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Organocatalytic Asymmetric Synthesis of *N*,*N*-Bis(dihydrofuranyl)hydroxyamines: A Cascade Reaction Involving Friedel–Crafts Alkylation, Internal Redox Reaction, and Umpolung

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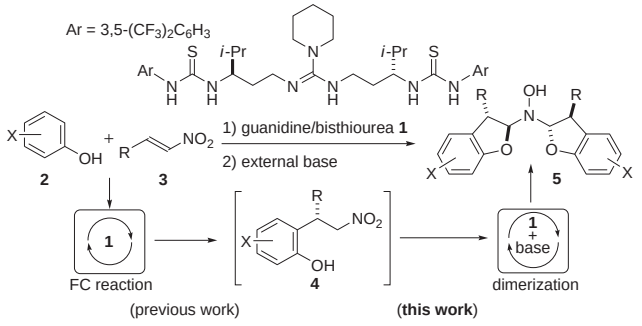
Stereoselective syntheses of *N*,*N*-bis(dihydrofuranyl)-hydroxyamines from phenols and nitroolefins have been accomplished by means of cycle-specific catalysis with guanidine/bisthiourea organocatalyst and achiral base. Circumstantial evidence supports the idea that a nitroso intermediate participates in the dimerization, which involves internal redox reaction/umpolung.

The sequence of multiple catalytic asymmetric reactions is one of the most powerful synthetic tactics to attain a rapid increase of molecular complexity.[1] Among the methods available, cycle-specific catalysis, which allows discrete control of individual bond-forming processes by utilizing distinct catalysts, has received much attention, because the strategy enables flexible access to a range of products, depending on the catalytic system used.[2] Such chiral-catalyst-based methodologies should effectively increase the stereochemical diversity of products that can be constructed with small molecules.[3] Here, we present our studies on the development of cycle-specific catalysis with the combination of guanidine/bisthiourea **1**[4–8] and an external achiral base, focusing on the synthesis of *N*,*N*-bis(dihydrofuranyl)hydroxyamines **5** from phenols **2** and nitroolefins **3** (Scheme 1).[9,10] The mechanism of the dimerization (**4** to **5**), which involves umpolung[11] and internal redox reaction[12,13] is also discussed.

Phenolates are potentially attractive nucleophiles for the design of cycle-specific cascade reactions, because multiple reactive sites are available in the aromatic moiety (i.e., *ortho*- and *para*-positions), in addition to the oxygen function. Although several examples of catalytic asymmetric reaction of phenolates have recently been reported, methodologies that can selectively access both **4** and **5** using phenolates have not been reported, likely due to the difficulty in controlling the reactivity of the multiple reactive sites.[9,10,14] For example, Chen and coworkers reported that cinchona-based thiourea organocatalysts promote the chemo- and regioselective Friedel–Crafts (FC) reaction of naphthols with nitroolefins **3** to afford the FC adducts **4** with 85–95% ee, but the dimeric dihydronaphthofurans **5** are also concomitantly formed. In contrast, we have successfully developed a catalytic system using 1,3-diamine-tethered guanidine/bisthiourea organocatalyst **1** that enables selective access to **4** (66–99% yield with 82–94% ee) with the generation of only a trace amount of dimer **5**.[10] These results suggest that the conformationally flexible organocatalyst **1** can effectively dissociate from the FC adduct **4** after the bond-forming reaction takes place in the FC reaction, thereby suppressing the conversion of **4** to the dimer **5**.

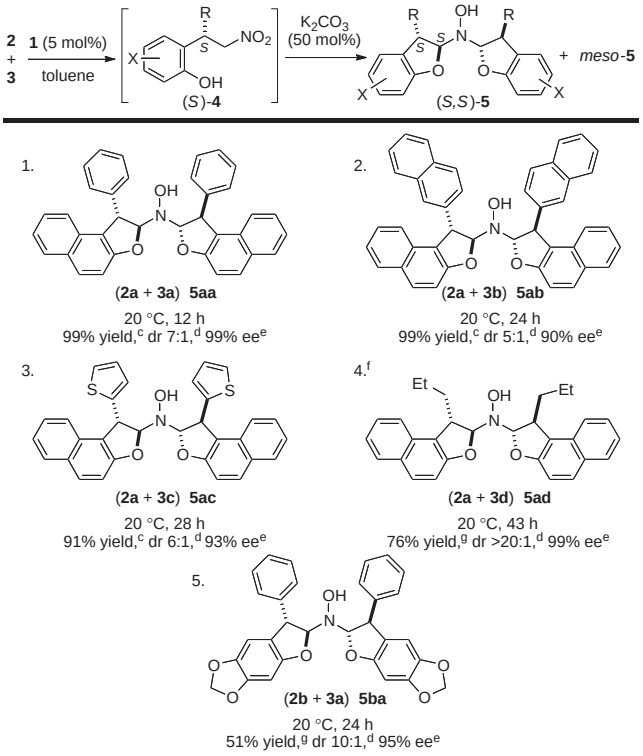


Scheme 1. Synthesis of **5** by utilizing cycle-specific catalysis.

Encouraged by these findings, we were inspired to examine the use of **1** to mediate the asymmetric cycle-specific cascade assembly of *N*,*N*-bis(dihydrofuranyl)hydroxyamines **5** from phenols **2** and nitroolefins **3**. We postulated that if the catalyst **1** or FC adducts **4** could be appropriately stimulated after the complete conversion of **2** to **4**, dimer formation should effectively take place. After extensive screening,[15,16] we were pleased to find that addition of potassium carbonate (50 mol %) after the completion of the **1**-catalyzed FC reaction is effective to promote the dimer-forming reaction of **4**, giving the corresponding (dihydrofuranyl)hydroxyamines **5** in a single-flask operation (Table 1).[17] Both aromatic (Entries 1–3) and aliphatic substituents (Entry 4) as the R group in **4** are available in the present system, giving the corresponding dimeric dihydrofurans **5** in 76–99% yield with 5:1 → 20:1 dr, 90–99% ee. Electron-enriched phenols such as **4ba** gave the dimeric product **5ba** with 10:1 dr and 95% ee, although there is still room to improve the reactivity.

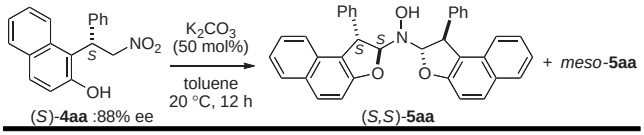
An understanding of the mechanism of this unusual dimerization (**4** to **5**) is of principal importance for further development of this unique cascade. To gain insight into the roles of the guanidine/bisthiourea organocatalyst **1** and potassium carbonate in the dimer-forming reaction, we utilized (*S*)-**4aa** (88% ee),[10] which was isolated by silica gel column chromatography, as a reaction substrate (Table 2). The cooperative procedure using **1** and potassium carbonate exhibited similar reactivity and selectivities to the single-flask procedure described in Table 1, Entry 1. In contrast, a significant decline of the reactivity was observed in the absence of **1**, resulting in lower conversion (34%) and recovery of (*S*)-**4aa** (65%). It is also important to note that the enantiomeric excess values of both the (*S*,*S*)-**5aa** and the recovered-(*S*)-**4aa** were apparently maintained in the absence of **1**. These results suggest that the catalyst and potassium carbonate cooperatively govern both the reaction rate

Table 1. Some examples of the cascade reaction using **1** for the preparation of (*S*,*S*)-**5**[a,b]



[a]Compounds (*S*)-**4** were prepared using the conditions reported in ref. 10a. [b]Potassium carbonate was added after verifying complete conversion of **2** to **4** in the **1**-catalyzed FC reaction.[10a] [c]Isolated yield. [d]Determined by ^{1}H NMR. [e]Determined by chiral HPLC. [f]10 mol % of **1** was used. [g]NMR yield.

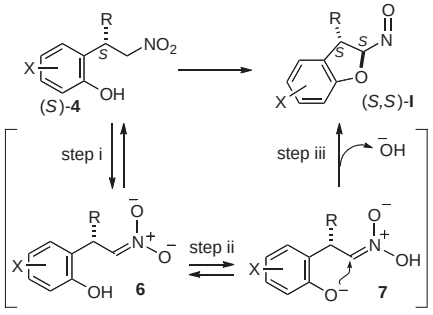
Table 2. The reaction of (*S*)-**4aa** in the presence and absence of **1**



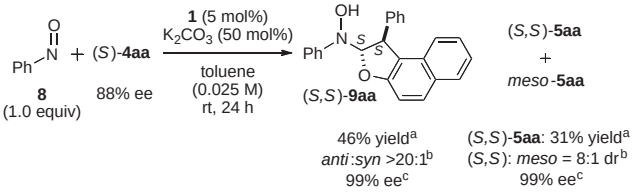
Entry	Catalyst **1**	(*S*,*S*)-**5aa**			(*S*)-**4aa**	
		Yield[a] /%	dr[b] (*S*,*S*):*meso*	ee (*S*,*S*)-**5aa**[c]	Recovery[a] /%	ee[c] /%
1	5 mol %	99	8:1	98	n.d.[d]	n.d.[d]
2	none	34	>20:1	87	65	89

[a]NMR yield. [b]Determined by ^{1}H NMR. [c]Determined by chiral HPLC. [d]Not determined.

and the stereoselection in the dimer-forming processes. Thus, we concluded that 1) the guanidine/bisthiourea **1** selectively promotes the chemo-, regio-, and enantioselective 1,4-type FC alkylation of **2** with **3** to produce **4**, and 2) the subsequent addition of potassium carbonate results in cooperative activation of the FC product **4** together with guanidine/bisthiourea **1**, facilitating the formation of the *N*,*N*-bis(dihydrofuranyl)-hydroxyamines **5**.



Scheme 2. Working hypothesis for the generation of (*S*,*S*)-**I**.



Scheme 3. The reaction of **8** with (*S*)-**4aa**. [a]NMR yield. [b]Determined by ^{1}H NMR. [c]Determined by chiral HPLC.

Another intriguing question concerns the unusual chemotype of the nitro group of **4**[18] in the transformation from **4** to **5**, which formally involves reversal of the inherent polarity in the nitro group (phenoxide anion attacks the α-position to the nitro group)[11] and internal redox reaction (oxidation at the α-position to the nitro group and reduction of the nitro group).[12,13] A mechanism that can well explain these umpolung/redox processes is in situ generation of the highly reactive aliphatic nitroso species (*S*,*S*)-**I**. We hypothesized that the intramolecular nucleophilic addition of phenolate to the α-position of nitronate (Scheme 2, step iii) might take place in an *anti*-selective manner due to the steric repulsion of the R group in **7**, leading to generation of (*S*,*S*)-**I**.[19]

These speculations stimulated us to examine the reaction of nitrosobenzene (**8**) with the isolated (*S*)-**4aa** (88% ee). We anticipated that nitroso-aldol reaction and subsequent elimination of the nitro group would lead to the construction of another dihydrofuran moiety.[20] As can be seen in Scheme 3, the highly diastereo- and enantioselective heterocoupling reaction of **8** with (*S*)-**4aa** took place both with catalyst **1**, giving the corresponding (dihydrofuranyl)hydroxyamine (*S*,*S*)-**9aa** with the concomitant generation of (*S*,*S*)-**5aa**.[21] Thus, the investigation using **8** provided circumstantial evidence in support of the idea that the nitroso species participates as an intermediate in the dimerization. It is also important to note that the results shown in Scheme 3 indicate that *mono*(dihydrofuranyl)hydroxyamine could be constructed by designing the reaction of (*S*)-**4** with suitable electrophiles.

In summary, we have explored a new cycle-specific catalysis by exploiting the combination of guanidine/bisthiourea **1** and potassium carbonate. Our findings show that organocatalyst **1** can effectively control the reactivity and selectivity of phenolates, enabling selective access to both chiral phenols **4** and *N*,*N*-bis(dihydrofuranyl)hydroxyamines **5** simply by alternating the reaction conditions. Further applications of cycle-specific catalysis utilizing the conformationally flexible organo-

catalysts to other types of cascade reactions are under examination.

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16 See Supporting Information.[22]

17 In general, the ee values of (*S*)-**5** are higher than those of (*S*)-**4**; **5aa** (99% ee) vs. **4aa** (88% ee), **5ab** (99% ee) vs. **4ab** (84% ee), **5ac** (93% ee) vs. **4ac** (84% ee), **5ad** (99% ee) vs. **4ad** (93% ee), and **5ba** (95% ee) vs. **4ba** (91% ee). Thus, the rate of the heterocoupling reaction of major (*S*)-**4** and minor enantiomer (*R*)-**4**, in which *meso*-**5** is generated, appears to proceed more rapidly than the homocoupling reaction to afford (*S*,*S*)-**5**, thereby increasing the ee value of (*S*,*S*)-**5** in the dimerization processes.

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