocatalytic enantioselective 3-component Michael–Michael–aldol and Michael–cyclization cascades with enals proceeds to give spiro-thiazolidinedione and -rhodanine frameworks and fused thiopyranoids, respectively, in a divergent manner.

Scheme 1. Construction of Functional, Stereochemical, and Skeletal Diversified Thiazolidinedione-Derived Library via Divergent Organocatalytic Cascades

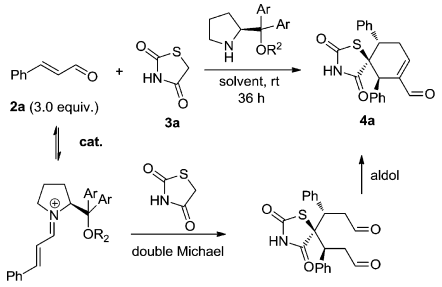


RESULTS AND DISCUSSION

Organocatalytic Enantioselective 3-Component Michael–Michael–Aldol Cascade Reaction of Thiazolidinedione with Enals: One-Pot Synthesis of Chiral Spiro-thiazolidinediones. Inspired by impressive organocatalytic asymmetric Michael–Michael–aldol cascade reaction in the synthesis of spiro-oxindoles,[15] we envisioned that such a process could be applied in reaction of thiazolidinedione (**3**) with enal **2** in a 3-component reaction (Table 1). Double Michael reaction of thiazolidinedione (**3**) with enal **2** (2 equiv) produces an adduct, which undergoes a subsequent intramolecular aldol reaction, leading to a spiro-thiazolidinedione **4**. To probe the feasibility, we initiated the study by reaction of thiazolidinedione (**3**) with *trans*-cinnamaldehyde (**2a**) catalyzed by **1a** (20 mol %)[16] at rt (Table 1). To our delight, by performing the reaction in CH_2Cl_2, we were able to isolate desired product **4a** in 87% yield with excellent enantioselectivity and moderate diastereoselectivity (entry 1). The yield was dropped when 10 mol % **1a** was used (entry 2). Lower diastereoselectivity was observed in other solvents (entries 2–8) and additives (entries 9–12) screened. Then catalysts **1b–d** were examined (entries 13–15). Improved diastereoselectivity, but with lower yields, was obtained when a larger side chain moiety was introduced (**1b**, dr, 9:1, yield, 59%; **1c**, dr, 10:1, yield, 46%). Enhancing reaction concentration by using **1b** led to a better yield (entries 16–17). Finally, the optimal reaction condition was established in the presence of catalyst **1b** without an acid additive (entry 16) in terms of yield, diastereoselectivity, and enantioselectivity. It should be noted that our study is inconsistent with the previous report, in which, no desired product was obtained without acid as additive.[15b,c] The absolute configuration was determined by X-ray crystal structure analysis

dx.doi.org/10.1021/co400022r | ACS Comb. Sci. 2013, 15, 298–308

Table 1. Exploration and Optimization of Organocatalytic Michael−Michael−Aldol Cascade Reaction of Thiazolidinedione 3a with *trans*-Cinnamaldehyde 2a[a]



entry	cat	solvent	additive	yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	DCM	none	87	6.7:1	>99
2	**1a**[e]	DCM	none	30	nd[f]	>99
3	**1a**	toluene	none	37	nd[f]	>99
4	**1a**	THF	none	<5	nd[f]	nd[f]
5	**1a**	EtOH	none	55	2.6:1	>99
6	**1a**	MeCN	none	64	5.5:1	>99
7	**1a**	$CHCl_3$	none	73	3.7:1	>99
8	**1a**	$Cl(CH_2)_2Cl$	none	73	6.1:1	>99
9	**1a**	DCM	BA[g]	83	2.4:1	>99
10	**1a**	DCM	PNBA	64	2.5:1	>99
11	**1a**	DCM	AcOH	60	4.0:1	>99
12	**1a**	DCM	AcOK	64	4.2:1	>99
13	**1b**	DCM	none	59	9.0:1	>99
14	**1c**	DCM	none	45	10.0:1	>99
15	**1d**	DCM	none	77	6.4:1	>99
16	**1b**	DCM[h]	none	73	8.4:1	>99
17	**1b**	DCM[i]	none	67	9.7:1	>99

[a]Reaction conditions were as follows: **2a** (0.9 mmol), **3a** (0.3 mmol), and catalyst **1** (0.06 mmol) in solvent (3 mL) at rt to give **4a**. [b]Isolated yields. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC (see the Supporting Information). [e]cat (10 mol %) was used. [f]Not determined. [g]BA, benzoic acid; PNBA, *p*-nitrobenzoic acid. [h]Reaction was conducted with a concentration of 0.3 M. [i]Reaction was conducted with a concentration of 0.6 M.

of the product (**4a**) as (5S,6R,10S),[17] when *S*-chiral secondary amine (**1b**) was used as catalyst (Figure 2).

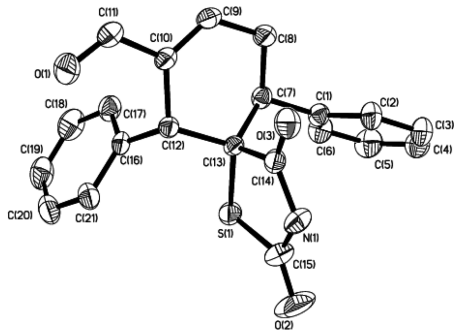
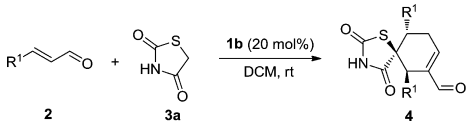


Figure 2. X-ray crystal structure of compound **4a**.

With the optimal reaction conditions in hand, the scope of the reaction of thiazolidinedione with α,β-unsaturated aldehydes **2** was explored next. As summarized in Table 2, excellent diastereo and enantioselectivities were obtained for enals bearing *p*-substituted aromatics and heterocyclics (entries 2−8). The diastereocontrol was less satisfying for substrates with o-substituted aryl groups (entries 9 and 10) although

Table 2. Substrate Scope in the Organocatalytic Cascade Reaction of Thiazolidinedione 3a with α,β-Unsaturated Aldehydes 2[a]

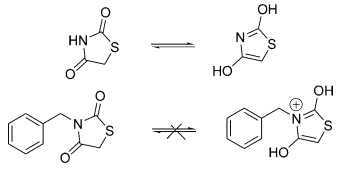


entry	R^1	*t* (h)	4	yield[b] (%)	dr[c]	ee[d] (%)
1	C_6H_5	36	**4a**	73	8.4:1	>99
2	*p*-BrC_5H_4	36	**4b**	83	6.6:1	>99
3	*p*-$MeOC_5H_4$	24	**4c**	75	7.3:1	>99
4	*p*-$Me_2NC_5H_4$	24	**4d**	89	>30:1	>99
5	*p*-$NO_2C_5H_4$	36	**4e**	64	12.4:1	>99
6	2-furyl	24	**4f**	90	22.3:1	>99
7	2-thienyl	24	**4g**	98	8.9:1	>99
8	2-naphthyl	36	**4h**	86	8.4:1	>99
9	*o*-$NO_2C_5H_4$	36	**4i**	80	2.4:1	>99
10	*o*-$MeOC_5H_4$	36	**4j**	79	3:1	>99
11	*n*-propyl	5	**4k**	trace	nd[e]	nd[e]

[a]Unless otherwise specified, see the Experimental Section. [b]Isolated yields. [c]Determined by ^{1}HNMR analysis. [d]The *ee* value of major diastereomer, determined by chiral HPLC (see the Supporting Information). [e]Not determined.

outstanding *ee* values were retained. Moreover, no spiro-thiazolidinedione product was detected for alkyl-substituted enals (entry 11). Notably, the process proceeded smoothly at a larger scale (1.5 mmol) with the similar results when **4f** was used an example. When *N*-benzyl-thiazolidinedione was reacted with compound **2a**, no desired product was obtained (data not shown), even with a base (e.g., DBU, K_2CO_3) as additive. It is suggested that thiazolidinedione can convert to an aromatic system to activate the methylene, whereas it is difficult for N-substituted thiazolidinedione to conduct this tautomerization (Scheme 2).

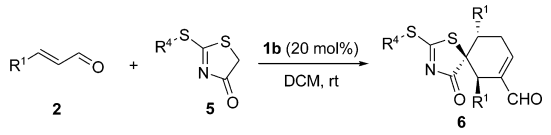
Scheme 2. Tautomerization of Thiazolidinediones



Organocatalytic Enantioselective Michael−Michael−Aldol Cascade Reaction of Rhodanine with Enals: One-Pot Synthesis of Chiral Spiro-rhodanines. Having developed a powerful **1b**-catalyzed Michael−Michael−aldol cascade reaction with thiazolidinediones, we questioned whether this strategy could be extended to rhodanines. New chiral spiro-rhodanines would be produced. To our delight, under the same reaction conditions, the cascade reactions between rhodanines and α, β-unsaturated aldehydes proceeded in even shorter reaction times (1−8 h) with good diastereoselectivity (3.9:1 to >30:1) and excellent enantioselectivities (>99% ee for all cases) despite relatively low yields (35−95%) (Table 3). The steric demand in rhodanine led to better diastereoselectivity (entries 1−10). In addition to aromatic enals, linear alkyl, furan and ester substituted enals can be tolerated (entries 11−16). Notably, as compared with the aryl-substituted enals, better drs were observed for these

dx.doi.org/10.1021/co400022r | ACS Comb. Sci. 2013, 15, 298−308

Table 3. Scope for the Reactions between Rhodanine and Its Derivatives 5 and α,β-Unsaturated Aldehydes 2[a]



2 5 6

entry	R^1/R^4	t (h)	6	yield[b] (%)	dr[c]	ee[d] (%)
1	C_6H_5/H	8	**6a**	96	3.9:1	>99
2	*n*-propyl/H	1.5	**6b**	56	7.5:1	>99
3	C_6H_5/Me	6	**6c**	88	3.7:1	>99
4	C_6H_5/*n*-butyl	6	**6d**	60	8.6:1	>99
5	C_6H_5/allyl	6	**6e**	57	4.7:1	>99
6	C_6H_5/Bn	6	**6f**	63	5.7:1	>99
7	C_6H_5/*p*-$NO_2C_6H_4CH_2$	6	**6g**	70	5.6:1	>99
8	C_6H_5/*o*-$FC_6H_4CH_2$	6	**6h**	61	7.8:1	>99
9	C_6H_5/*m*-$ClC_6H_4CH_2$	6	**6i**	60	8.5:1	>99
10	C_6H_5/naphthalen-2-methyl	6	**6j**	73	9.4:1	>99
11	2-furyl/Bn	6	**6k**	68	11:1	>99
12	CO_2Et/Bn	1	**6l**	95	>30:1	>99
13[e]	CO_2Et/Bn	2	**6l**	80	>30:1	>99
14	methyl/Bn	1	**6m**	44	>30:1	>99
15	*n*-propyl/Bn	1	**6n**	67	>30:1	>99
16	*n*-hexyl/Bn	1	**6o**	72	>30:1	>99

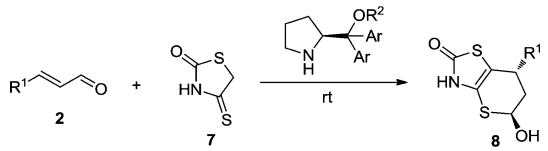
[a]Unless otherwise specified, see the Experimental Section. [b]Product isolated. [c]Determined by ^{1}HNMR analysis. [d]The *ee* value of the major diastereomer, determined by chiral HPLC (see Supporting Information). [e]At 1.6 mmol scale.

enals. Again, the reaction proceeded smoothly at a larger scale as well (1.6 mmol) with **2l** (entry 13).

Organocatalytic Enantioselective Michael−Cyclization Cascade Reaction of Isorhodanine with Enals: One-Pot Synthesis of Fused Thiopyranoids. Having demonstrated the high efficiency in the synthesis of structurally diverse spiro-thiazolidinediones using the divergent organocatalytic Michael−Michael−aldol cascade reactions with thiazolidinediones and rhodanines, we further explored the strategy for isorhodanine **7** (Table 4). Unexpectedly, under the similar reaction conditions, reactions of isorhodanine with enals underwent a Michael−cyclization cascade. A new structurally different fused thiopyranoid scaffold **8** with good enantioselectivity and stereoselectivity was constructed instead. It is noted that the reactions with isorhodanine were somewhat complicated. Only a small amount of desired product was observed under the reaction conditions (data not shown). Therefore, we took effort to further optimize the reaction conditions. Better *ee* values (up to 89%) were obtained when more bulky catalyst **1e** was used in toluene (entries 1−5). Lowering the temperature to −20 °C did not improve the stereoselectivity of the reaction but led to a lower yield (entries 3 and 5). It is noteworthy that the product can be purified through a simple washing and filtrating process due to the bad solubility of **8a** in hexane (see Experimental Section). The process served as a general approach to the thiopyranoids **8** under the optimized reactions. Generally good yields and enantioselectivities were attained with various enals bearing electron-neutral (entry 3), -withdrawing (entries 8 and 9), and -donating (entry 10) substituents. Furthermore, heterocyclic substituted enals were able to participate in the process. The steric effect is also limited (entry 10). A single crystal of the product (**8a**) obtained for X-ray crystallographic analysis allowed to determine its absolute configuration with (5*S*,7*S*) (Figure 3).[18]

Synthetic Elaboration of Chiral Spiro-thiazolidinediones and -rhodanines and Fused Thiopyranoids: Facile Construction of Natural-Product-like Complex Molecular Architectures through Simple Operation. We have shown the divergent organocatalytic cascade strategy as a powerful approach to construct structurally diverse, chiral privileged substructures from simple achiral substances in one-pot operation. The resulting products have complex structures containing multiple stereogenic centers and functionalities. They are expected to serve as good starting point for further synthetic elaboration to assemble more complex natural product-like molecules. Here we chose the products **4f**, **6l**, and **8a** as examples to produce new scaffolds with higher structural complexity and diversity (Scheme 3). Notably,

Table 4. Scope for the Reactions between Isorhodanine and α,β-Unsaturated Aldehydes[a]



2 7 8

entry	cat.	R^1	solvent	t (h)	8	yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	C_6H_5	toluene	10	**8a**	87	5.6:1	55
2	**1b**	C_6H_5	toluene	10	**8a**	84	3.0:1	79
3	**1e**	C_6H_5	toluene	10	**8a**	82	5.5:1	89
4	**1e**	C_6H_5	DCM	10	**8a**	54	5.5:1	79
5	**1e**[e]	C_6H_5	toluene	16	**8a**	50	5.3:1	90
6	**1e**	2-furyl	toluene	10	**8b**	87	5.5:1	56
7	**1e**	2-thienyl	toluene	10	**8c**	90	4.5:1	78
8	**1e**	*p*-$NO_2C_6H_4$	toluene	10	**8d**	56	5.4:1	79
9	**1e**	*p*-BrC_6H_4	toluene	10	**8e**	87	4.3:1	89
10	**1e**	*o*-$MeOC_6H_4$	toluene	10	**8f**	66	5.9:1	73

[a]Unless otherwise specified, see Experimental Section. [b]Isolated yields. [c]Determined by ^{1}HNMR analysis. [d]The *ee* value of the major diastereomer, determined by chiral-phase HPLC analysis of hydroxyl TBS-derived product (with TBSCl/imidazole/DMF) of **8** (see the Supporting Information). [e]The reaction was conducted at −20 °C.

dx.doi.org/10.1021/co400022r | ACS Comb. Sci. 2013, 15, 298−308

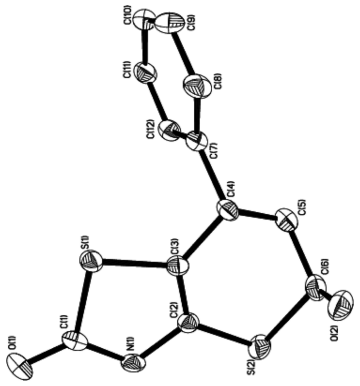
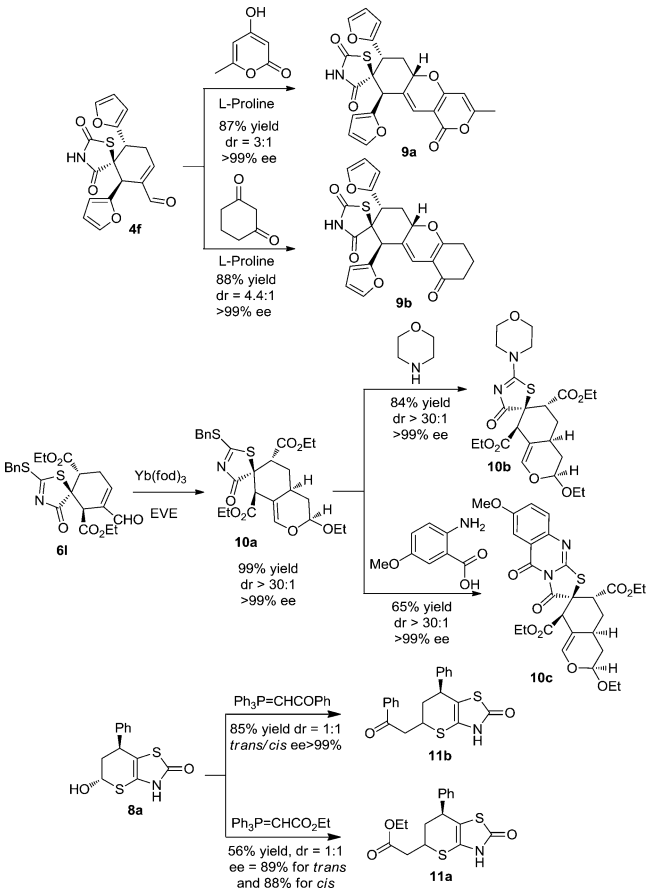


Figure 3. X-ray crystal structure of compound **8a**.

straightforward reactions involving only 1−2 steps enabled to create polyheterocyclic structures.

Scheme 3. Generation of Diverse and Complex Ring Systems from the Products of Divergent Organocatalytic Cascade Reactions



In the light of the pyran moiety being widely distributed in natural and biological active compounds,[19] L-proline catalyzed 3,3′-dipolar cycloaddition reactions of **4f** with 1,3-dicarbonyls were developed to form pyran and 2*H*-pyran rings (Scheme 3).[20] Fused pyrans **9a** and **b** incorporated into spiro-thiazolidinedione and spiro-rhodanine frameworks were successfully installed in high yields and with good enantioselectivity (*ee* up to >99%) and moderate diastereoselectivity (4:1 dr). It is noted that the fused thiopyranecycle and thiazolidine scaffolds are also reported to possess anticancer activity.[21] The hetero-Diels−Alder cycloaddition of **6l** to ethylvinylether (EVE) was carried out to create a new framework **10a** in excellent yield (99%) and stereoselectivity. Further treatment with morpholine and *o*-aminobenzoic acid gave new polyheterocyclic ring systems **10b**[22] and **10c**.[23] The absolute configurations of new scaffolds **9a** and **10a** were further assigned to be (5aS,5′S,7S,9S) and (3S,4aS,5′S,6S,8S) according to NOESY and ^{1}H NMR spectra (see Supporting Information) (Figure 4) on the basis of X-ray crystallographic

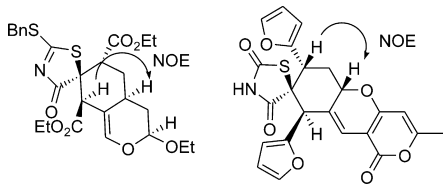


Figure 4. NOESY effects of compound **10a** and **9a**.

analysis of **8a**. Finally, new functionalities **11a** and **11b** were constructed by the simple Witting reactions of **8a** with high enantioselectivity (up to 99% *ee*).

Screening of the pDOS Library for Biological Studies. With the methodologies for the synthesis of spirothiazolidinedione, spiro-rhodanine and fused thiopyranoid libraries were completed, these compounds were screened for their antitumor and antifungal activities. In probe of anticancer properties, their inhibitory activity against three human cancer cell-lines, A549 (lung cancer), ZR-75-30 (breast cancer), and HCT116 (colon cancer), were determined using MTT assay.[24] As shown in Table 5, several compounds **4f**, **8a**, and **10a** showed inhibitory

Table 5. In Vitro Antitumor Activities of Thiazolidinedione-Derived Compounds

entry	compounds	ZR-75-30 (IC_{50} μM)[a]	A549 (IC_{50} μM)[b]	HCT116 (IC_{50} μM)[c]
1	**4f**	77.4	>100	>100
2	**ent-4f**[d]	22.0	>100	>100
3	**8a**	19.1	>100	>100
4	**9a**	40.1	>100	>100
5	**9b**	>100	>100	>100
6	**10a**	14.7	>100	94.5
7	**10b**	>100	>100	>100
8	**10c**	>100	>100	>100
9	irinotecan	10.7	53.5	17.3

[a]ZR-75-30: Breast cancer cells. [b]A549: Lung cancer cell. [c]HCT116: Colon cancer cell. [d]Generated with R-1b as catalyst.

activity against the ZR-75-30 cancer cell line. Among them, compound **10a** showed the best activity with an IC_{50} value of 14.7 μM, which can be used as a lead for the development of new antitumor agents.

Moreover, the compounds were assayed for their antifungal activities.[25] In vitro antifungal activity of each compound was expressed as the minimal inhibitory concentration (MIC) that achieved 80% inhibition of the tested fungi (Table 6). The results revealed that compounds **9a**, **9b**, and **8a** showed inhibitory activities against *Candida albicans* and *Cryptococcus neoformans*, which are leading causes of life-threatening fungal infections. Moreover, compounds **11a** and **11b** were only active against *Cryptococcus neoformans*. The most active antifungal

dx.doi.org/10.1021/co400022r | *ACS Comb. Sci.* 2013, 15, 298−308

Table 6. Antifungal in Vitro Activities of Thiazolidinedione-Derived Compounds (MIC, μg/mL)

entry	compounds	*Candida albicans*[a]	*Cryptococcus neoformans*[b]
1	**4f**	>64	>64
2	ent-**4f**[c]	>64	>64
3	**6l**	>64	>64
4	**8a**	64	32
5	**9a**	16	8
6	**9b**	32	32
7	**10a**	>64	>64
8	**10b**	>64	>64
9	**10c**	>64	>64
10	trans-**11a**	>64	8
11	cis-**11a**	>64	64
12	**11b**	>64	64
13	fluconazole	2	2

[a]Strain number: SC5314. [b]Strain number: 32609. [c]Generated with *R*-1b as catalyst.

compound is **9a** and its structure is completely different from traditional antifungal drugs, which provides a novel scaffold for further antifungal drug discovery. Interestingly, **9a** and **9b** displayed inhibitory activity against pathogenic fungi, while **4f** and **10a** showed better activity against human cancer cell line. These results show the importance of core skeletons embedded with privileged thiazolone motif.

CONCLUSION

In conclusion, motivated by the broadly application of pDOS in generating biologically active molecules and the lack of efficient synthetic methods to facilely assemble structurally diverse complex molecular architectures, we have developed a new powerful divergent organocatalytic cascade reactions of thiazolidinedione analogies to α,β-unsaturated aldehydes to generate diverse scaffolds with high stereoselectivity and synthetic efficiency. As demonstrated in this study, the power of the divergent organocatalytic cascade strategies has been fueled by its high synthetic efficiency to create functional, stereochemical and skeletal diversified thiazolidinedione-derived privileged substructure library compounds. The collection of these natural product-like polyheterocycles has been subjected to antifungal and antitumor bioassays to generate new promising leads for further development. In particular, compounds **8a**, **9a**, and **9b** exhibit strong antifungal activities against *Candida albicans* and *Cryptococcus neoformans*, while their structures are different from triazole antifungal drugs. Therefore, they could serve as good lead compounds for the development of new generation antifungal agents. Furthermore, the application of the synthetic strategy in the construction of new pDOS libraries is being actively pursued in our laboratories.

EXPERIMENTAL PROCEDURES

General Procedure for Reactions of 2 with 3 (Table 2, 4a as Example). The catalyst **1b** (22.0 mg, 0.06 mmol, 0.2 equiv) was added to a solution of α,β-unsaturated aldehyde **2a** (120.0 mg, 0.9 mmol, 3 equiv) and thiazolidinedione **3** (35.0 mg, 0.3 mmol, 1 equiv) in DCM (1 mL). The resulted solution was stirred for 36 h at room temperature. After evaporation of the solvent, the product was purified though column chromatography over silica gel with hexane/EtOAc (10:1−8:1) as the eluent to yield **4a** (79.6 mg, 73% yield) as white solid. The pure product is used to determine *ee* by chiral HPLC analysis and for structural characterization (see Supporting Information for detail).

General Procedure for Reactions of 2 with 5 (Table 3, 6a as Example). The catalyst **1b** (17.0 mg, 0.05 mmol, 0.2 equiv) was added to a solution of α,β-unsaturated aldehyde **2a** (100 mg, 0.8 mmol, 3 equiv) and rhodanine **5a** (35 mg, 0.3 mmol, 1 equiv) in DCM (1 mL). The resulted solution was stirred for 8 h at room temperature. After evaporation of the solvent, the product was purified though column chromatography over silica gel with hexane/EtOAc (10:1−8:1) as the eluent to yield **6a** (94.0 mg, 95% yield) as white solid. The pure product is used to determine *ee* by chiral HPLC analysis and for structural characterization (see Supporting Information for detail).

General Procedure for Reactions of 2 with 7 (Table 4, 8a as Example). The catalyst **1e** (22.0 mg, 0.04 mmol, 0.1 equiv) was added to a solution of α, β-unsaturated aldehyde **2a** (74.0 mg, 0.6 mmol, 1.5 equiv) and isorhodanine **7** (50.0 mg, 0.4 mmol, 1 equiv) in toluene (1 mL). The mixture was stirred for 10h, then the resulting thick solution was diluted with hexane (10 mL), and stirred for another 30 min at room temperature, filtrated and washed with hexane to give the desired product **8a** (82.0 mg, 82% yield) as white solid. The pure product is used for characterization (see Supporting Information for detail). It was further converted to more stable hydroxyl TBS-derived product to determine the corresponding *ee* value.

(*5aS,5′S,7S,9S*)-7,9-Di(furan-2-yl)-3-methyl-6,7-dihydro-1*H*-spiro[pyrano[4,3-*b*]chromene-8,5′-thiazolidine]-1,2′,4′(5*aH*,9*H*)-trione (9a). A solution of **4f** (50.0 mg, 0.15 mmol, 1.0 equiv), 4-hydroxy-6-methyl-2-pyrone (190.0 mg, 0.15 mmol, 1.0 equiv), and L-proline (86.0 mg, 0.075 mmol, 0.5 equiv) in 5 mL of ethyl acetate was heated at 70 °C under an argon atmosphere for 24 h. The mixture was cooled to room temperature, diluted with 50 mL of ethyl acetate, washed twice with 30 mL of brine, dried (Na_2SO4), filtered, and concentrated. Column chromatography on silica gel of the crude product using a gradient mixture of ethyl acetate/hexane (1:5−1:3) as eluent gave 59.0 mg (87% yield) of **9a**.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.06 (br s, 1H), 7.37−7.38 (m, 1H), 7.32−7.33 (m, 1H), 6.38−6.39 (m, 1H), 6.32−6.33 (m, 2H), 6.29 (d, J = 3.3 Hz, 1H), 6.25 (d, J = 3.3 Hz, 1H), 5.76 (s, 1H), 5.66 (dd, J = 5.8, 11.2 Hz, 1H), 4.26 (s, 1H), 4.00 (dd, J = 4.1, 13.7 Hz, 1H), 3.15 (q, J = 12.8 Hz, 1H), 2.45 (dt, J = 4.3, 12.9 Hz, 1H), 2.20 (s, 3H); ^{13}CNMR (150 MHz, $CDCl_3$) δ =173.1, 168.6, 164.0, 163.0, 162.4, 152.5, 151.7, 142.7, 142.5, 126.1, 114.8, 111.0, 110.7, 109.6, 109.5, 97.8, 97.6, 75.5, 66.2, 50.0, 41.2, 34.6, 20.3; HRMS (ESI) calcd for $C_{23}H_{17}NO_7S$ ($M + H^+$) 452.0804, found 452.0792; HPLC (Chiralpak OD, 0.46 cm I.D. × 10 cm L × 5 um, ethanol/hexane =20/80, 35 °C, flow rate 1.0 mL/min, λ = 230 nm) t_{major} = 6.4 min, t_{minor} = 10.5 min, *ee* > 99%; $[\alpha]_D^{25}$ = 47.2 (c = 0.2 in EtOAc).

(1′*S*,2′*S*,3′*S*,4*a*′*S*)-1′,3′-Di(furan-2-yl)-4′,4*a*′,6′,7′-tetrahydrospiro[thiazolidine-5,2′-xanthene]-2,4,8′(1′*H*,3′*H*,5′*H*)-trione (9b). A solution of **4g** (50.0 mg, 0.15 mmol, 1 equiv), 1,3-dimedone (320.0 mg, 0.30 mmol, 2 equiv), and L-proline (170.0 mg, 0.15 mmol, 1 equiv) in 5 mL of ethyl acetate was heated at 70 °C under an argon atmosphere for 12 h. The mixture was cooled to room temperature, diluted with 50 mL of ethyl acetate, washed twice with 30 mL of brine, dried (Na_2SO_4), filtered, and concentrated. Column chroma-

dx.doi.org/10.1021/co400022r | ACS Comb. Sci. 2013, 15, 298−308

tography on silica gel of the crude product using a gradient mixture of ethyl acetate/hexane (1:5−1:3) as eluent gave 57.0 mg (88% yield) of **9b**.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.42 (br s, 1H), 7.34−7.36 (m, 1H), 7.30−7.31 (m, 1H), 6.35−6.36 (m, 2H), 6.31 (dd, J = 1.9, 3.2 Hz, 1H), 6.25 (d, J = 3.2 Hz, 1H), 6.23 (d, J = 3.3 Hz, 1H), 5.57 (ddd, J = 1.7, 5.9, 11.1 Hz, 1H), 4.22 (s, 1H), 3.97 (dd, J = 4.0, 13.7 Hz, 1H), 3.11 (q, J = 12.8 Hz, 1H), 2.33−2.45 (m, 5H), 1.92−1.99 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 195.0, 174.6, 172.8, 168.6, 153.0, 151.9, 142.5, 142.4, 124.0, 114.5, 111.0, 110.7, 110.2, 109.4, 109.0, 75.4, 66.3, 50.0, 41.2, 36.3, 34.6, 29.8, 28.2; HRMS (ESI) calcd for $C_{23}H_{19}NO_6S$ ($M + H^+$) 438.1011, found 438.1003; HPLC (Chiralpak OD, Φ 0.46 × 25 cm, ethanol/hexane = 20/80, 35 °C, flow rate 1.0 mL/min, λ = 230 nm): t_{major} = 3.5 min, t_{minor} = 8.5 min, *ee* > 99%; $[\alpha]_D^{25}$ = −21.9 (c = 0.2 in EtOAc).

(3*S*,4*aS*,5′*S*,6*S*,8*S*)-Diethyl-2′-(benzylthio)-3-ethoxy-4′-oxo-3,4,4a,5,6,8-hexahydro-4′*H*-spiro[isochromene-7,5′-thiazole]-6,8-dicarboxylate (10a). To a solution of **6l** (50.0 mg, 0.11 mmol) in ethyl vinyl ether (2 mL) was added $Yb(fod)_3$ (10 mg, 20% w/w). The mixture was stirred three days under argon and after this time ethyl vinyl ether was evaporated under reduced pressure. Flash chromatography on silica gel (ethyl acetate/hexanes =15:1−10:1) afforded 58.0 mg (99% yield) of pure **10a** as amorphous solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.30−7.39 (m, 5H), 6.12 (t, J = 1.5 Hz, 1H), 4.98 (dd, J = 2.6, 4.8 Hz, 1H), 4.60−4.62 (m, 3H), 4.13−4.16 (m, 4H), 3.80 (dq, J = 7.2, 9.6 Hz, 1H), 3.51 (dq, J = 7.2, 9.6 Hz, 1H), 3.03−3.10 (m, 1H), 2.87 (dd, J = 2.0, 4.7 Hz, 1H), 2.14 (ddd, J = 2.4, 7.7, 13.6 Hz, 1H), 2.02 (dt, J = 5.2, 14.1 Hz, 1H), 1.96 (ddd, J = 1.8, 5.5, 14.1 Hz, 1H), 1.61 (dt, J = 4.7, 14.0 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.20−1.25 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 199.1, 188.1, 171.4, 169.4, 136.8, 134.7, 129.4, 129.0, 128.3, 113.1, 97.1, 73.3, 64.1, 61.5, 61.4, 50.2, 47.7, 38.3, 34.7, 33.1, 27.2, 15.4, 14.2, 14.1; HRMS (ESI) calcd for $C_{26}H_{31}NO_7S_2$ ($M + H^+$) 534.2620, found 534.2628; HPLC (Chiralpak AD, Φ 0.46 × 25 cm, 25 °C, ethanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm) t_{minor} = 14.7 min, t_{major} = 22.3 min, *ee* > 99%; $[\alpha]_D^{25}$ = −97.3 (c = 3.1 in EtOAc).

(3*S*,4*aS*,5′*S*,6*S*,8*S*)-Diethyl-3-ethoxy-2′-morpholino-4′-oxo-3,4,4*a*,5,6,8-hexahydro-4′*H*-spiro[isochromene-7,5′-thiazole]-6,8-dicarboxylate (10b). A solution of **10a** (30.0 mg, 0.056 mmol, 1.0 equiv) and morpholine (24.0 mg, 0.28 mmol, 5.0 equiv) in acetonitrile (5 mL) was heated to 55 °C for 1 h, then cooled to room temperature, concentrated to give the crude product. It was purified through column chromatography on silica gel (ethyl acetate/hexanes = 5:1−1:1), 23.5 mg (84% yield) of pure **10b** was obtained as amorphous solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.09 (s, 1H), 4.95−4.98 (m, 1H), 4.60 (s, 1H), 4.11−4.21 (m, 4H), 3.97−4.00 (m, 2H), 3.73−3.87 (m, 5H), 3.46−3.58 (m, 3H), 3.07−3.15 (m, 1H), 2.86 (d, J = 4.8 Hz, 1H), 2.15 (dd, J = 8.0, 13.6 Hz, 1H), 2.00 (dd, J = 5.2, 14.0 Hz, 1H), 1.92 (dt, J = 5.1, 13.4 Hz, 1H), 1.58 (dt J = 5.7, 13.4 Hz, 1H), 1.25−1.29 (m, 6H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 187.6, 179.3, 171.9, 169.7, 136.6, 113.5, 97.5, 73.8, 66.5, 66.2, 64.2, 61.2, 61.1, 50.9, 48.7, 48.2, 46.7, 35.0, 34.0, 27.4, 15.4, 14.2; HRMS (ESI) calcd for $C_{23}H_{32}N_2O_8S$ ($M + H^+$) 497.1958, found 497.1959; HPLC (Chiralpak AD, Φ 0.46 × 25 cm, 25 °C, ethanol/hexane =20/80, flow rate 1.0 mL/min, λ = 230 nm): t_{major} = 8.7 min, t_{minor} = 29.7 min, *ee* > 99%; $[\alpha]_D^{25}$ = −53.7 (c = 1.2 in EtOAc).

(2′*S*,3*S*,4*aS*,6*S*,8*S*)-Diethyl-3-ethoxy-7′-methoxy-3′,5′-dioxo-3,3′,4,4a,5,5′,6,8-octahydrospiro[isochromene-7,2′-thiazolo[2,3-*b*]quinazoline]-6,8-dicarboxylate (10c). A solution of **10a** (25.0 mg, 0.047 mmol, 1.0 equiv) and 2-amino-5-methoxybenzoic acid (15.0 mg, 0.094 mmol, 2.0 equiv) in glacial acetic acid (2 mL) was heated to gentle reflux for 2.5 h, then cooled to room temperature. The pH was adjusted to 7 with saturated $NaHCO_3$ (aq), extracted with ethyl acetate (20 mL × 3), dried over Na_2SO_4, concentrated to give the crude product. It was purified through column chromatography on silica gel (ethyl acetate/hexanes =10:1−8:1), 17.0 mg (65% yield) of pure **10c** was obtained as amorphous solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.67 (d, J = 3.0 Hz, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.31 (dd, J = 3.0, 8.8 Hz, 1H), 6.20 (s, 1H), 5.05 (t, J = 3.0 Hz, 1H), 4.75 (s, 1H), 4.10−4.27 (m, 4H), 3.90 (s, 3H), 3.84 (dq, J = 7.3, 9.5 Hz, 1H), 3.54 (dq, J = 7.2, 9.3 Hz, 1H), 3.03−3.09 (m, 1H), 3.00−3.03 (m, 1H), 2.29 (dt, J = 5.5, 14.1 Hz, 1H), 2.16 (ddd, J = 2.3, 7.7, 14.2 Hz, 1H), 1.92 (dd, J = 4.7, 14.0 Hz, 1H), 1.71 (dt, J = 3.6, 14.1 Hz, 1H), 1.27−1.31 (m, 6H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (15025 MHz, $CDCl_3$) δ = 171.6, 171.3, 169.5, 158.5, 158.4, 152.5, 141.6, 138.1, 127.9, 125.4, 120.8, 111.1, 108.4, 96.8, 64.2, 63.8, 61.9, 61.9, 56.0, 50.8, 48.6, 32.8, 32.3, 29.8, 26.8, 15.5, 14.1; HRMS (ESI) calcd for $C_{27}H_{30}N_2O_9S$ ($M + H^+$) 559.1750, found 559.1757; HPLC (Chiralpak AD, Φ 0.46 × 25 cm, 25 °C, ethanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm): t_{minor} = 11.0 min, t_{major} = 16.5 min, *ee* > 99%; $[\alpha]_D^{25}$ = −120.0 (c = 0.3 in EtOAc).

(7*S*)-5-(2-Oxo-2-phenylethyl)-7-phenyl-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-2-one (11b). **8a** (50.0 mg, 0.19 mmol, 1.0 equiv) and 1-phenyl-2-(triphenylphosphoranylidene) ethanone (140.0 mg, 0.38 mmol, 2.0 equiv) were dissolved into DCM (5 mL). The resulting mixture was stirred for 12 h at room temperature. After that time, the insoluble solid was removing through filtrating, and the organic phase was concentrated to give the crude product. It was purified through column chromatography on silica gel (ethyl acetate/hexanes =10:1−5:1), 59.5 mg (85% yield) of pure **11b** (trans/cis = 1:1) was obtained as white solid. Two diastereoisomers were separated through further careful column chromatography on silica gel.

11b (*trans*): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.93 (br s, 1H), 7.93 (d, J = 7.3 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.35 (t, J = 7.4 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.23 (d, J = 7.4 Hz, 2H), 4.01−4.05 (m, 1H), 3.93 (dd, J = 5.8, 7.5 Hz, 1H), 3.52 (dd, J = 8.3, 17.6 Hz, 1H), 3.31 (dd, J = 5.4, 17.5 Hz, 1H), 2.34−2.42 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 196.6, 173.2, 142.5, 136.4, 133.8, 129.0, 128.9, 128.2, 128.0, 127.7, 120.1, 107.4, 43.2, 39.1, 38.7, 35.0; HRMS (ESI) calcd for $C_{20}H_{17}NO_2S_2$ ($M + H^+$) 368.0774, found 368.0782; HPLC (Chiralpak AD, Φ 0.46 × 25 cm, 25 °C, *i*-propanol/hexane = 30/70, flow rate 0.8 mL/min, λ = 230 nm) t_{major} = 13.7 min, t_{minor} = 20.9 min, *ee* > 99%; $[\alpha]_D^{25}$ = 88.1 (c = 0.4 in EtOAc).

11b (*cis*): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.00 (br s, 1H), 7.90 (d, J = 7.4 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.27 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 7.4 Hz, 2H), 4.17−4.23 (m, 1H), 4.03 (dd, J = 5.5, 10.8 Hz, 1H), 3.29 (dd, J = 7.8, 17.5 Hz, 1H), 3.23 (dd, J = 5.8, 17.5 Hz, 1H), 2.60 (ddd, J = 1.9, 5.5, 13.7 Hz, 1H), 2.05 (dt, J = 11.0, 13.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 196.2,

dx.doi.org/10.1021/co400022r | *ACS Comb. Sci.* 2013, 15, 298−308

173.3, 142.5, 136.3, 133.9, 129.0, 128.2, 128.0, 127.7, 119.8, 109.8, 43.2, 42.2, 41.7, 38.1; HRMS (ESI) calcd for $C_{20}H_{17}NO_2S_2$ (M + H^+) 368.0779, found 368.0772; HPLC (Chiralpak AD, Φ 0.46 × 25 cm, 25 °C, *i*-propanol/hexane = 30:70, flow rate 0.8 mL/min, λ = 230 nm) t_{major} = 17.5 min, t_{minor} = 42.0 min, *ee* > 99%; $[\alpha]_D^{25}$ =15 (*c* = 0.4 in $CHCl_3$).

Ethyl-2-((*7S*)-2-oxo-7-phenyl-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*]thiazol-5-yl)acetate (11a). To a solution of **8a** (50.0 mg, 0.19 mmol, 1.0 equiv) in DCM (5 mL), 1-phenyl-2-(triphenylphosphoranylidene)ethanone (130.0 mg, 0.38 mmol, 2.0 equiv) was added, the resulting mixture was stirred, and the solution was gradually clear (12h), concentrated to give the crude product. It was purified through column chromatography on silica gel (ethyl acetate/hexanes = 10:1−5:1), 35.6 mg (56% yield) of pure **11a** (trans/cis = 1:1) was obtained as white solid.

Compounds 11a (trans and cis). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.53 (br s, 1H), 9.49 (brs 1H), 7.20−7.36 (m, 10H), 4.11−4.18 (m, 4H), 3.96 (dd, *J* = 5.4, 11.1 Hz, 1H), 3.93−3.98 (m, 1H), 3.90 (dd, *J* = 5.7, 7.0 Hz, 1H), 3.74−3.79 (m, 1H), 2.76 (dd, *J* = 8.2, 16.0 Hz, 1H), 2.68 (dd, *J* = 8.2, 16.0 Hz, 1H), 2.60 (d, *J* = 7.1 Hz, 2H), 2.53 (ddd, *J* = 1.9, 5.5, 13.9 Hz, 1H), 2.26−2.35 (m, 2H), 2.00 (dt, *J* = 11.2, 13.7 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 173.8, 173.7, 170.4, 170.2, 142.6, 142.4, 129.0, 128.0, 127.9, 127.8, 127.6, 120.0, 119.9, 109.8, 107.4, 61.3, 61.2, 42.4, 41.6, 39.4, 38.9, 38.9, 38.5, 35.7, 14.3, 14.2; HRMS (ESI) calcd for $C_{16}H_{17}NO_3S_2$ (M + H^+) 336.0728 found 336.0730; HPLC (Chiralpak OZ, 0.46 cm I.D. × 25 cm L × 5 mm, ethanol/hexane =20/80, 35 °C, flow rate 0.8 mL/min, λ = 230 nm) t_{1minor} = 11.1 min, t_{1major} = 12.9 min/t_{2minor} = 17.6 min, t_{2major} = 19.0 min, *ee* = 89%/88%; $[\alpha]_D^{25}$ = 4.3 (*c* = 2.2 in EtOAc).

In Vitro Antitumor Activity Assay. Cells were plated in 96-well microtiter plates at a density of 5 × 10^3/well and incubated in a humidified atmosphere with 5% CO_2 at 37 °C for 24 h. Test compounds were added onto triplicate wells with different concentrations and 0.1% DMSO for control. After they had been incubated for 72 h, 20 μL of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] solution (5 mg/mL) was added to each well and the plate was incubated for an additional 4 h. The formazan was dissolved in 100 μL of DMSO. The absorbance (OD) was read on a WellscanMK-2 microplate reader (Labsystems) at 570 nm. The concentration causing 50% inhibition of cell growth (IC_{50}) was determined by the Logit method. Irinotecan, a clinically available antitumor agent, was used as the positive control. All experiments were performed three times.

In Vitro Antifungal Activity Assay. In vitro antifungal activity was measured by means of the minimal inhibitory concentrations (MIC) using the serial dilution method in 96-well microtest plates. Test fungal strains were obtained from the ATCC (American type culture collection). Fluconazole was used as a positive control. The MIC determination was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) recommendations with RPMI 1640 (Cell culture from Sigma) buffered with 0.165MMOPS buffer [(3-*N*-morpholino)propanesulfonic acid, Sigma] as the test medium. The MIC value was defined as the lowest concentration of test compounds that resulted in a culture with turbidity less than or equal to 80% inhibition when compared with the growth of the control. Test compounds were dissolved in DMSO serially diluted in growth medium. The fungal strains were incubated at 35 °C, and the growth MIC was determined at 24 h for *Candida albicans* and at 72 h for *Cryptococcus. neoformans*.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ^{1}H and ^{13}C NMR, chiral HPLC analysis data for products **4**, **6**, **8**, **9**, and **10** and X-ray data (CIF files) of **4a** and **8a**. The antitumor inhibitory curve of compound **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel./Fax: 86-21-81871243 (W.Z.); 86-21-81871243 (C.S.). Phone: (505) 277-0756 (W.W.). Fax: (505) 277-2609 (W.W.). E-mail: zhangwnk@hotmail.com (W.Z.); shengcq@hotmail.com (C. S.); wwang@unm.edu (W.W.).

Author Contributions

Yongqiang Zhang and Shengzheng Wang contributed equally to this article.

Funding

Financial support of this research by the National Natural Science Foundation of China (Grant 81222044, C.-Q.S.), the 863 Hi-Tech Program of China (Grant 2012AA020302, C.-Q.S.), Shanghai Rising-Star Program (grant 12QH1402600, C.-Q.S.), the National Science Foundation (CHE-1057569, W. W.), and East China University of Science & Technology (W.W.) is gratefully acknowledged.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) For reviews, see: (a) Duarte, C. D.; Barreiro, E. J.; Fraga, C. A. Privileged Structures: A Useful Concept for the Rational Design of New Lead Drug Candidates. *Mini. Rev. Med. Chem.* **2007**, *7*, 1108−1119. (b) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. Privileged Scaffolds for Library Design and Drug Discovery. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347−361. (c) DeSimone, R. W.; Currie, S. A. K. S.; Mitchell; Darrow, J. W.; Pippin, D. A. Privileged Structures: Applications in Drug Discovery. *Comb. Chem. High Throughput Screen* **2004**, *7*, 473−494.

(2) For reviews, see: (a) Nielsen, T. E.; Schreiber, S. L. Towards the Optimal Screening Collection: A Synthesis Strategy. *Angew. Chem., Int. Ed.* **2008**, *47*, 48−56. (b) Galloway, W. R.; Isidro-Llobet, A.; Spring, D. R. Diversity-Oriented Synthesis as a Tool for the Discovery of Novel Biologically Active Small Molecules. *Nat. Commun* **2010**, *1*, 80. (c) Spandl, R. J.; Bender, A.; Spring, D. R. Diversity-Oriented Synthesis: A Spectrum of Approaches and Results. *Org. Biomol. Chem.* **2008**, *6*, 1149−1158. (d) Spring, D. R. Diversity-Oriented Synthesis: A Challenge for Synthetic Chemists. *Org. Biomol. Chem.* **2003**, *1*, 3867−3870. (e) Schreiber, S. L. Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery. *Science* **2000**, *287*, 1964−1969. (f) Thomas, G. L.; Wyatt, E. E.; Spring, D. R. Enriching Chemical Space with Diversity-Oriented Synthesis. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 700−712. (g) Dandapani, S.; Marcaurelle, L. A. Current Strategies for Diversity-Oriented Synthesis. *Curr. Opin. Chem. Biol.* **2010**, *14*, 362−370. (h) Spandl, R. J.; Diaz-Gavilan, M.; O'Connell, K. M.; Thomas, G. L.; Spring, D. R. Diversity-Oriented Synthesis. *Chem. Rec.* **2008**, *8*, 129−142. (i) Beckmann, O. C. C. H. S.; Spring, D. R. Diversity-Oriented Synthesis: Producing Chemical Tools for Dissecting Biology. *Chem. Soc. Rev.* **2012**, *41*, 4444−4456. (j) Eberhardt, L.; Kumar, K.; Waldmann, H. Exploring and Exploiting Biologically Relevant Chemical Space. *Curr. Drug Targets* **2011**, *12*, 1531−1546.

(k) Proco, J. A. Special Issue on "Recent Developments in Chemical Diversity". *Beilstein J. Org. Chem.* **2012**, 8−827.

(3) Oh, S.; Park, S. B. A Design Strategy for Drug-Like Polyheterocycles with Privileged Substructures for Discovery of Specific Small-Molecule Modulators. *Chem. Commun* **2011**, *47*, 12754−12761.

(4) (a) Bose, D. S.; Idrees, M.; Todewale, I. K.; Jakka, N. M.; Rao, J. V. Hybrids of Privileged Structures Benzothiazoles and Pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one, and Diversity-Oriented Synthesis of Benzothiazoles. *Eur. J. Med. Chem.* **2012**, *50*, 27−38. (b) Ko, S. K.; Jang, H. J.; Kim, E.; Park, S. B. Concise and Diversity-Oriented Synthesis of Novel Scaffolds Embedded with Privileged Benzopyran Motif. *Chem. Commun.* **2006**, 2962−2964. (c) Oh, S.; Kim, S. J.; Hwang, J. H.; Lee, H. Y.; Ryu, M. J.; Park, J.; Jo, Y. S.; Kim, Y. K.; Lee, C. H.; Kweon, K. R.; Shong, M.; Park, S. B. Antidiabetic and Antiobesity Effects of Ampkinone (6f), a Novel Small Molecule Activator of AMP-activated Protein Kinase. *J. Med. Chem.* **2010**, *53*, 7405−7413. (d) Cha, M. Y.; Lee, K. O.; Kim, J. W.; Lee, C. G.; Song, J. Y.; Kim, Y. H.; Lee, G. S.; Park, S. B.; Kim, M. S. Discovery of a Novel Her-1/Her-2 Dual Tyrosine Kinase Inhibitor for the Treatment of Her-1 Selective Inhibitor-resistant Non-small Cell Lung Cancer. *J. Med. Chem.* **2009**, *52*, 6880−6888. (e) Zhu, M.; Kim, M. H.; Lee, S.; Bae, S. J.; Kim, S. H.; Park, S. B. Discovery of Novel Benzopyranyl Tetracycles that Act as Inhibitors of Osteoclastogenesis Induced by Receptor Activator of NF-κB Ligand. *J. Med. Chem.* **2010**, *53*, 8760−8764. (f) Oh, S.; Cho, S. W.; Yang, J.-Y.; Sun, H. J.; Chung, Y. S.; Shin, C. S.; Park, S. B. Discovery of a Novel Benzopyranyl Compound as a Potent in Vitro and in Vivo Osteogenic Agent. *MedChemComm* **2011**, *2*, 76−80.

(5) (a) Liu, W.; Khedkar, V.; Baskar, B.; Schurmann, M.; Kumar, K. Branching cascades: A Concise Synthetic Strategy Targeting Diverse and Complex Molecular Frameworks. *Angew. Chem., Int. Ed.* **2011**, *50*, 6900−6905. (b) Feng, X.; Cui, H. L.; Xu, S.; Wu, L.; Chen, Y.-C. Organocatalytic Direct Vinylogous Michael Addition of α,β-Unsaturated γ-Butyrolactam to α,β-Unsaturated Aldehydes and an Illustration to Scaffold Diversity Synthesis. *Chem.—Eur. J.* **2010**, *16*, 10309−10312. (c) Fitzmaurice, R. J.; Etheridge, Z. C.; Jumel, E.; Woolfson, D. N.; Caddick, S. Microwave Enhanced Palladium Catalysed Coupling Reactions: a Diversity-Oriented Synthesis Approach to Functionalised Flavones. *Chem. Commun.* **2006**, 4814−4816. (d) Lee, S. C.; Park, S. B. Novel Application of Leuckart−Wallach Reaction for Synthesis of Tetrahydro-1,4-benzodiazepin-5-ones library. *Chem. Commun.* **2007**, 3714−3716. (e) Oh, S.; Jang, H. J.; Ko, S. K.; Ko, Y.; Park, S. B. Construction of a Polyheterocyclic Benzopyran Library with Diverse Core Skeletons through Diversity-Oriented Synthesis Pathway. *J. Comb. Chem.* **2010**, *12*, 548−558. (f) Park, S. O.; Kim, J.; Koh, M.; Park, S. B. Efficient Parallel Synthesis of Privileged Benzopyranylpyrazoles via Regioselective Condensation of β-Keto Aldehydes with Hydrazines. *J. Comb. Chem.* **2009**, *11*, 315−326. (g) Bose, D. S.; Idrees, M.; Jakka, N. M.; Rao, J. V. Diversity-Oriented Synthesis of Quinolines via Friedlander Annulation Reaction under Mild Catalytic Conditions. *J. Comb. Chem.* **2010**, *12*, 100−110. (h) Chen, L. H.; Chang, C. M.; Salunke, D. B.; Sun, C. M. Divergent Synthesis of Unsymmetrical Annulated Biheterocyclic Compound Libraries: Benzimidazole Linked Indolo-benzodiazepines/quinoxaline. *ACS Comb. Sci.* **2011**, *13*, 391−398. (i) Zhu, M.; Lim, B. J.; Koh, M.; Park, S. B. Construction of Polyheterocyclic Benzopyran Library with Diverse Core Skeletons through Diversity-Oriented Synthesis Pathway: Part II. *ACS Comb. Sci.* **2012**, *14*, 124−134. (j) An, H.; Eum, S. J.; Koh, M.; Lee, S. K.; Park, S. B. Diversity-Oriented Synthesis of Privileged Benzopyranyl Heterocycles from s-*cis*-Enones. *J. Org. Chem.* **2008**, *73*, 1752−1761. (k) Sagar, R.; Park, J.; Koh, M.; Park, S. B. Diastereoselective Synthesis of Polycyclic Acetal-Fused Pyrano[3,2-*c*]pyran-5(2*H*)-one Derivatives. *J. Org. Chem.* **2009**, *74*, 2171−2174. (l) Cui, H. L.; Huang, J. R.; Lei, J.; Wang, Z. F.; Chen, S.; Wu, L.; Chen, Y.-C. Direct Asymmetric Allylic Alkylation of Butenolides with Morita−Baylis−Hillman Carbonates. *Org. Lett.* **2010**, *12*, 720−723.

(6) Recent reviews of organocatalyzed cascade reactions, see: (a) Enders, D.; Grondal, C.; Huttl, M. R. Asymmetric Organocatalytic Domino Reactions. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570−1581. (b) Guillena, G.; Ramon, D. J.; Yus, M. Organocatalytic Enantioselective Multicomponent Reactions. *Tetrahedron: Asymmetry* **2007**, *18*, 693−700. (c) Yu, X.; Wang, W. Organocatalysis: Asymmetric Cascade Reactions Catalysed by Chiral Secondary Amines. *Org. Biomol. Chem.* **2008**, *6*, 2037−2046. (d) Wu, L. Y.; Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. Organocascade Reactions of Enones Catalyzed by a Chiral Primary Amine. *Angew. Chem., Int. Ed.* **2009**, *48*, 7196−7199. (e) Alba, A.-N.; Companyo, X.; Viciano, M.; Rios, R. Organocatalytic Domino Reactions. *Curr. Org. Chem.* **2009**, *13*, 1432−1474. (f) Grondal, C.; Jeanty, M.; Enders, D. Organocatalytic Cascade Reactions as a New Tool in Total Synthesis. *Nat. Chem.* **2010**, *2*, 167−178. (g) Westermann, B.; Ayaz, M.; van Berkel, S. S. Enantiodivergent Organocascade Reactions. *Angew. Chem., Int. Ed.* **2010**, *49*, 846−849. (h) Peng, F.-Z.; Shao, Z.-H. Asymmetric Organocatalytic Cascade Reactions Catalyzed by Chiral Bronsted Acids. *Curr. Org. Chem.* **2011**, *15*, 4144−4160. (i) Ruiz, M.; Lopez-Alvarado, P.; Giorgi, G.; Menéndez, J. C. Domino Reactions for the Synthesis of Bridged Bicyclic Frameworks: Fast Access to Bicyclo[*n*.3.1]alkanes. *Chem. Soc. Rev.* **2011**, *40*, 3445−3454. (j) Pellissier, H. Recent Developments in Asymmetric Organocatalytic Domino Reactions. *Adv. Synth. Catal.* **2012**, *354*, 237−294.

(7) For reviews, see: (a) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. Recent Advances in Organocatalytic Methods for the Synthesis of Disubstituted 2- and 3-Indolinones. *Chem. Soc. Rev.* **2012**, *41*, 7247−7290. (b) Bradshaw, B.; Bonjoch, J. The Wieland−Miescher Ketone: A Journey from Organocatalysis to Natural Product Synthesis. *Synlett* **2012**, *23*, 337−356. (c) Maltsev, O. V.; Beletskaya, I. P.; Zlotin, S. G. Organocatalytic Michael and Friedel−Crafts Reactions in Enantioselective Synthesis of Biologically Active Compounds. *Russ. Chem. Rev.* **2011**, *80*, 1067−1113. (d) Raj, M.; Singh, V. K. In *Catalytic Methods in Asymmetric Synthesis*; Gruttadauria, M., Giacalone, F., Ed.; Wiley: Hoboken, NJ, 2011; p 415. (e) Rueping, M.; Dufour, J.; Schoepke, F. R. Advances in Catalytic Metal-Free Reductions: From Bio-inspired Concepts to Applications in the Organocatalytic Synthesis of Pharmaceuticals and Natural Products. *Green Chem.* **2011**, *13*, 1084−1105. (f) Marques-Lopez, E.; Herrera, R. P.; Christmann, M. Asymmetric Organocatalysis in Total Synthesis—A Trial by Fire. *Nat. Prod. Rep.* **2010**, *27*, 1138−1167. (g) de Figueiredo, R. M.; Christmann, M. Organocatalytic Synthesis of Drugs and Bioactive Natural Products. *Eur. J. Org. Chem.* **2007**, 2575−2600. (h) Zhang, Y.; Wang, W. Recent Advances in Organocatalytic Asymmetric Michael Reactions. *Catal. Sci. Technol.* **2012**, *2*, 42−53.

(8) For reviews, see: (a) Tejedor, D.; Gonzalez-Cruz, D.; Santos-Exposito, A.; Marrero-Tellado, J. J.; de Armas, P.; Garcia-Tellado, F. Multicomponent Domino Processes Based on the Organocatalytic Generation of Conjugated Acetylides: Efficient Synthetic Manifolds for Diversity-Oriented Molecular Construction. *Chem.—Eur. J.* **2005**, *11*, 3502−3510. (b) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. Development of Cascade Reactions for the Concise Construction of Diverse Heterocyclic Architectures. *Acc. Chem. Res.* **2012**, *45*, 1278−1293. (c) Yu, J.; Shi, F.; Gong, L.-Z. Bronsted-Acid-Catalyzed Asymmetric Multicomponent Reactions for the Facile Synthesis of Highly Enantioenriched Structurally Diverse Nitrogenous Heterocycles. *Acc. Chem. Res.* **2011**, *44*, 1156−1171. (d) Gasperi, T.; Punzi, P.; Migliorini, A.; Tofani, D. An Organocatalytic Approach to the Synthesis of Six-Membered Heterocycles. *Curr. Org. Chem.* **2011**, *15*, 2098−2146. (e) Nielsen, M.; Jacobsen, C. B.; Holub, N.; Paixao, M. W.; Joergensen, K. A. Asymmetric Organocatalysis with Sulfones. *Angew. Chem., Int. Ed.* **2010**, *49*, 2668−2679.

(9) For selected examples, see: (a) Fenster, E.; Hill, D.; Reiser, O.; Aubé, J. Automated Three-Component Synthesis of a Library of γ-Lactams. *Beilstein J. Org. Chem.* **2012**, *8*, 1804−1813. (b) Tan, B.; Hernandez-Torres, G.; Barbas, C. F., III Highly Efficient Hydrogen-Bonding Catalysis of the Diels-Alder Reaction of 3-Vinylindoles and Methyleneindolinones Provides Carbazolespirooxindole Skeletons. *J. Am. Chem. Soc.* **2011**, *133*, 12354−12357. (c) Riguet, E. Enantioselective Organocatalytic Friedel-Crafts Alkylation Reaction

of Indoles with 5-Hydroxyfuran-2(5H)-one: Access to Chiral γ-Lactones and Gamma-Lactams via a Ugi 4-Center 3-Component Reaction. *J. Org. Chem.* **2011**, *76*, 8143−8150. (d) Tan, B.; Candeias, N. R.; Barbas, C. F., III Construction of Bispirooxindoles Containing Three Quaternary Stereocentres in a Cascade Using a Single Multifunctional Organocatalyst. *Nat. Chem.* **2011**, *3*, 473−477. (e) Tan, B.; Candeias, N. R.; Barbas, C. F., III Core-Structure-Motivated Design of a Phosphine-Catalyzed [3 + 2] Cycloaddition Reaction: Enantioselective Syntheses of Spirocyclopenteneoxindoles. *J. Am. Chem. Soc.* **2011**, *133*, 4672−4675. (f) Boddaert, T.; Coquerel, Y.; Rodriguez, J. Organocatalytic Activity of N-Heterocyclic Carbenes in the Michael Addition of 1,3-Dicarbonyl Compounds: Application to a Stereoselective Spirocyclization Sequence. *Adv. Synth. Catal* **2009**, *351*, 1744−1748. (g) Liu, Y.-K.; Liu, H.; Du, W.; Yue, L.; Chen, Y.-C. Reaction Control in the Organocatalytic Asymmetric One-Pot, Three-Component Reaction of Aldehydes, Diethyl α-Aminomalonate and Nitroalkenes: Toward Diversity-Oriented Synthesis. *Chem.—Eur. J.* **2008**, *14*, 9873−9877. (h) Ramachary, D. B.; Narayana, V. V.; Ramakumar, K. Direct Ionic Liquid Promoted Organocatalyzed Diazo-Transfer Reactions: Diversity-Oriented Synthesis of Diazo-Compounds. *Tetrahedron Lett.* **2008**, *49*, 2704−2709. (i) Deobald, A. M.; Correa, A. G.; Rivera, D. G.; Paixao, M. W. Organocatalytic Asymmetric Epoxidation and Tandem Epoxidation/Passerini Reaction under Eco-Friendly Reaction Conditions. *Org. Biomol. Chem.* **2012**, *10*, 7681−7684.

(10) The studies from our group, see ref 6c and selected examples: (a) Zhang, S.-L.; Xie, H.-X.; Zhu, J.; Li, H.; Zhang, X.-S.; Li, J.; Wang, W. Organocatalytic Enantioselective β-Functionalization of Aldehydes by Oxidation of Enamines and Their Application in Cascade Reactions. *Nat. Commun.* **2011**, *2*, 211−217. (b) Zhang, X.-S.; Zhang, S.-L.; Wang, W. Iminium−Allenamine Cascade Catalysis: One-Pot Access to Chiral 4*H*-Chromenes by a Highly Enantioselective Michael−Michael Sequence. *Angew. Chem., Int. Ed.* **2010**, *49*, 1481−1484. (c) Liu, C.-L.; Zhang, X.-S.; Wang, R.; Wang, W. "One-Pot" Access to 4*H*-Chromenes with Formation of a Chiral Quaternary Stereogenic Center by a Highly Enantioselective Iminium−Allenamine Involved Oxa−Michael−Aldol Cascade. *Org. Lett.* **2010**, *12*, 4948−4951. (d) Zu, L.-S.; Zhang, S.-L.; Xie, H.-X.; Wang, W. Catalytic Asymmetric Oxa−Michael−Michael Cascade for Facile Construction of Chiral Chromans via an Aminal Intermediate. *Org. Lett.* **2009**, *11*, 1627−1630. (e) Wang, J.; Xie, H.-X.; Li, H.; Zu, L.-S.; Wang, W. A Highly Stereoselective Hydrogen-Bond-Mediated Michael−Michael Cascade Process through Dynamic Kinetic Resolution. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177−4179. (f) Zu, L.-S.; Xie, H.-X.; Li, H.; Wang, J.; Yu, X.-H.; Wang, W. Chiral Amine-Catalyzed Enantioselective Cascade Aza-ene-type Cyclization Reactions. *Chem.—Eur. J.* **2008**, *14*, 6333−6335. (g) Wang, J.; Li, H.; Xie, H.-X.; Zu, L.-S.; Shen, X.; Wang, W. Organocatalytic Enantioselective Cascade Michael−Aldol Condensation Reactions: Efficient Assembly of Densely Functionalized Chiral Cyclopentenes. *Angew. Chem., Int. Ed.* **2007**, *46*, 9050−9053. (h) Xie, H.-X.; Zu, L.-S.; Li, H.; Wang, J.; Wang, W. Organocatalytic Enantioselective Cascade Michael−Alkylation Reactions: Synthesis of Chiral Cyclopropanes and Investigation of Unexpected Organocatalyzed Stereoselective Ring Opening of Cyclopropanes. *J. Am. Chem. Soc.* **2007**, *129*, 10886−10894. (i) Zu, L.-S.; Wang, J.; Li, H.; Xie, H.-X.; Jiang, W.; Wang, W. Cascade Michael−Aldol Reactions Promoted by Hydrogen Bonding Mediated Catalysis. *J. Am. Chem. Soc.* **2007**, *129*, 1036−1037. (j) Zu, L.-S.; Li, H.; Xie, H.-X.; Wang, J.; Jiang, W.; Tang, Y.; Wang, W. Synthesis of Highly Functionalized Chiral Cyclopentanes by Catalytic Enantio- and Diastereoselective Double Michael Addition Reactions. *Angew Chem., Int. Ed.* **2007**, *46*, 3732−3734.

(11) We reported the first divergent organocatalytic cascade reaction: Zhang, X.-S.; Song, X.-X.; Li, H.; Zhang, S.-L.; Chen, X.-B.; Yu, X.-H.; Wang, W. An Organocatalytic Cascade Aproach toward Polysubstituted Quinolines and Chiral 1,4-Dihydroquinolines—Unanticipated Effect of N-Protecting Groups. *Angew. Chem., Int. Ed.* **2012**, *51*, 7282−7286.

(12) Recent reviews of application of cascade reactions in DOS: (a) Mueller, T. J. J.; D'Souza, D. M. Diversity-Oriented Syntheses of Functional π-Systems by Multicomponent and Domino Reactions. *Pure Appl. Chem.* **2008**, *80*, 609−620. (b) Shaw, J. T. Naturally Diverse: Highlights in Versatile Synthetic Methods Enabling Target- and Diversity-Oriented Synthesis. *Nat. Prod. Rep.* **2009**, *26*, 11−26.

(13) (a) Verma, A.; Saraf, S. K. 4-Thiazolidinone—A Biologically Active Scaffold. *Eur. J. Med. Chem.* **2008**, *43*, 897−905. (b) Tomasic, T.; Masic, L. P. Rhodanine as a Scaffold in Drug Discovery: A Critical Review of its Biological Activities and Mechanisms of Target Modulation. *Expert Opin. Drug Discovery* **2012**, *7*, 549−560. (c) Mendgen, T.; Steuer, C.; Klein, C. D. Privileged Scaffolds or Promiscuous Binders: a Comparative Study on Rhodanines and Related Heterocycles in Medicinal Chemistry. *J. Med. Chem.* **2012**, *55*, 743−753. (d) Tomasic, T.; Masic, L. P. Rhodanine as a Privileged Scaffold in Drug Discovery. *Curr. Med. Chem.* **2009**, *16*, 1596−1629.

(14) (a) Balfour, J. A.; Plosker, G. L. Rosiglitazone. *Drugs* **1999**, *57*, 921−930. (b) Deeks, E. D.; Keam, S. J. Rosiglitazone: A Review of Its Use in Type 2 Diabetes Mellitus. *Drugs* **2007**, *67*, 2747−2779. (c) Gillies, P. S.; Dunn, C. J. Pioglitazone. *Drugs* **2000**, *60*, 333−343. (d) Plosker, G. L.; Faulds, D. Troglitazone: A Review of Its Use in the Management of Type 2 Diabetes Mellitus. *Drugs* **1999**, *57*, 409−438. (e) Wagstaff, A. J.; Goa, K. L. Rosiglitazone: A Review of Its use in the Management of Type 2 Diabetes Mellitus. *Drugs* **2002**, *62*, 1805−1837. (f) Waugh, J.; Keating, G. M.; Plosker, G. L.; Easthope, S.; Robinson, D. M. Pioglitazone: A Review of Its Use in Type 2 Diabetes Mellitus. *Drugs* **2006**, *66*, 85−109. (g) Steele, J. W.; Faulds, D.; Goa, K. L. Epalrestat, A Review of Its Pharmacology, and Therapeutic Potential in Late-Onset Complications of Diabetes Mellitus. *Drugs Aging* **1993**, *3*, 532−555. (h) Petrie, J.; Small, M.; Connell, J. "Glitazones", A Prospect for Non-Insulin-Dependent Diabetes. *Lancet* **1997**, *349*, 70−71.

(15) Examples of Michael−Michael−aldol cascade reactions in the synthesis of spiro-heterocycles, see: (a) Carlone, A.; Cabrera, S.; Marigo, M.; Jorgensen, K. A. A New Approach for an Organocatalytic Multicomponent Domino Asymmetric Reaction. *Angew. Chem., Int. Ed.* **2007**, *46*, 1101−1104. (b) Cassani, C.; Tian, X.; Escudero-Adan, E. C.; Melchiorre, P. Multiple Approaches to Enantiopure Spirocyclic Benzofuranones Using Organocatalytic Cascade Reactions. *Chem. Commun.* **2011**, *47*, 233−235. (c) Companyo, X.; Zea, A.; Alba, A. N.; Mazzanti, A.; Moyano, A.; Rios, R. Organocatalytic Synthesis of Spiro Compounds via a Cascade Michael−Michael−aldol Reaction. *Chem. Commun.* **2010**, *46*, 6953−6955. (d) Zea, A.; Alba, A. N.; Mazzanti, A.; Moyano, A.; Rios, R. Highly Enantioselective Cascade Synthesis of Spiropyrazolones. *Org. Biomol. Chem.* **2011**, *9*, 6519−6523. (e) Alba, A.-N. R.; Zea, A.; Valero, G.; Calbet, T.; Font-Bardía, M.; Mazzanti, A.; Moyano, A.; Rios, R. Highly Stereoselective Synthesis of Spiropyrazolones. *Eur. J. Org. Chem.* **2011**, 1318−1325. (f) Bergonzini, G.; Melchiorre, P. Dioxindole in Asymmetric Catalytic Synthesis: Routes to Enantioenriched 3-Substituted 3-Hydroxyoxindoles and the Preparation of Maremycin A. *Angew. Chem., Int. Ed.* **2012**, *51*, 971−974.

(16) For leading works in using diarylprolinol silyl ethers in organocatalysis, see: (a) Marigo, M.; Wabnitz, T.; Fielenbach, C. D.; Jørgensen, K. A. Enantioselective Organocatalyzed α-Sulfenylation of Aldehydes. *Angew. Chem., Int. Ed.* **2005**, *44*, 794−797. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. Diphenylprolinol Silyl Ethers as Efficient Organocatalysts for the Asymmetric Michael Reaction of Aldehydes and Nitroalkenes. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212−4215. (c) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. The Diarylprolinol silyl Ether System: a General Organocatalyst. *Acc. Chem. Res.* **2012**, *45*, 248−264.

(17) CCDC-912681 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk and see Supporting Information.

(18) CCDC-912682 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk and see Supporting Information.

(19) (a) McKee, T. C.; Covington, C. D.; Fuller, R. W.; Bokesch, H. R.; Young, S.; Cardellina, I. J.; Kadushin, M. R.; Soejarto, D. D.; Stevens, P. F.; Cragg, G. M.; Boyd, M. R. Pyranocoumarins from Tropical Species of the Genus *Calophyllum*: A Chemotaxonomic Study of Extracts in the National Cancer Institute Collection. *J. Nat. Prod.* **1998**, *61*, 1252−1256. (b) McKee, T. C.; Fuller, R. W.; Covington, C. D.; Cardellina, J. H., 2nd; Gulakowski, R. J.; Krepps, B. L.; McMahon, J. B.; Boyd, M. R. New Pyranocoumarins Isolated from *Calophyllum lanigerum* and *Calophyllum teysmannii*. *J. Nat. Prod.* **1996**, *59*, 754−758. (c) Ulubelen, A.; Meriçli, A. H.; Meriçli, F.; Kaya, Ü. An Alkaloid and Lignans from *Haplophyllum telephioides*. *Phytochemistry* **1994**, *35*, 1600−1601. (d) Shwu-Jen, W.; Ih-Sheng, C. Alkaloids from *Zanthoxylum simulans*. *Phytochemistry* **1993**, *34*, 1659−1661. (e) Campbell, W. E.; Davidowitz, B.; Jackson, G. E. Quinolinone Alkaloids from an *Agathosma* Species. *Phytochemistry* **1990**, *29*, 1303−1306. (f) Khalid, S. A.; Waterman, P. G. Alkaloids from Stem Barks of *Oricia renieri* and *Oricia gabonensis*. *Phytochemistry* **1981**, *20*, 2761−2763. (g) Stermitz, F. R.; Sharifi, I. A. Alkaloids of *Zanthoxylum monophyllum* and *Z. punctatum*. *Phytochemistry* **1977**, *16*, 2003−2006. (h) Tang, Y.; Oppenheimer, J.; Song, Z.; You, L.; Zhang, X.; Hsung, R. P. Strategies and Approaches for Constructing 1-Oxadecalins. *Tetrahedron* **2006**, *62*, 10785−10813.

(20) Hua, D. H.; Chen, Y.; Sin, H. S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J. P.; Chiang, P. K. A One-Pot Condensation of Pyrones and Enals. Synthesis of 1*H*,7*H*-5*a*,6,8,9-Tetrahydro-1-oxopyrano[4,3-*b*][1]benzopyrans. *J. Org. Chem.* **1997**, *62*, 6888−6896.

(21) (a) Lesyk, R.; Zimenkovsky, B.; Atamanyuk, D.; Jensen, F.; Kiec-Kononowicz, K.; Gzella, A. Anticancer Thiopyrano[2,3-*d*][1,3]-thiazol-2-ones with Norbornane Moiety. Synthesis, Cytotoxicity, Physico-Chemical Properties, and Computational Studies. *Bioorg. Med. Chem.* **2006**, *14*, 5230−5240. (b) Razdan, R. K.; Bruni, R. J.; Mehta, A. C.; Weinhardt, K. K.; Papanastassiou, Z. B. A New Class of Antimalarial Drugs: Derivatives of Benzothiopyrans. *J. Med. Chem.* **1978**, *21*, 643−649. (c) Elslager, E. F. New Perspectives on the Chemotherapy of Malaria, Filariasis, and Leprosy. *Prog. Drug Res.* **1974**, *18*, 99−172.

(22) Pulici, M.; Quartieri, F. Traceless Solid-Phase Synthesis of 2-Amino-5-alkylidene-thiazol-4-ones. *Tetrahedron Lett.* **2005**, *46*, 2387−2391.

(23) Daboun, H. A.; Abdel Aziz, M. A. Synthesis of Some New Derivatives of Thiazolo[4,3-*b*]- and Thiazolo[2,3-*b*]quinazolone. *Arch. Pharm.* **1983**, *316*, 394−399.

(24) Dong, G.; Sheng, C.-Q.; Wang, S.; Miao, Z.; Yao, J.; Zhang, W.-N. Selection of Evodiamine as a Novel Topoisomerase I Inhibitor by Structure-Based Virtual Screening and Hit Optimization of Evodiamine Derivatives as Antitumor Agents. *J. Med. Chem.* **2010**, *53*, 7521−7531.

(25) Sheng, C.-Q.; Zhang, W.-N.; Ji, H.; Zhang, M.; Song, Y.; Xu, H.; Zhu, J.; Miao, Z.; Jiang, Q.; Yao, J.; Zhou, Y.; Lu, J. Structure-Based Optimization of Azole Antifungal Agents by CoMFA, CoMSIA, and Molecular Docking. *J. Med. Chem.* **2006**, *49*, 2512−2525.