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Asymmetric Cycloetherification of in Situ Generated Cyanohydrins through the Concomitant Construction of Three Chiral Carbon Centers

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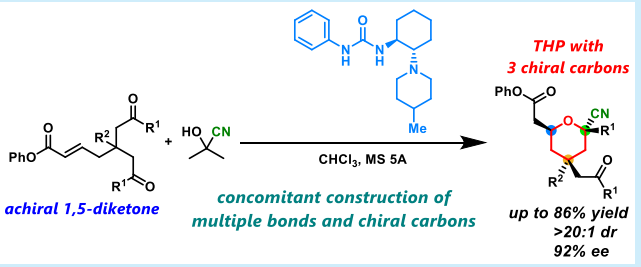
Supporting Information

ABSTRACT: The organocatalytic enantio- and diastereoselective cycloetherification of in situ generated cyanohydrins through the concomitant construction of three chiral carbon centers is reported. This protocol facilitates the concise synthesis of optically active tetrahydropyran derivatives, which are ubiquitous scaffolds found in various bioactive compounds, through the simultaneous construction of multiple bonds and stereogenic centers, including tetrasubstituted chiral carbons. The resulting products also contain multiple synthetically important functional groups, which expand their possible usefulness as chiral building blocks.

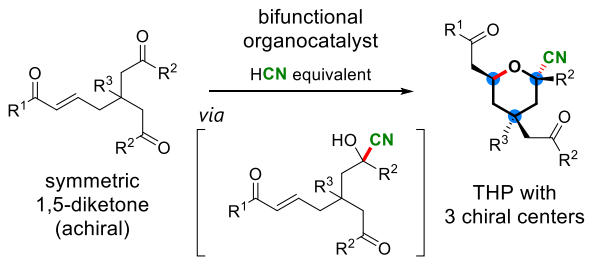


The ability to rapidly increase molecular complexity is of great significance in synthetic chemistry because it provides concise access to functional molecules including bioactive compounds. In particular, optically active cyclic molecules containing multiple chiral carbons provide three-dimensional scaffolds that promote important functions within organisms.[1] Hence, to explore unexploited molecular functions including pharmaceutical activities, it is necessary to pursue asymmetric catalysis that facilitates the construction of such architectures in a single operation from achiral substrates.

In the context of accessing chiral ring structures, the cyclizations of achiral molecules that possess enantiotopic functional groups through successive bond formation[2] and desymmetrization[3] enables the concomitant generation of stereochemical complexity. In this study, we present an organocatalytic enantio- and diastereoselective method for the cycloetherification of symmetrical 1,5-diketone-bearing enones that involves the in situ generation of intermediary cyanohydrins (Scheme 1). This transformation simultaneously constructs two bonds and three stereogenic centers with control of relative and absolute stereochemistry while forming a tetrahydropyran (THP) ring,[4] which is a ubiquitous scaffold found in a range of bioactive natural products and pharmaceuticals.[5] In addition, the resulting product contains three chiral carbons, two of which bear carbonyl-group-containing substituents, with the other bearing a cyano group;[6] these substituents are useful for further derivatization, thereby increasing synthetic utility.

Following our recent studies on asymmetric cycloetherifications through the dynamic kinetic resolution of reversibly generated chiral cyanohydrins,[7] we began our investigations using (*E*)-5-(2-oxo-2-phenylethyl)-1,7-diphenylhept-2-ene-1,7-dione (**1a**) and acetone cyanohydrin (**2**) with 10 mol % of the

Scheme 1. Organocatalytic Asymmetric Cycloetherification of Cyanohydrins Generated in Situ from 1,5-Diketones



bifunctional organocatalysts **4** (Figure 1)[8] in CH_2Cl_2 at 25 °C (Table 1, entries 1−10). Preliminary investigations revealed that the addition of the cyanating reagent **2** in two parts resulted in better yields and enantioselectivities (see the Supporting Information for details), and this protocol was employed in all reactions. Bifunctional piperidyl-group-containing organocatalysts **4c** and **4d** gave better diastereoselectivities than the dimethylamino-group-containing **4a** and **4b** (Table 1, entries 1−4). In addition, analogous catalysts **4e** and **4f** (Table 1, entries 5 and 6), and additional catalysts **4g**−**4j** bearing 4-methylpiperidyl groups (Table 1, entries 7−10) were also investigated; among them, catalysts **4e**, **4f**, **4i**, and **4j**, bearing phenyl groups on the thiourea or urea moieties, gave higher enantioselectivities (Table 1, entries 5, 6, 9, and 10). Furthermore, the urea-based catalyst

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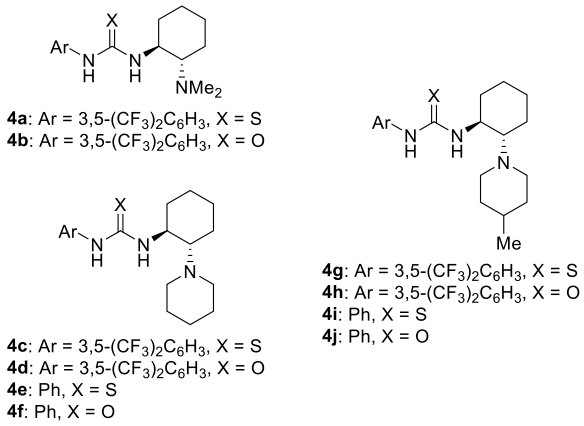


Figure 1. Bifunctional organocatalysts.

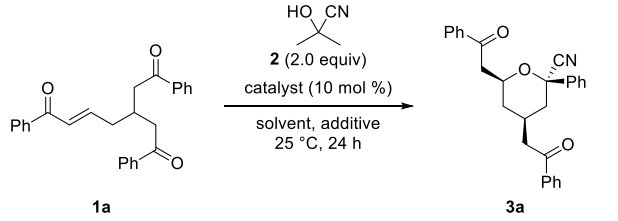
was more reactive than the thiourea-based catalyst within each category (**4a** vs **4b**; **4c** vs **4d**; **4e** vs **4f**; **4g** vs **4h**; **4i** vs **4j**). These investigations identified **4j** as the most efficient catalyst for this transformation. Alternative cyanating reagents were also investigated (Table 1, entries 11 and 12). Trimethylsilyl cyanide in the presence of 2-propanol afforded good stereoselectivity but a lower yield (Table 1, entry 11); the use of trimethylsilyl cyanide alone provided the product in even better enantioselectivity, but in much lower yield (Table 1, entry 12).

Various solvents were next investigated using **4j** and **2** as substrates (Table 1, entries 13−24). The use of $CHCl_3$ resulted in high diastereoselectivity and good yield (Table 1, entry 13); however, hydrocarbon solvents resulted in lower stereoselectivities (Table 1, entries 14−17), and polar solvents resulted in lower reactivities and stereoselectivities (Table 1, entries 18−24). Molecular sieves (MS), as additives, were also investigated (Table 1, entries 25−28). Among them, MS 5A and MS 13X led to improved stereoselectivities with only slight losses in yield (Table 1, entries 27 and 28). These additives might play roles as bases that remove detrimental acids since similar reaction outcomes were obtained using $CHCl_3$ passed through an alumina column (Table 1, entry 29).

With the established conditions in hand, we next investigated substrates bearing other substituents on their enone moieties (Table 2). Electron-donating groups resulted in higher stereoselectivities (Table 2, entries 2 and 4), while an electron-withdrawing group resulted in a lower stereoselectivity (Table 2, entry 3). In addition, although the 4-bromophenyl group resulted in a lower yield and moderate stereoselectivity (Table 2, entry 5), the 2-naphthyl group provided results comparable to those of the reaction that afforded **3a** (Table 2, entry 6). An aliphatic substituent was also tolerated in this transformation, providing **3g** with good stereoselectivity (Table 2, entry 7). Furthermore, to our delight, an α,β-unsaturated ester, which is useful for further synthetic transformations due to its higher oxidation state,[9] gave the highest enantioselectivity, with **3h** formed in high yield and good diastereoselectivity (Table 2, entry 8). Moreover, a thioester, which is another synthetically important functional group,[10] was also tolerated in this reaction; **3i** was obtained in high stereoselectivity (Table 2, entry 9). The absolute configurations of the two main diastereomers of **3e** were determined by X-ray crystallography (see the Supporting Information for details), and the configurations of all other products **3** were assigned on the basis of these structures.

We further explored the substrate scope using α,β-unsaturated esters (Scheme 2). Electron-rich substrate **1j** was less reactive (25

Table 1. Optimization of Conditions[a]



entry	catalyst	solvent	additive	yield (%)[b]	dr[c]	ee (%)
1	**4a**	CH_2Cl_2		48	1.5:1	71
2	**4b**	CH_2Cl_2		67	3.0:1	35
3	**4c**	CH_2Cl_2		73	4.6:1	69
4	**4d**	CH_2Cl_2		93	14:1	56
5	**4e**	CH_2Cl_2		45	17:1	89
6	**4f**	CH_2Cl_2		90	16:1	81
7	**4g**	CH_2Cl_2		trace		
8	**4h**	CH_2Cl_2		90	11:1	52
9	**4i**	CH_2Cl_2		24	8.3:1	87
10	**4j**	CH_2Cl_2		77	11:1	83
11[d]	**4j**	CH_2Cl_2		44	>20:1	82
12[e]	**4j**	CH_2Cl_2		5	>20:1	88
13	**4j**	$CHCl_3$		72	19:1	83
14	**4j**	benzene		59	14:1	73
15	**4j**	toluene		64	9.6:1	71
16	**4j**	*c*-hexane		67	7.6:1	71
17	**4j**	*n*-hexane		71	6.8:1	66
18	**4j**	Et_2O		14	6.4:1	77
19	**4j**	THF		11	19:1	71
20	**4j**	CPME[f]		17	19:1	76
21	**4j**	EtOAc		9	20:1	70
22	**4j**	acetone		20	15:1	73
23	**4j**	CH_3CN		31	5.8:1	76
24	**4j**	EtOH		<5		
25	**4j**	$CHCl_3$	MS 3A[g]	71	17:1	86
26	**4j**	$CHCl_3$	MS 4A[g]	64	13:1	85
27	**4j**	$CHCl_3$	MS 5A[g]	68	>20:1	85
28	**4j**	$CHCl_3$	MS 13X[g]	64	>20:1	85
29	**4j**	$CHCl_3$[h]		63	>20:1	84

[a]Reactions were run using **1a** (0.15 mmol), **2** (0.30 mmol), and the catalyst (0.015 mmol) in the solvent (0.30 mL) with **2** added in two parts. [b]Yield of the major diastereomer. [c]Ratio of the two major diastereomers among the four diastereomers detected in total. [d]Reaction was run using trimethylsilyl cyanide (0.30 mmol) with 2-propanol (0.30 mmol) instead of **2**. [e]Reaction was run using trimethylsilyl cyanide (0.30 mmol) instead of **2**. [f]CPME = cyclopentyl methyl ether. [g]Molecular sieves (60 mg) were used. [h]$CHCl_3$ was used after passing it through an alumina column.

°C, 24 h: 15%, >20:1 dr, 91% *ee*); this reaction was performed at 35 °C for 48 h to afford a slightly higher yield than that at 25 °C for 24 h, but with lower diastereoselectivity and high enantioselectivity. However, electron-deficient substrates **1k** and **1l** were highly reactive and afforded good stereoselectivities that are comparable to those of the reaction involving **1h**. Heterocyclic substrate **1m** required modified conditions to afford the corresponding product **3m** in high yield, but the enantioselectivity was high irrespective of the reaction conditions (25 °C, 24 h: 25%, 13:1 dr, 91% *ee*). Substrates **1n** and **1o** bearing 4-methylphenyl and 3,5-dimethylphenyl groups, respectively, also afforded THPs **3n** and **3o** with high enantioselectivities at 35 °C after 48 h (25 °C, 24 h: **3n**, 20%, >20:1 dr, 93% *ee*; **3o**, 35%, >20:1 dr, 94% *ee*). In addition, aliphatic substrate **1p** also gave

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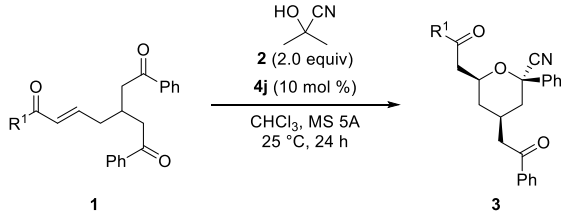
Table 2. Investigating the Michael Acceptor Substituents[a]



entry	R^1 (3)	yield (%)[b]	dr[c]	ee (%)
1	Ph (**3a**)	68	>20:1	85
2	4-$MeOC_6H_4$ (**3b**)	57	20:1	90
3	4-$CF_3C_6H_4$ (**3c**)	68	7.3:1	70
4	4-MeC_6H_4 (**3d**)	49	>20:1	89
5	4-BrC_6H_4 (**3e**)	38	12:1	79
6	2-naphthyl (**3f**)	73	20:1	82
7	Me (**3g**)	69	20:1	89
8	PhO (**3h**)	71	20:1	92
9	2,6-$Me_2C_6H_3S$ (**3i**)	61	>20:1	88

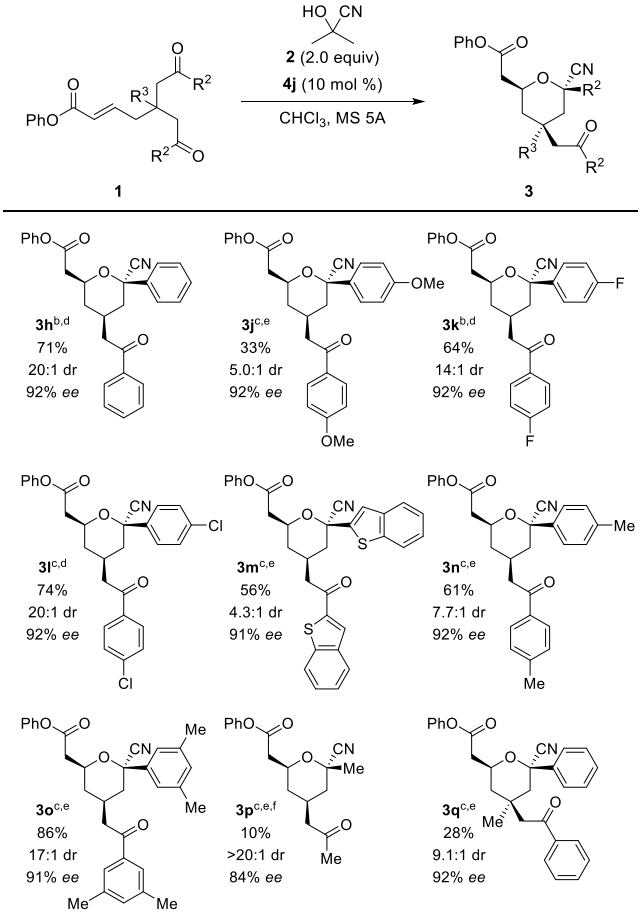
[a]Reactions were run using **1** (0.15 mmol), **2** (0.30 mmol), and **4j** (0.015 mmol), MS 5A (60 mg) in $CHCl_3$ (0.30 mL) with **2** added in two parts. [b]Yield of the major diastereomer. [c]Ratio of the two major diastereomers among the four diastereomers detected in total.

optically active THP **3p**; the use of **4f** as the catalyst resulted in a higher enantioselectivity (84% *ee*) than **4j** (11%, >20:1 dr, 81% *ee*), although the yields were low in each case. Furthermore, THP **3q**, containing two tetrasubstituted stereogenic centers, was synthesized with high enantio- and diastereoselectivity, albeit in modest yield even at 35 °C over 48 h (25 °C, 24 h: 12%, >20:1 dr, 92% *ee*).

The reaction of methyl ester **1r** was also examined under the optimized conditions (Scheme 3). In this case, only a trace amount of the THP product **3r** was obtained, with the corresponding cyanohydrin **1r′** isolated instead; **1r′** was much less optically pure than the cyclized products **3** listed in Scheme 2. These results indicate that the nucleophilic 1,2-addition step that forms the cyanohydrin does not determine the enantioselectivity associated with the formation of **3**; rather it arises in a synchronized manner through desymmetrization involving the asymmetric oxy-Michael addition of the in situ generated cyanohydrin, one stereoisomer of which is selectively recognized and activated through multipoint hydrogen bonding interactions involving the bifunctional organocatalyst.[11,12]

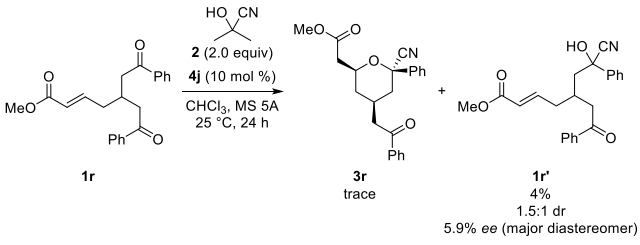
In summary, we demonstrated the organocatalytic enantio- and diastereoselective cycloetherification of in situ generated cyanohydrins that involves the concomitant construction of three chiral carbon centers. This transformation provides a concise synthetic route to optically active THP derivatives accompanied by the simultaneous construction of multiple bonds and stereogenic centers, including tetrasubstituted chiral carbon centers. The resulting products also contain multiple synthetically important functional groups in different oxidation states (ketone, ester, and cyano groups); hence, this synthesis method facilitates the construction of complex heterocyclic architectures. Further studies that expand the range of optically active heterocycles accessible using this methodology, including those bearing other substitution patterns or scaffolds, are ongoing in our laboratory and will be reported in due course.

Scheme 2. Substrate Scope[a]



[a]Yields are for the major diastereomer and represent material isolated after silica gel column chromatography. Diastereomeric ratios relate to the two major diastereomers among the four diastereomers detected in total. [b]Reactions were run using **1** (0.15 mmol), **2** (0.30 mmol), and **4j** (0.015 mmol), MS 5A (60 mg) in $CHCl_3$ (0.30 mL) with **2** added in two parts. [c]Reactions were run using **1** (0.10 mmol), **2** (0.20 mmol), and **4j** (0.010 mmol), MS 5A (40 mg) in $CHCl_3$ (0.20 mL) with **2** added in two parts. [d]Reactions were run at 25 °C for 24 h. [e]Reactions were run at 35 °C for 48 h. [f]Reaction was run using **4f** instead of **4j**.

Scheme 3. Reaction of Methyl Ester 1r



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00462.

Experimental procedures including spectroscopic and analytical data (PDF)

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Accession Codes

CCDC 1895615−1895616 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_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.

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