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Asymmetric Cycloetherification via the Kinetic Resolution of Alcohols Using Chiral Phosphoric Acid Catalysts

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In this study, novel asymmetric cycloetherification via the kinetic resolution of secondary or tertiary alcohols using chiral phosphoric acid catalysts was developed, affording tetrahydropyrans (THPs) with two stereogenic centers. The cyclization of the recovered optically active alcohols afforded other stereoisomers of THPs. These protocols offer efficient synthetic routes to various optically active THP derivatives, which are important structures found in a range of biologically active agents.

The kinetic resolution of chiral alcohols has been extensively investigated because of their importance as a feedstock for optically active materials.[1] As chiral oxacycles are versatile frameworks found in a wide range of natural products and bioactive molecules (Figure 1),[2] it is also essential to develop enantioselective cycloetherification via kinetic resolution starting from racemic secondary or tertiary alcohols. However, few examples of such methodologies for enabling the synthesis of chiral cyclic ethers are available.[3] Meanwhile, we have recently reported several asymmetric cycloetherification reactions using bifunctional amino(thio)urea catalysts.[4,5] In these studies, the utilization of the multipoint recognition of substrates using bifunctional organocatalysts via hydrogen bonding[6] for enantioselective C–O bond formation via intramolecular oxy-Michael addition has proven to be efficient.[7] As a result, these insights have stimulated us to use organocatalysts by utilizing hydrogen bonding for intramolecular oxy-Michael addition accompanied by the kinetic resolution of racemic alcohols, affording oxacycles bearing two stereogenic centers (Scheme 1). In this study, we demonstrate novel organocatalytic asymmetric cycloetherification via the kinetic resolution of secondary or tertiary alcohols, affording tetrahydropyrans (THPs) with two asymmetric centers.

Initially, the reaction of (±)-(*E*)-7-hydroxy-1,7-diphenylhept-2-en-1-one ((±)-**1a**) was performed at 0 °C using bifunctional aminothiourea catalysts **3a** and **3b**, and the observed selectivity factors were not satisfactory (Table 1, entries 1 and 2, respectively).[8] Next, we focused on chiral phosphoric acid catalysts **3c**–**3e**[9] as they also contain both acidic and basic sites, allowing for the multipoint recognition of substrates via hydrogen bonding;[10] on the other hand, sterically bulky substituents near catalytic sites are well known to help in the recognition of substituents on substrates, thereby affording high stereoselectivity.[11] In this context, we envisioned that chiral phosphoric acid catalysts would be more suitable for the kinetic resolution of alcohols.[12]

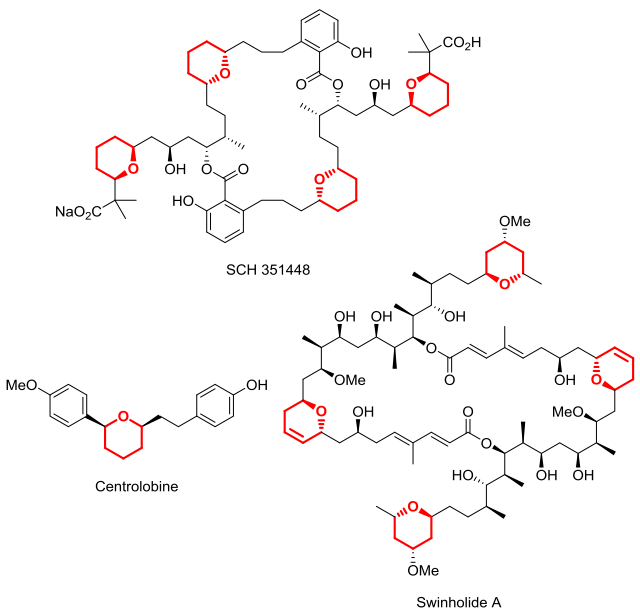
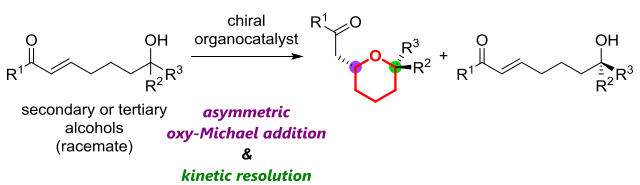


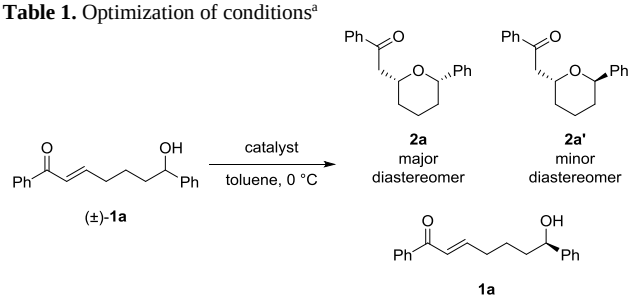
Figure 1. Chiral THPs in natural products.



Scheme 1. Asymmetric intramolecular oxy-Michael addition via kinetic resolution of chiral alcohols

As expected, phosphoric acid catalyst **3c**[13] with a BINOL backbone performed significantly better than aminothiourea catalysts (Table 1, entry 3), although other phosphoric acids with different backbones gave less satisfactory results (Table 1, entries 4 and 5).[14] With **3c**, lower temperatures were subsequently utilized. Although the stereoselectivity was not improved for the reaction performed at –20 °C (Table 1, entry 6), the use of 4 Å molecular sieves (4 Å MS) as an additive was found to dramatically accelerate the reaction (Table 1, entry 7); in the presence of 4 Å MS, the reaction was performed even at lower temperature, and the selectivity factor was significantly improved (Table 1, entry 8).

Table 1. Optimization of conditions[a]



Entry	Catalyst (mol %)	Time (h)	Conv. (%)[b]	dr **2a**:**2a'**	ee (%) **2a**, **2a'**, **1a**	*s* factor[c]
1	**3a** (30)	48	58	4.3:1	70, 28, 72	6.5
2	**3b** (30)	48	68	2.1:1	–69, –7, –93	8.0
3	**3c** (1)	2	55	16:1	80, 80, 85	15
4	**3d** (0.3)	3	48	24:1	22, 10, 19	1.8
5	**3e** (1)	24	28	24:1	62, 31, 23	4.7
6[d]	**3c** (1)	12	44	19:1	87, 61, 62	16
7[d,e]	**3c** (1)	2	44	19:1	88, 79, 62	16
8[e,f]	**3c** (5)	4	51	24:1	89, 87, 85	27

[a]Reactions were run using (±)-**1a** (0.15 mmol) and the catalyst in toluene (15 mL). [b]Conversions were calculated from the ee values. See the Supporting Information for details. [c]Selectivity factors (*s*) were calculated from the dr and ee values (ref 8). See the Supporting Information for details. [d]Reactions were run at –20 °C. [e]Reactions were run using 4 Å MS (300 mg). [f]Reaction was run at –40 °C.

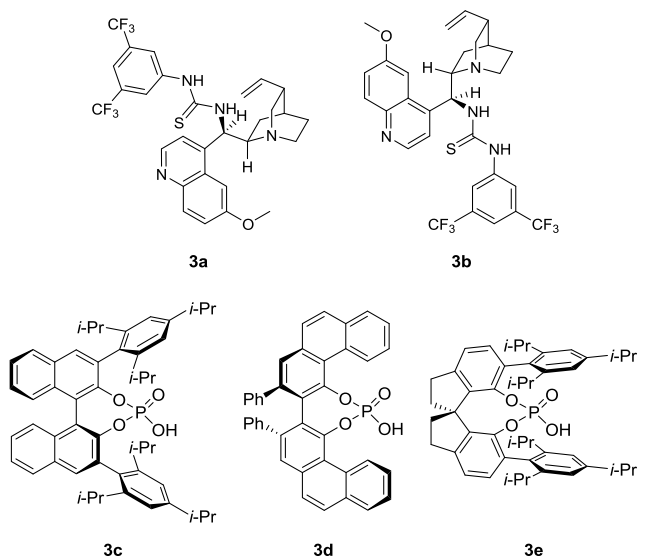
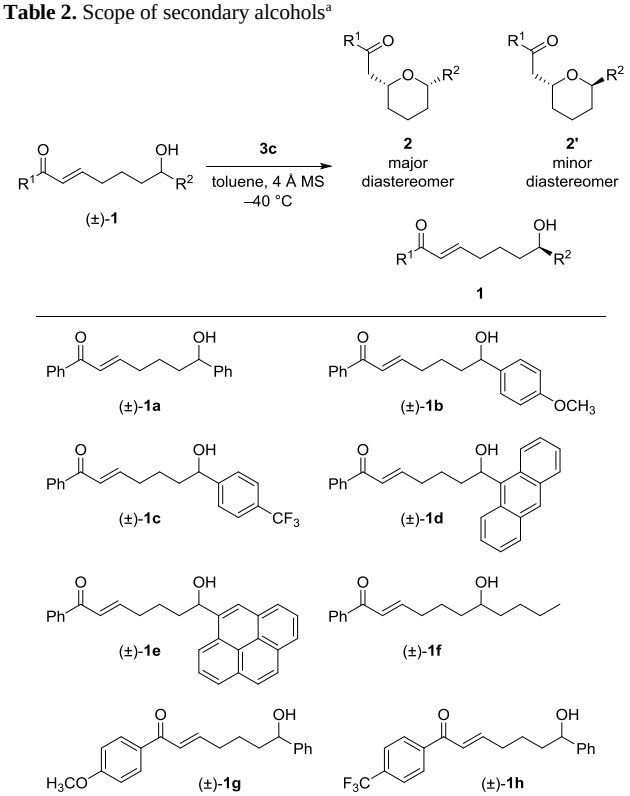


Figure 2. Chiral organocatalysts.

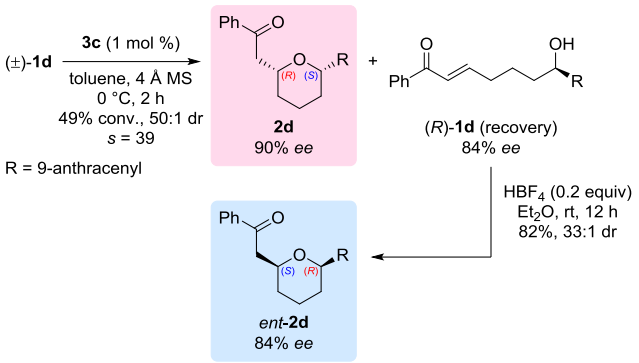
With the established optimal conditions, we explored the substrate scope. Although poor stereoselectivity was observed for the reaction of a substrate containing an alcohol with a *p*-methoxyphenyl group (Table 2, entry 2), in the case of a substrate containing a *p*-trifluoromethyl group, a good selectivity factor was obtained (Table 2, entry 3). Substrates bearing larger substituents, such as 9-anthracenyl and 4-pyrenyl groups, also exhibited high stereoselectivities (Table 2, entries 4 and 5, respectively); the selectivity factor of the reaction using (±)-**1d** increased to 39. A substrate with an aliphatic substituent also participated in kinetic resolution, affording moderate selectivity (Table 2, entry 6). In addition, substrates with electron-rich and electron-poor enones were also applicable, both of which exhibited high stereoselectivities (Table 2, entries 7 and 8, respectively). The absolute configurations of **2a** and **2a'** were determined by NOE and HPLC analyses (see the Supporting Information for details), and the configurations of all other examples were assigned analogously.

Table 2. Scope of secondary alcohols[a]



Entry	(±)-**1**	**3c** (mol %)	Time (h)	Conv. (%)[b]	dr **2**:**2'**	ee (%) **2**, **2'**, **1**	*s* factor[c]
1	(±)-**1a**	5	4	51	24:1	89, 87, 85	27
2	(±)-**1b**	5	36	63	4.3:1	58, 96, 50	1.8
3	(±)-**1c**	5	4	52	16:1	90, 90, 87	26
4[d]	(±)-**1d**	1	2	49	50:1	90, 83, 84	39
5[d]	(±)-**1e**	1	1	58	17:1	79, 71, 98	26
6	(±)-**1f**	5	2.5	53	14:1	82, 84, 81	15
7	(±)-**1g**	5	4	52	19:1	90, 85, 89	30
8	(±)-**1h**	5	7	57	12:1	86, 88, 97	26

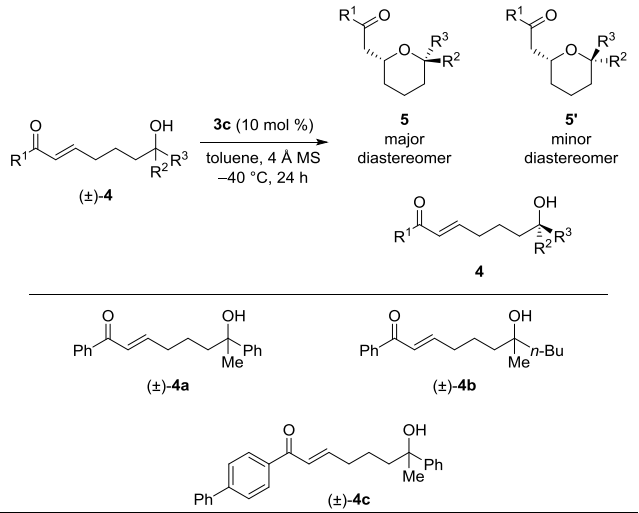
[a]Reactions were run using (±)-**1** (0.15 mmol), **3c**, and 4 Å MS (300 mg) in toluene (15 mL). [b]Conversions were calculated from the ee values. See the Supporting Information for details. [c]Selectivity factors (*s*) were calculated from the dr and ee values (ref 8). See the Supporting Information for details. [d]Reactions were run at 0 °C.



Scheme 2. Enantiodivergent synthesis of *cis*-2,6-disubstituted THPs

For demonstrating the utility of the recovered chiral secondary alcohols, the cyclization of the recovered optically active **1d** was further performed (Scheme 2). The treatment of the recovered (*R*)-**1d** with tetrafluoroboric acid afforded *ent*-**2d** as a *cis*-isomer without the loss of enantiomeric purity. In total, these protocols provided both enantiomers of *cis*-2,6-disubstituted THPs by using **3c** as the only chiral source.

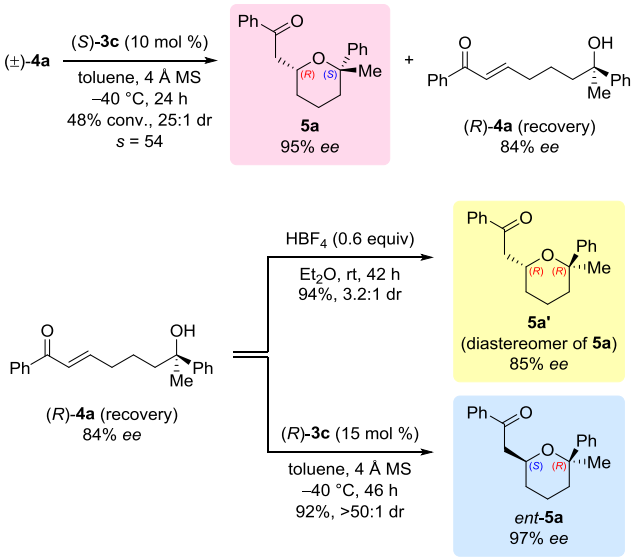
Table 3. Kinetic resolution of tertiary alcohols[a]



Entry	(±)-**4**	Conv. (%)[b]	dr **5**:**5'**	ee (%) **5**, **5'**, **4**	*s* factor[c]
1[d]	(±)-**4a**	48	25:1	95, 10, 84	54
2	(±)-**4b**	58	10:1	79, 76, 89	13
3	(±)-**4c**	47	11:1	81, 74, 61	9.7

[a]Reactions were run using (±)-**4** (0.15 mmol), **3c** (0.015 mmol), and 4 Å MS (300 mg) in toluene (15 mL). [b]Conversions were calculated from the ee values. See the Supporting Information for details. [c]Selectivity factors (*s*) were calculated from the dr and ee values (ref 8). See the Supporting Information for details. [d]Reaction was run using (±)-**4a** (0.3 mmol), **3c** (0.03 mmol), and 4 Å MS (600 mg) in toluene (30 mL).

Furthermore, this kinetic resolution method can also be applied to tertiary alcohols (Table 3). The kinetic resolution of (±)-**4a** afforded good stereoselectivity, with a selectivity factor of 54 (Table 3, entry 1). In addition, an alcohol with two different aliphatic substituents also successfully completed the reaction (Table 3, entry 2). A substrate with a biphenyl group at the enone moiety also afforded the corresponding products; the absolute configurations of **5c** and **5c'** were determined by X-ray analysis (see the Supporting Information for details), and the configurations of all other examples were assigned analogously.



Scheme 3. Stereodivergent synthesis of 2,2,6-trisubstituted THPs

In contrast to the cyclization from the secondary alcohol described in Scheme 2, that of the recovered tertiary alcohol (*R*)-**4a** by treatment with tetrafluoroboric acid afforded **5a'**, which is the diastereomer of **5a**, as the major product while simultaneously maintaining enantiomeric purity (Scheme 3). On the other hand, the treatment of (*R*)-**4a** with (*R*)-**3c** afforded *ent*-**5a**, the enantiomer of **5a**, as the major product with 97% *ee*. These results imply that not only enantioselectivity but also diastereoselectivity is controlled by using chiral phosphoric acid catalysts in these asymmetric cycloetherification reactions utilizing steric interactions as well as multipoint recognition via hydrogen bonding; as cyclizations with chiral catalysts preferentially yield kinetic products, the synthetic protocols involving tertiary alcohols can facilitate synthetic routes to all possible stereoisomers of the THPs with two chiral centers including a tetrasubstituted carbon.

In summary, novel asymmetric cycloetherification, accompanied by the kinetic resolution of secondary or tertiary alcohols to afford THPs bearing two chiral centers, was developed. The recovered optically active alcohols were also transformed to other stereoisomers of the THPs. These protocols provide efficient synthetic routes to various stereoisomers of substituted THP derivatives, which would be useful for constructing a library of such pharmaceutically important compounds. Currently, further studies on the application of these protocols to the asymmetric synthesis of bioactive agents containing THP rings are underway in our laboratory, and the results will be reported in due course.

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