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Procedure-Controlled Enantioselectivity Switch in Organocatalytic 2-Oxazolidinone Synthesis

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Supporting Information

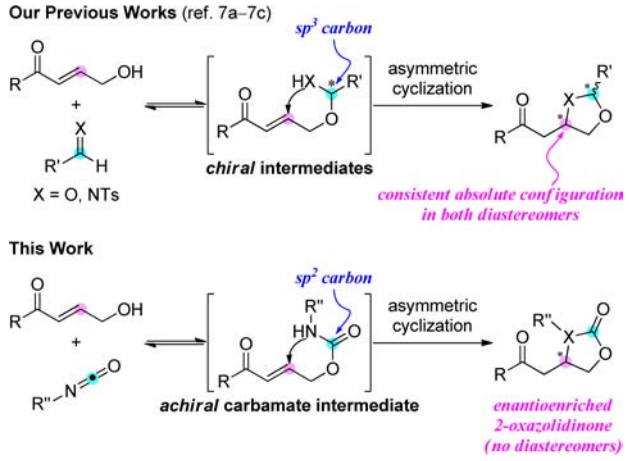
ABSTRACT: In a novel organocatalytic formal [3 + 2] cycloaddition to afford chiral 2-oxazolidinones, an enantioselectivity switch could be induced by changing the manner of addition of the reactants, even when the reaction components (cinchona-alkaloid-derived aminothiourea catalyst, substrates, and solvent) were the same.

Protein function can be altered by post-translational modification or by genetic mutation as a result of chemical damage or ionizing radiation. Post-translational modification of biological catalysts, such as phosphorylation of enzymes like Smurf1[1a] or MEK,[1b] can dramatically alter the selectivity of the enzyme and downstream biological events. In chemical synthesis, asymmetric catalysts, especially biomimetic organocatalysts, may undergo similar functional switches in response to environmental changes.[2] For example, reversal of enantioselectivity by using a single chiral source has been accomplished in several reactions simply by changing an achiral component (e.g., the solvent) or using additional achiral additives.[3,4]

Chiral 2-oxazolidinones are important frameworks found in a wide range of bioactive compounds[5] and chiral auxiliaries for asymmetric synthesis.[6] We recently reported asymmetric formal [3 + 2] cycloaddition reactions via intermediates generated in situ from γ-hydroxy-α,β-unsaturated carbonyls with aldehydes or imines (Scheme 1).[7a−c] In the presence of cinchona-alkaloid-based aminothiourea catalysts (Figure 1),[8] those intermediates underwent intramolecular hetero-Michael addition with high enantioselectivity to afford a diastereomeric mixture.[7] Thus inspired, we envisioned that reactions of an isocyanate with γ-hydroxy-α,β-unsaturated carbonyl compounds could also be carried out enantioselectively to furnish chiral 2-oxazolidinones (Scheme 1).[9] Moreover, the use of a heterocumulene as a nitrogen source would circumvent the generation of diastereomers, thereby allowing more effective enantioselective amination of the β-carbon.

In the present study, we found that a slight change in the reaction procedure led to a reversal of the enantioselectivity, even when the chiral catalyst, substrates, and solvent used were unaltered. Herein we present a novel asymmetric reaction to afford 2-oxazolidinones in which a procedure-controlled enantioselectivity switch was observed when using a single cinchona-alkaloid-derived organocatalyst. To the best of our knowledge, there has been no previous report of such an inversion behavior that requires no change in the reaction components.

Scheme 1. Formal [3 + 2] Cycloaddition via Asymmetric Intramolecular Hetero-Michael Addition by Aminothiourea Catalysts



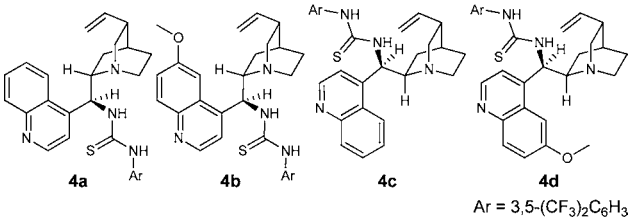
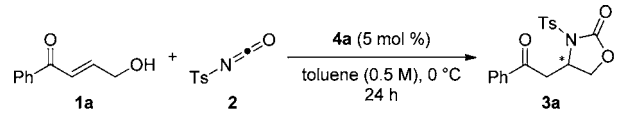


Figure 1. Cinchona-alkaloid-derived aminothiourea catalysts.

We initially carried out the cycloaddition of (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**1a**) and 4-methylbenzenesulfonyl isocyanate (**2**) using 5 mol % cinchonidine-derived catalyst **4a** (Scheme 2). The reaction was effected by mixing the starting

Scheme 2. Effect of the Amount of Isocyanate 2 in the Formal [3 + 2] Cycloaddition of 1a with 2



2 (1.0 equiv): 60%, er 70:30 (*R*)
2 (1.5 equiv): 69%, er 26:74 (*S*)

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materials and the catalyst in one portion in toluene at 0 °C. The addition of 1.0 equiv of **2** resulted in the formation of the (*R*)-2-oxazolidinone (*R*)-**3a** in an enantiomeric ratio (er) of 70:30, while the use of 1.5 equiv of **2** afforded (*S*)-**3a** with an er of 26:74.

To gain insight into the unusual effect of an excess amount of the isocyanate on the stereoselectivity, spectroscopic studies were carried out. ^{1}H NMR analysis of a solution of **2** and **4a** in toluene-d_8 indicated that the signals associated with the protons adjacent to the quinuclidine nitrogen of **4a** were shifted downfield in the presence of **2** [Figure S1 in the Supporting Information (SI)]. In addition, ^{13}C NMR analysis of the solution revealed the disappearance of the sp carbon of **2** in the presence of **4a** (Figure S2). Furthermore, high-resolution mass spectrometry analysis of a solution of **2** and **4a** (20:1 mixture) detected their 1:1 adduct (found, m/z 762.2000; calcd for $[M + H]^+$, 762.2002) but not oligomeric n:1 adducts ($n > 1$) (see Scheme S1 in the SI for details). These results strongly suggested that **4a** was mutated by **2** to form a zwitterionic 1:1 adduct by addition of the quinuclidine nitrogen of **4a** to **2** (Figure 2),[10] which had a significant influence on the

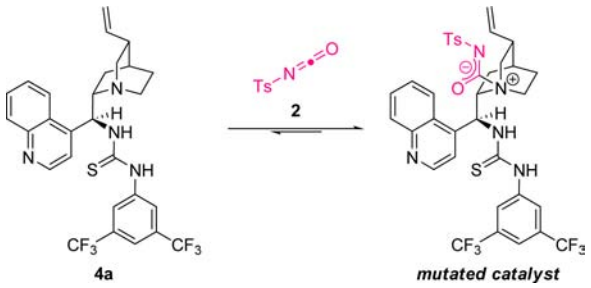
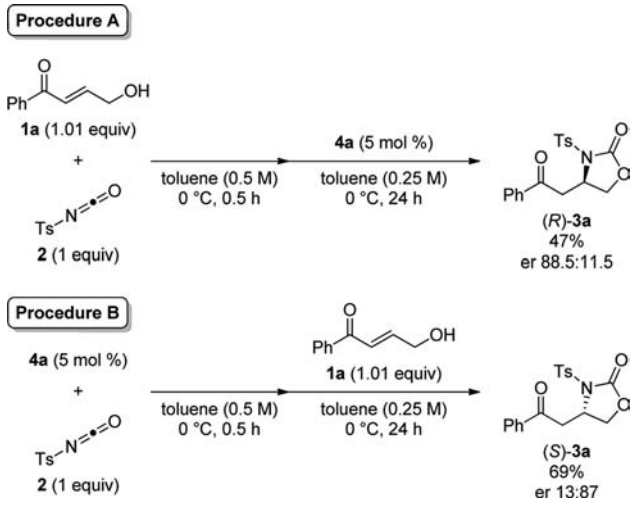


Figure 2. Proposed structure of the catalyst mutated by **2**.

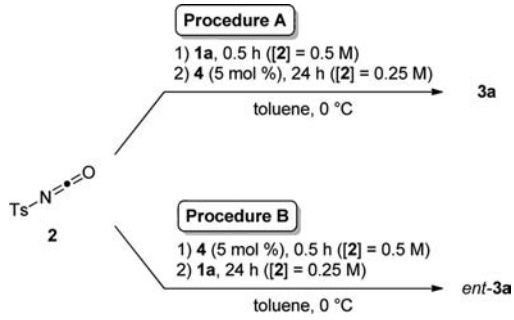
stereoselectivity. Thus, we modified the reaction procedure as follows: **1a** (1.01 equiv) was first treated with **2** (1.0 equiv) until the latter was completely consumed, generating the carbamate intermediate; subsequently, **4a** (5 mol %) was added (Scheme 3, procedure A).[11,12] This sequential protocol yielded (*R*)-**3a** with improved enantioselectivity.[13] In contrast, when **4a** (5 mol %) was mutated by treatment with **2** (1.0 equiv) before

Scheme 3. Enantioselectivity Switch in the Formal [3 + 2] Cycloaddition Using Sequential Protocols



the addition of 1.01 equiv of **1a** (Scheme 3, procedure B), the opposite enantiomer, (*S*)-**3a**, was obtained selectively.[14] We carried out the aforementioned reaction protocols in the presence of catalysts derived from other readily available cinchona alkaloids (Table 1)[15] and found that all of them led to reversal of the enantioselectivity.

Table 1. Investigation of the Enantioselectivity Switch with Cinchona-Alkaloid-Based Catalysts 4[a]



		procedure A		procedure B	
entry	catalyst	yield (%)[b]	er	yield (%)[b]	er
1	**4a**	47	88.5:11.5 (*R*)	69	13:87 (*S*)
2	**4b**	75	79:21 (*R*)	57	20:80 (*S*)
3	**4c**	53	26:74 (*S*)	50	83:17 (*R*)
4	**4d**	61	20.5:79.5 (*S*)	46	82:18 (*R*)

[a]Reactions were run using **1a** (0.253 mmol), **2** (0.25 mmol), and the catalyst (0.0125 mmol) in toluene. [b]Isolated yields.

With the established procedures and conditions using **4a** as a single catalyst, we next explored the substrate scope (Table 2).[16] Reversal of enantioselectivity was observed in all of the reactions with γ-hydroxy-α,β-unsaturated ketones **1a**–**h** (Table 2, entries 1–16). Both electron-rich and electron-deficient substrates were tolerated under the employed reaction conditions (entries 3–6). A substrate bearing a *p*-bromo group also selectively afforded both enantiomers of the 2-oxazolidinone product (entries 7 and 8). In addition, enones bearing bulky biphenyl and naphthyl groups yielded the corresponding products with high enantioselectivity (entries 9–12), and a heterocycle-substituted substrate also allowed for the enantiodivergent synthesis (entries 13 and 14). An aliphatic ketone could also be used in the reaction (entries 15 and 16), although the enantioselectivity with procedure A (entry 15) was modest in comparison with that in other cases. However, in the reaction using a γ-hydroxy-α,β-unsaturated ester, the same 2-oxazolidinone enantiomer was obtained as the major product in both procedures, and higher enantioselectivity was observed with procedure B (Table 2, entries 17 and 18).

To demonstrate the utility of the products as valuable synthetic intermediates, transformations of (*R*)-**3a** with high optical purity obtained after one-time recrystallization were carried out. The tosyl group of **3a** could be removed by treatment with sodium naphthalenide to afford **5** without significant loss of optical purity (Scheme 4). In addition, treatment of (*R*)-**3a** with lithium hydroxide and hydrogen peroxide gave optically active 1,2-amino alcohol **6** (Scheme 5). Thus, the proposed 2-oxazolidinone synthesis protocol and transformation methods would constitute a facile, practical enantiodivergent route to optically active 2-oxazolidinones and chiral 1,2-amino alcohols. The absolute configuration of **5** was

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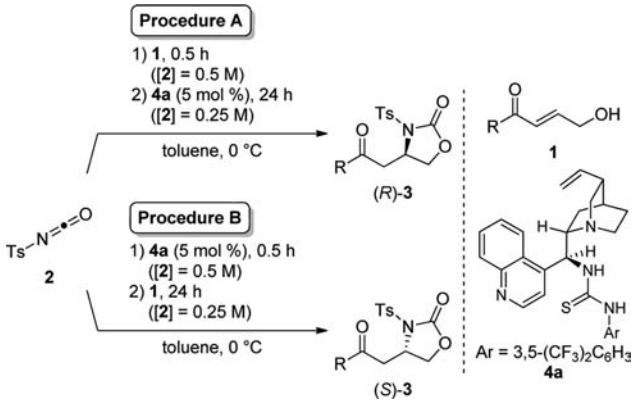
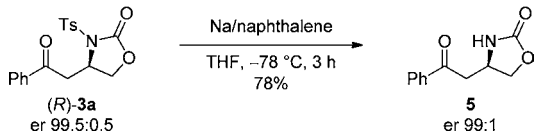
Table 2. Substrate Scope[a]



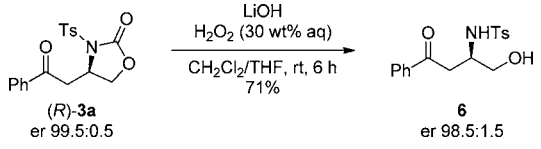
entry	R (3)	procedure	yield (%)[b]	er
1	Ph (**3a**)	A	47	88.5:11.5 (*R*)
2		B	69	13:87 (*S*)
3[c]	4-$CH_3OC_6H_4$ (**3b**)	A	67	73:27 (*R*)
4[c]		B	49	25.5:74.5 (*S*)
5[c]	4-$CF_3C_6H_4$ (**3c**)	A	79	80.5:19.5 (*R*)
6[c]		B	71	6.5:93.5 (*S*)
7	4-BrC_6H_4 (**3d**)	A	95	81:19 (*R*)
8		B	74	14:86 (*S*)
9	4-PhC_6H_4 (**3e**)	A	27	89.5:10.5 (*R*)
10		B	19	15.5:84.5 (*S*)
11	2-naphthyl (**3f**)	A	66	91:9 (*R*)
12		B	49	18:82 (*S*)
13	2-thienyl (**3g**)	A	53	81.5:18.5 (*R*)
14		B	53	16.5:83.5 (*S*)
15	$PhCH_2CH_2$ (**3h**)	A	83	68:32 (*R*)
16		B	73	17.5:82.5 (*S*)
17[d]	PhO (**3i**)	A	73	55:45 (*R*)
18[d]		B	30	88:12 (*R*)

[a]Reactions were run using **1** (0.253 mmol), **2a** (0.25 mmol), and **4a** (0.0125 mmol) in toluene. [b]Isolated yields. [c]Run at −20 °C for 48 h. [d]Run at 15 °C for 120 h.

Scheme 4. Deprotection of 3a



Scheme 5. Synthesis of Chiral 1,2-Amino Alcohol 6



determined by comparing its optical rotation with the literature value[17] (see the SI for details), and the configurations of all other products were assigned analogously.

In summary, we have presented a novel enantioselective route to 2-oxazolidinones via formal [3 + 2] cycloadditions between γ-hydroxy-α,β-unsaturated carbonyls and an isocyanate in the presence of a cinchona-alkaloid-derived amino-thiourea catalyst. Notably, the two enantiomers could be synthesized selectively without changing the reaction components (chiral catalyst, substrates, and solvent). The absolute configurations of the products were controlled only by the employed reaction procedure. The proposed reaction protocols are particularly valuable for catalysts derived from chiral natural products, including cinchona alkaloids, since these compounds are available in only one enantiomeric form. Studies to clarify the enantioselectivity switch in further detail and the application of this methodology to other asymmetric reactions are currently underway in our laboratory, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) The formation of the carbamate intermediate was confirmed by thin-layer chromatography analysis and a ^{1}H NMR study of a 1.01:1 mixture of **1a** and **2** in toluene-d_8; 2-oxazolidinone **3a** was not formed in the absence of catalyst. See the SI for details (Figure S3).
(12) Investigations revealed that 1.01 equiv of **1a** relative to **2** was efficient for reproducibility.
(13) Results of further screening of other conditions (isocyanates, solvents, temperature, and catalysts) are described in the SI (Tables S1−S3).
(14) The mutated catalyst yielding (*S*)-**3a** easily decomposed at higher temperature; the concentration of the solution of a 1:1 mixture of **4a** and **2** gave **4a′**, which was different from that generated in situ (Figure S1). In addition, the use of **4a′** in procedure A did not bring about the enantioselectivity switch (Scheme S2).
(15) Catalysts with a cyclohexanediamine structure also afforded **3a** enantioselectively (Table S3), but no enantioselectivity switch was observed (Scheme S3).
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