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Facile Domino Access to Chiral Mono-, Bi-, and Tricyclic 2,3-Dihydrofurans

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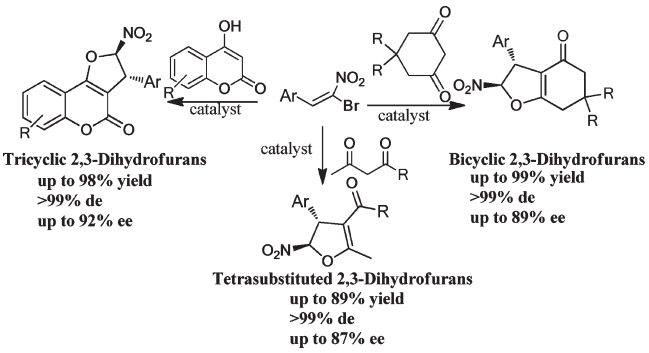

The asymmetric domino Michael-S_N2 reaction of various 1,3-dicarbonyl compounds to α-bromonitroalkenes is described for the first time, employing readily available cinchona-derived bifunctional thioureas as organocatalysts. The novel transformations were highly regio-, chemo-, diastereo-, and enantioselective, which simultaneously gave the chiral tricyclic 2,3-dihydrofurans, bicyclic 2,3-dihydrofurans, and tetrasubstituted 2,3-dihydrofurans with two vicinal chiral carbon centers.

The highly functionalized 2,3-dihydrofurans are very important compounds that are recognized for their importance as precursors for the asymmetric synthesis of tetrahydrofurans.[1] For example, they could serve as precursors for the construction of pharmacologically important furanoid lignans (Figure 1).[2] The asymmetric synthesis of chiral dihydrofuran derivatives has thus attracted much attention in the past few decades.[3] Ozawa and co-workers obtained enantioenriched 2,3-dihydrofurans from 2,3-dihydrofurans through a palladium-catalyzed asymmetric arylation of 2,3-dihydrofurans involving a kinetic resolution process.[3a] Recently, Tang et al. employed stereoselective formal [4 + 1] ylide annulation to generate 2,3-dihydrofuran derivatives, in which camphor-derived sulfur ylides were treated with α-ylidene-β-diketones in the presence of Cs_2CO_3.[3b] Gais et al. also reported the stereoselective synthesis of 2,3-dihydrofuran derivatives from chiral sulfoximine in more than eight steps.[3c]

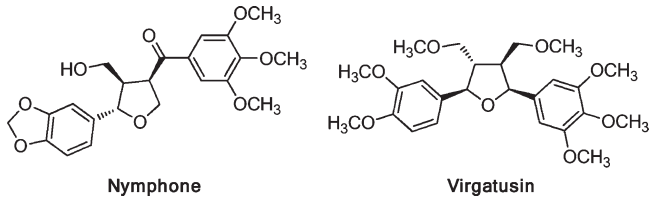

FIGURE 1. Some representative examples of biologically active compounds derived from 2,3-dihydrofurans.

However, these methods usually needed rather specific substrates (e.g., α-ylidene-β-diketones and ylide auxiliaries), most of which were not readily available and had inevitably lowered the overall atomic efficiency. As such, the application of chiral 2,3-dihyrofurans in natural product synthesis has been hampered by the lack of general methods for their asymmetric synthesis.[4,5] Therefore, there is an eager desire for a new synthetic method that allows the easy preparation of chiral mono-, bi-, and tricyclic dihydrofurans with high atomic efficiency and, more importantly, good feasibility to assemble various substitution patterns.

Organocatalytic asymmetric reactions have been used as an efficient tool for the synthesis of enantiopure molecules under mild, environmentally benign conditions over the past decades.[6] Meanwhile, domino reactions have been served as

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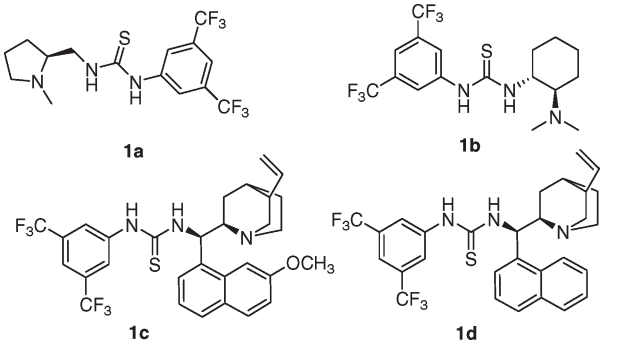


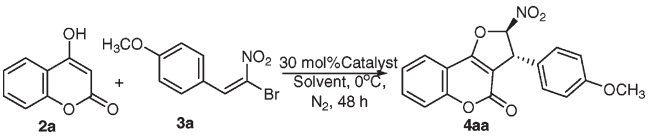
FIGURE 2. Structures of bifunctional organocatalysts **1a**−**1d**.

a powerful tool for the rapid and efficient assembly of complex structures from simple starting materials with minimized waste production.[7] Herein we present such an advance and its direct application in an atom-economical synthesis of chiral mono-, bi-, and tricyclic 2,3-dihydrofurans based on the development of a new organocatalytic enantioselective domino Michael-S_N2 reaction of 1,3-dicarbonyl compounds to α-bromonitroalkenes. Notably, the designed reactions are highly regio-, chemo-, diastereo-, and enantioselective and simultaneously give the desired multifunctional products with two vicinal chiral carbon centers.

Recently, bifunctional thioureas **1a**−**c** have appeared to be efficient organocatalysts for asymmetric additions of nucleophiles to nitroolefins (Figure 2).[8−11] In the course of our investigations on the use of α-bromonitroalkenes in organic synthesis, the α-bromonitroalkenes turned out to be highly reactive and versatile.[12,13] Especially, the bromo or nitro group could behave as a better leaving group in the reaction in comparison with bromoalkenes or nitroalkenes. We envisioned that the bifunctional organocatalysts **1a**−**c** would be efficient catalysts for the domino Michael-S_N2 reaction of 1,3-dicarbonyl compounds to α-bromonitroalkenes. Table 1 shows some screening results for the reaction of **2a** with **3a**. Initially, bifunctional thiourea **1a** was investigated as the organocatalyst, but only 21% ee was obtained (Table 1, entry 1). To our delight, when the reaction was catalyzed by Takemoto's catalyst **1b**, chiral **4aa** was formed in moderate yields and 51% ee (Table 1, entry 2). Subsequently, organocatalyst **1c**, derived from quinine, was proved to be superior to **1a**, **1b**, and **1d**, and product **4aa** was obtained with up to 64% ee (Table 1, entry 3). Various solvents were screened, and chloroform turned out to be optimal to give the product in higher enantioselectivities and yields (Table 1, entries 5−7). Interestingly, clean and quantitative product **4aa** was obtained without affecting the ee when achiral 1,4-diazabicyclo[2.2.2]octane (DABCO) was used as additive (entry 8). Among the additives examined, the use of *N*,*N*-diisopropylethylamine (DIPEA) as additive gave the best result (entry 9). By lowing the temperature to −40 °C, we got an excellent enantioselectivity (92% ee) and yield (90%) in the presence of **1c** (30 mol %) and *N*,*N*-diisopropylethylamine (DIPEA, 30 mol %) while the reaction time should be extended (entry 11). The ee was dramatically decreased when the catalyst loadings were reduced to 20 mol %, as well as when 50 mol % of DIPEA was added (entries 12 and 13).

With the optimal reaction conditions in hand, the scope of the present organocatalytic asymmetric domino Michael-S_N2 reaction using catalyst **1c**-DIPEA was extended to various cyclic 1,3-dicarbonyl compounds (Figure 3) and α-bromonitroalkenes. Only the *anti*-products were detected for all the reactions. As illustrated in Table 2, for the reactions of

TABLE 1. Screening Studies of Organocatalytic Domino Reaction of 4-Hydroxylcoumarin 2a to α-Bromonitroalkene 3a[a]



entry	catalyst	base	solvent	yield[b] (%)	ee[c] (%)
1	**1a**		DCM	35	21
2	**1b**		DCM	52	51
3	**1c**		DCM	58	64
4	**1d**		DCM	64	53
5	**1c**		toluene	54	64
6	**1c**		THF	42	60
7	**1c**		$CHCl_3$	62	71
8[d]	**1c**	DABCO	$CHCl_3$	quant	70
9[d]	**1c**	DIPEA	$CHCl_3$	quant	73
10[d]	**1c**	DBU	$CHCl_3$	quant	69
11[e]	**1c**	**DIPEA**	**$CHCl_3$**	**90**	**92**
12[f]	**1c**	DIPEA	$CHCl_3$	78	83
13[g]	**1c**	DIPEA	$CHCl_3$	quant	78

[a]Unless otherwise noted, reactions performed with 0.1 mmol of **2a**, 0.12 mmol of **3a**, 30 mol % of **1** in 1 mL of solvent at 0 °C under N_2 for 48 h. [b]Isolated yield. [c]Determined by the chiral HPLC analysis. [d]Adding 30 mol % base. [e]At −40 °C under N_2 for 96 h. [f]20 mol % of **1c** and 20 mol % of DIPEA. [g]50 mol % DIPEA.

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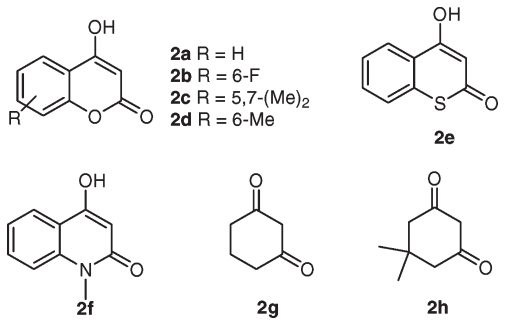
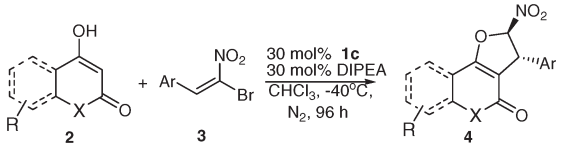


FIGURE 3. Structures cyclic 1,3-dicarbonyl compounds.

TABLE 2. Asymmetric Domino Reaction of 1,3-Dicarbonyl Compounds 2 to α-Bromonitroalkenes 3[a]

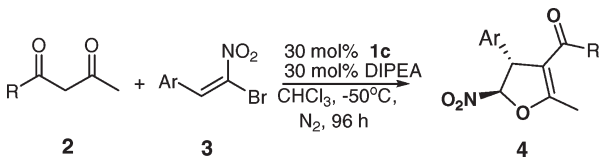


entry	sub. (**2**)	Ar (**3**)	yield[b] (%)	ee[c] (%)	**4**
1	**2a**	*p*-MeO-Ph (**3a**)	90	92	**4aa**
2	**2a**	*p*-Me-Ph (**3b**)	94	86	**4ab**
3	**2a**	Ph (**3c**)	96	85	**4ac**
4	**2a**	*p*-Cl-Ph (**3d**)	89	92	**4ad**
5	**2a**	*p*-Br-Ph (**3e**)	89	90	**4ae**
6	**2b**	*p*-MeO-Ph (**3a**)	89	82	**4ba**
7	**2c**	*p*-MeO-Ph (**3a**)	87	79	**4ca**
8	**2d**	*p*-MeO-Ph (**3a**)	92	89	**4da**
9	**2d**	*p*-Cl-Ph (**3d**)	98	92	**4dd**
10	**2d**	2-furanyl (**3f**)	96	84	**4df**
11	**2e**	*p*-MeO-Ph (**3a**)	86	82	**4ea**
12	**2f**	*p*-MeO-Ph (**3a**)	89	90	**4fa**
13	**2g**	*p*-MeO-Ph (**3a**)	96	82	**4ga**
14	**2g**	*p*-Me-Ph (**3b**)	98	84	**4gb**
15	**2g**	Ph (**3c**)	97	84	**4gc**
16	**2g**	*p*-Cl-Ph (**3d**)	99	87	**4gd**
17	**2g**	*p*-Br-Ph (**3e**)	98	85	**4ge**
18	**2h**	*p*-MeO-Ph (**3a**)	97	84	**4ha**
19	**2h**	*p*-Cl-Ph (**3d**)	98	88[d]	**4hd**

[a]Unless otherwise noted, reactions performed with 0.1 mmol of **2**, 0.12 mmol of **3**, 30 mol % of **1c**, and 30 mol % of DIPEA in 1 mL of $CHCl_3$ at −40 °C under N_2 for 96 h. [b]Isolated yield. [c]Determined by the chiral HPLC analysis. [d]The absolute configuration was determined to be (C9*R*,C10*R*), see Supporting Information.

4-hydroxycoumarins **2a** and **2d**, excellent results were achieved with α-bromonitroalkenes **3a**−**3e** bearing various *β*-aryl substitutions or heteroaryl substitutions (Table 2, entries 1−5, 8−10). Subsequently, a few 4-hydroxycoumarin derivatives **2b**−**2d** with different substitutions were investigated. The electronic effect was very marginal, and remarkable enantioselectivity was achieved (entries 6−10). 4-Hydroxythiocoumarin **2e** also exhibited a good reactivity, and a good ee (82%, entry 11) was still obtained. Although a very low solubility of **2f** was observed in chloroform, gratifyingly, the domino reaction proceeded very well at −40 °C due to the very high solubility of product **4fa** in chloroform, and an excellent ee (90%) was achieved in a yield of 89% after 96 h (entry 12). Having succeeded in synthesizing chiral tricyclic 2,3-dihydrofurans **4aa**−**4fa**, we then turned our attention to the synthesis of chiral bicyclic 2,3-dihydrofurans. The domino reactions proceeded in good yields with high enantioselectivities

TABLE 3. Synthesis of Chiral Monocyclic 2,3-Dihydrofurans 4[a]



entry	R (**2**)	**3**	**4**	yield[b] (%)	ee[c] (%)
1	OMe (**2i**)	**3a**	**4ia**	86	87
2	OMe (**2i**)	**3d**	**4id**	88	87
3	CH_3 (**2j**)	**3a**	**4ja**	89	77
4	CH_3 (**2j**)	**3d**	**4jd**	86	76

[a]Unless otherwise noted, reactions performed with 0.1 mmol of **2**, 0.12 mmol of **3**, 30 mol % of **1c**, and 30 mol % of DIPEA in 1 mL of$CHCl_3$ at −50 °C under N_2 for 96 h. [b]Isolated yield. [c]Determined by the chiral HPLC analysis.

when cyclohexane-1,3-dione (**2g**) and 5,5-dimethylcyclohexane-1,3-dione (**2h**) (Table 2, entries 13−19) were used, as well as when 4-hydroxythiocoumarins were used as Michael donors.

To extend the scope of the domino reaction further, acyclic 1,3-dicarbonyl compounds **2h**−**2i** were utilized as Michael donors in the reaction with α-bromonitroalkenes in the presence of **1c**-DIPEA (Table 3). As demonstrated in Table 3, the domino Michael-S_N2 process takes place with α-bromonitroalkene Michael acceptors, which possess electron-donating, electron-withdrawing groups in the phenyl ring at −50 °C. It appeared that substituents' electronics have a minimal impact on efficiencies, enantioselectivities, and diastereoselectivities of the domino Michael-S_N2 reactions when ethyl acetoacetate **2i** was used as Michael donor (Table 3, entries 1 and 2). The ee was decreased when acetylacetone **2j** was used as Michael donor (Table 3, entries 3 and 4).

In summary, we have developed the first organocatalytic asymmetric domino Michael-S_N2 reaction of various 1,3-dicarbonyl compounds to α-bromonitroalkenes with excellent chemo- and stereoselectivities, employing an easily available organic catalyst. This novel, versatile, and efficient domino reaction affords chiral tricyclic 2,3-dihydrofurans, bicyclic 2,3-dihydrofurans, and tetrasubstituted 2,3-dihydrofurans in high yields and enantioselectivities that, to date, have not been reported in the literature. This novel methodology should be of great potential for natural product synthesis due to the mild reaction conditions.

Experimental Section

General Procedure for Asymmetric Domino Reaction of 1,3-Dicarbonyl Compounds 2 to α-Bromonitroalkenes 3. Compounds **2a** 16.2 mg (0.1 mmol), **3a** 30.7 mg (1.2 mmol), **1c** 17.8 mg (0.03 mol), and DIPEA 5.0 *μ*L (0.03 mol) were stirred in $CHCl_3$ (1 mL) at −40 °C under N_2 for 96 h. Then flash chromatography on silica gel (10% ethyl acetate/petroleum ether) gave **4aa** as a white solid (30 mg, 90% yield).

3-(4-Methoxyphenyl)-2-nitro-2*H*-furo[3,2-*c*]chromen-4(3*H*)-one (4aa). 90% yield. ^1H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.87 (d, *J* = 8.6 Hz, 1H), 7.70−7.68 (m, 1H), 7.47−7.41 (m, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.22 (d, *J* = 1.6 Hz, 1H), 4.91 (d, *J* = 2.0 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 193.8, 175.9, 159.6, 128.8, 128.1, 116.3, 114.6, 111.1, 55.3, 52.4, 36.8, 23.4, 21.6; IR (KBr) cm^{-1} 2957, 2925, 1726, 1659, 1576, 1498, 1367, 1082, 820, 761; ESI-HRMS calcd for $C_{18}H_{13}NO_6$ + Na 362.0635, found 362.0635; $[\alpha]^{25}_D = -24.0$

(c 0.32, CH_2Cl_2), 92% ee. The enantiomeric ratio was determined by HPLC on a Chiralpak OD column (30% 2-propanol/hexane, 1 mL/min), t_{major} = 10.68 min, t_{minor} = 15.45 min.

Crystal data for **4hd**: $C_{16}H_{16}ClNO_4$ (321.75), orthorhombic, space group $P2(1)2(1)2(1)$, a = 6.5771(2), b = 7.3843(2), c = 32.6590(8) Å, U = 1586.16(8) Å^3, Z = 4, specimen 0.371 × 0.230 × 0.128 mm^3, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 0.258 mm^{-1}, reflections collected 25743, independent reflections 3683 [R(int) = 0.0312], refinement by full-matrix least-squares on F^2, data/restraints/parameters 3683/1/199, goodness-of-fit on F^2 = 1.032, final R indices [$I > 2\sigma(I)$] $R1$ = 0.0399, $wR2$ = 0.1034, R indices (all data) $R1$ = 0.0505, $wR2$ = 0.1104, largest diff. peak and hole 0.202 and −0.302 e Å^{-3}.

Crystal data for **4ga**: $C_5H_{15}NO_5$ (289.28), monoclinic, space group $C2/c$, a = 22.0833(10), b = 7.0950(3), c = 20.9180(10) Å, U = 2856.5(2) Å^3, Z = 8, specimen 0.653 × 0.263 × 0.248 mm^3, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 0.102 mm^{-1}, reflections collected 21781, independent reflections 3315 [R(int) = 0.0258], refinement by full-matrix least-squares on F^2, data/restraints/parameters 3315/0/190, goodness-of-fit on F^2 = 1.039, final R indices [$I > 2\sigma(I)$] $R1$ = 0.0431, $wR2$ = 0.1166, R indices (all data) $R1$ = 0.0561, $wR2$ = 0.1283, largest diff. peak and hole 0.219 and −0.249 e Å^{-3}.

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Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds and X-ray structural data for **4hd** and **4ga** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.