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Sequential Stereodivergent Organocatalysis and Programmed Organocascades

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Asymmetric organocatalysis has attracted great interest as a synthetic strategy during the past decade. But, although the inertness of organocatalysts to moisture and oxygen offers great opportunities to tune the reaction conditions, the stereoswitchable character of organocatalysts has not been systematically studied, and most findings have been serendipitous. In this Perspective, we emphasize the importance of *in situ* tunability in dynamic asymmetric organocatalysis for obtaining different functional outcomes with single-flask operation.

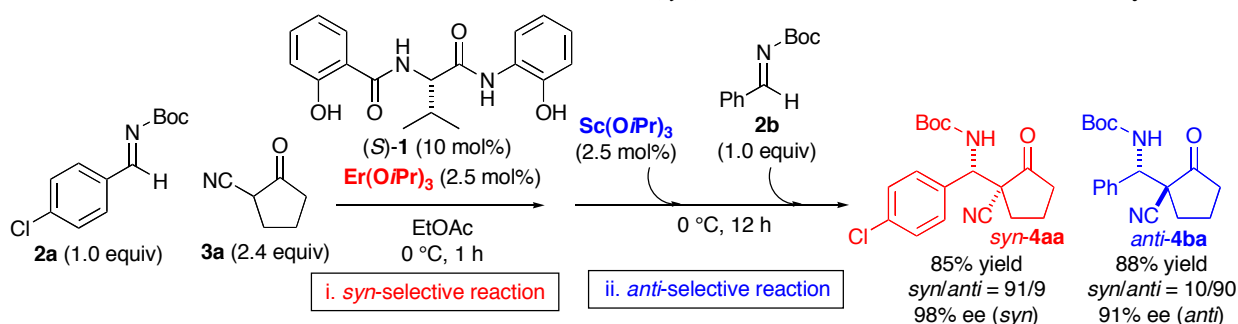
Introduction

Exploration of conceptually new catalytic activation modes has been a mainstream topic in the history of asymmetric organocatalysis.^{1,2} By exploiting various combinations of catalytic active site(s) and chiral scaffold, the repertoire of available organocatalytic transformations has been rapidly expanded.³ Another significant line of inquiry is dynamic asymmetric organocatalysis, in which a single organocatalyst can afford different functional outcomes as a result of tuning the reaction conditions.⁴⁻⁶ The concept of dynamic asymmetric organocatalysis has garnered attention from the synthetic community because of the analogy with enzymes, which can display an enormous variety of functions in living cells by exploiting three-dimensional structural diversity together with post-transcriptional modification, even though the only constituents are a limited number of amino acids.⁷ One of the simplest models to examine the feasibility of constructing asymmetrically distinct chiral environments using a single chiral organocatalyst is stereodivergent organocatalysis, in which each stereoisomer can be catalytically produced under different reaction conditions using two distinct flasks.^{8,9} Despite significant advances in stereodivergent organocatalysis, *in situ*-tunable dynamic stereodivergent organocatalysis has only rarely been reported.¹⁰⁻¹² Considering that efficient dissociation of the catalyst/product complex is a key requirement to attain high catalyst turnover, *in situ* generation of another catalytically

active species after the first catalytic reaction has been completed, in order to activate the product, is potentially an attractive way to design a sequential reaction cascade in a single flask.¹² In this Perspective, we highlight recent developments in *sequential asymmetric organocatalysis*, through which two differential functional outcomes can be obtained with single-flask operation. We focus particularly on the *in situ* tunability of the stereoselectivity of organocatalysts. Other examples of stereodivergent catalysis have been collected in recent review articles, which may be helpful to envisage how to regulate the toggling of stereoselectivity while utilizing a single chiral source.^{7,8}

Sequential Diastereodivergent Catalysis

Before describing recent developments in sequential diastereodivergent organocatalysis, we will first briefly comment on a seminal example using (*S*)-bis(hydroxyphenyl)diamides **1**/rare-earth (RE) metal complexes developed by Kumagai and Shibasaki for sequential diastereodivergent catalysis in 2009, in order to illustrate the mechanistic differences between metal catalysis and organocatalysis.^{13,14} In the designed protocol (Scheme 1), the first Mannich-type reaction of *N*-Boc-alimine **2a** (1.0 equiv) with α -cyanoketone **3a** (2.4 equiv) in the presence of (*S*)-**1**/Er³⁺ catalyst afforded *syn*-**4aa** [85% yield, *syn/anti* = 91/9, 98% ee (*syn*)], while reversal of diastereoselectivity in the second



Scheme 1 Sequential diastereodivergent Mannich-type reaction of **2** with **3**.

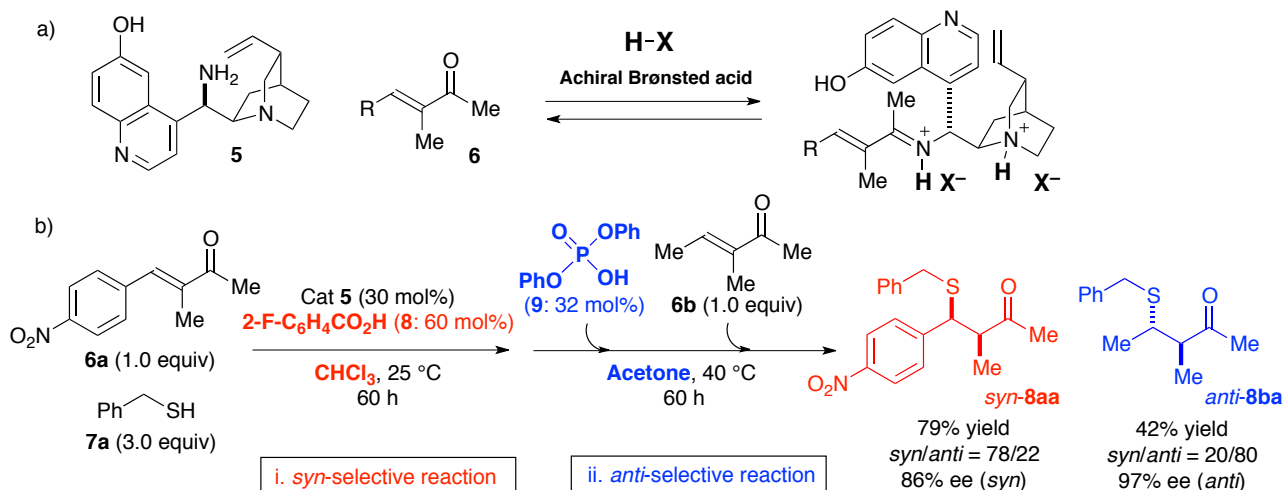
Mannich-type reaction was induced by adding $\text{Sc}(\text{O}i\text{Pr})_3$ (2.5 mol%) with subsequent addition of another imine **2b**, affording *anti*-**4ab** [88% yield, *syn/anti* = 10/90, 91% ee (*anti*)]. The obtained diastereo- and enantioselectivity of *syn*-**4aa** and *anti*-**4ab** were as high as those obtained under the standard reaction conditions using two different flasks. Importantly, the reaction sequence described above provides a basic platform to examine the stereoswitchable character of the catalyst in the presence of an enantio-enriched concomitant (*i.e.*, the first adduct), and the role of the same catalyst in the following stereodivergent reaction. The significance of three-dimensional structural change between (*S*)-**1**/ Er^{3+} catalyst and (*S*)-**1**/ Er^{3+} / Sc^{3+} catalyst is evident from a comparison of the CD spectra. Although the precise catalytically active structures in the *syn*- and *anti*-selective reactions are still unclear, complex equilibration of the catalytically active species based on ligand design incorporating multiple hydrogen-bond donors and acceptors, as well as the dynamic nature of REs, is a key feature of sequential diastereodivergent catalysis using the one-shot protocol. Thus, at the core of metal-dependent switching reactions is the preparation of different sets of catalytically active species by selecting suitable ligand and metal, leading to construction of two distinct asymmetric environments with a single chiral ligand.

Since organocatalysts generally utilize heteroatoms such as O, N and P for activating the substrates, highly coordinative additives often cause a decrease in organocatalytic reactivity. In 2011, Melchiorre reported a fascinating approach for *in-situ* diastereo-switching in the primary-amine **5**-catalyzed sulfa-Michael reaction of α -branched- α,β -unsaturated enone **6** and benzylthiol (**7a**) by exploiting achiral acidic additives (Scheme 2).^{10,15} They anticipated that conformational change of the catalyst **5**¹⁶ might be induced through hypothetical ion-pair assembly, thus constructing diastereomerically different transition states with a single primary-amine organocatalyst (Scheme 2-a). Another notable feature of their work resides in identifying characteristic diastereoselectivity switching depending on the acidity of the additive; weaker carboxylic acids gave *syn*-**8**, while stronger acids (pKa < 2.5 in water) afforded *anti*-**8**. Because acid-base equilibria in the catalytic system are dominated by the acidity of the acid used, *syn*-selectivity controlled by a weaker acid can be switched to *anti*-selectivity by adding a stronger acid. For example, 2-fluorobenzoic acid (**9**: 60 mol%) in CHCl_3 gave *syn*-**8aa** in the

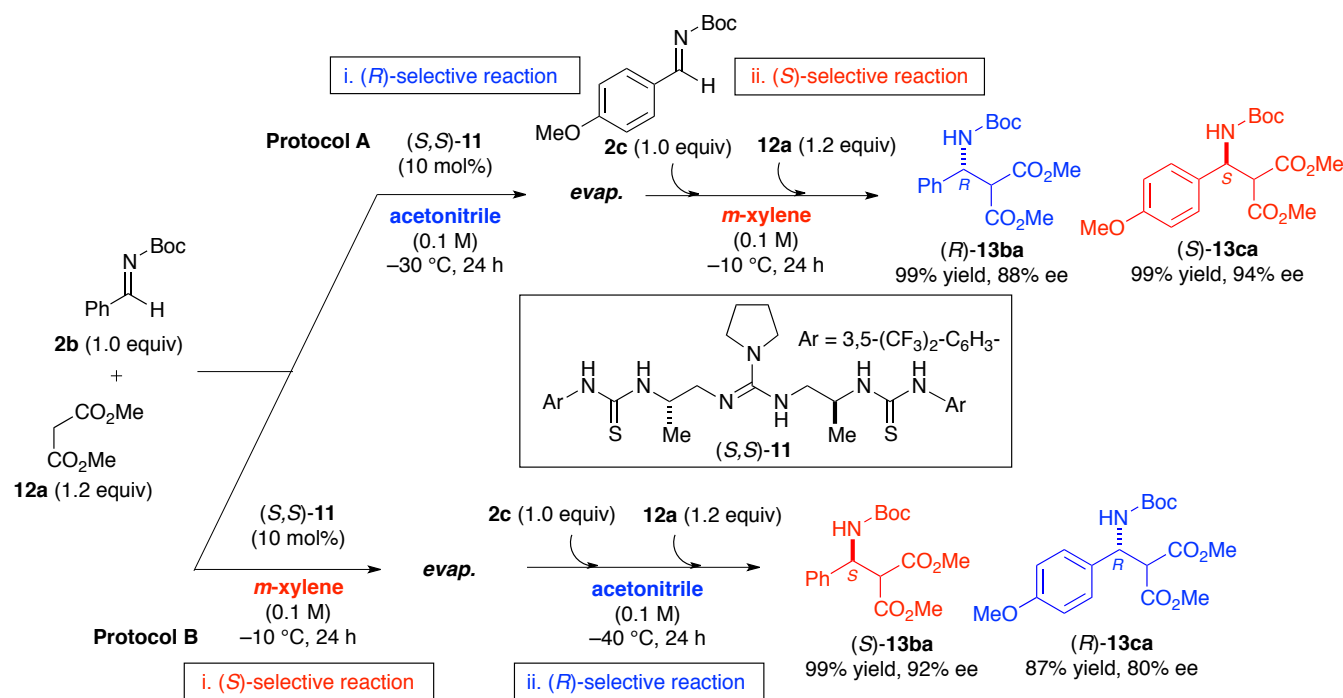
first sulfa-Michael reaction [79% yield, *syn/anti* = 78/22, 86% ee (*syn*)]. Subsequent solvent exchange from CHCl_3 to acetone followed by addition of diphenyl hydrogen phosphate (DPP, **10**: 32 mol%) and another enone **6b** resulted in switching of the diastereoselectivity to give *anti*-**8ab** [42% yield, *syn/anti* = 20/80, 97% ee (*anti*)]. This example is an important illustration that a single organocatalyst can construct two distinct diastereomeric environments in single-flask operation. Further spectroscopic and/or theoretical studies are needed to understand the origin of the diastereoswitching behavior.

Sequential Enantiodivergent Organocatalysis

The strategies described above were focused on construction of two different diastereomeric transition states by adding switching triggers, such as REs¹³ or Brønsted acid.¹⁰ A limitation of these approaches is irreversibility due to the difficulty in removing the switching triggers. In order to regulate the chiral environment in a flexible and timely manner with a single organocatalyst as required, exploration of *reversible* switching reactions is desirable. In 2013, Sohtome and Nagasawa reported a conceptually different approach for bidirectional sequential enantiodivergent Mannich-type reaction of *N*-Boc imines **2** with malonates **12**, as shown in Scheme 3.¹¹ The dynamic system was designed based on the mechanistic hypothesis that the population of the conformers of acyclic guanidine/bisthiourea (*S,S*)-**11**, in which the relative arrangements of guanidine and thiourea functional groups are enantiomerically distinct, can be altered by tuning the reaction solvent.¹⁷ A key feature for applying their catalytic system to sequential reactions is solvent-dependency of enantioswitching. For example, non-polar solvents such as *m*-xylene produce (*S*)-**13**, while polar aprotic solvents afford (*R*)-**13**. By exploiting ease of evacuation and exchange of the solvents, bidirectional protocols using (*S,S*)-**11** (10 mol%) for sequential enantiodivergent Mannich-type reactions that can flexibly switch both (*R*) to (*S*) and (*S*) to (*R*) were developed; protocol A [(*R*)-**13ba**: 99% yield, 88% ee, (*S*)-**13ca**: 99% yield, 94% ee], protocol B [(*S*)-**13ba**: 99% yield, 92% ee, (*R*)-**13ca**: 87% yield, 80% ee]. The authors also reported that the enantiodivergent Mannich-type reaction using (*S,S*)-**11** is indeed highly responsive to the nature of the solvent. Although the stereoselectivity was difficult to predict, kinetic analyses



Scheme 2 a) A working model for dynamic conformational switching of **5** using achiral Brønsted acid; b) Sequential diastereodivergent sulfa-Michael reaction of **6** and **7**.



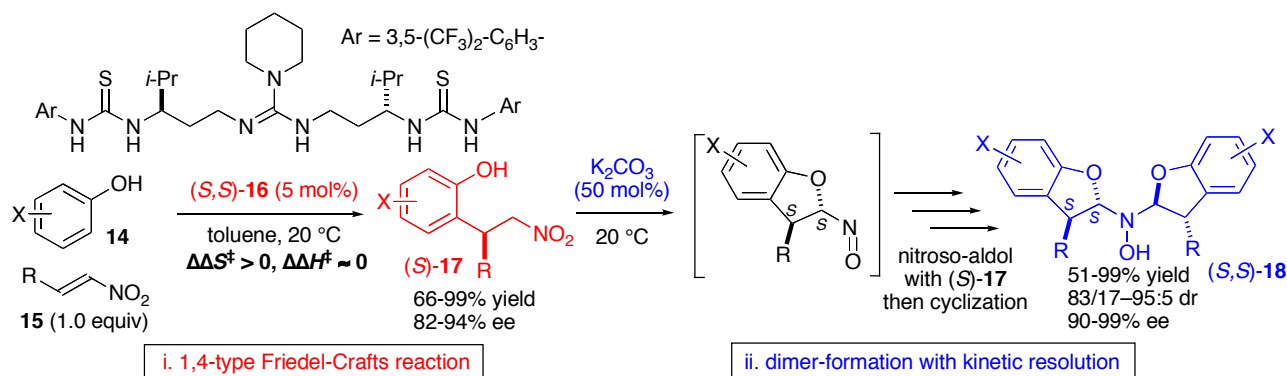
Scheme 3 Bidirectional sequential enantiodivergent Mannich-type reaction of **2** with **12**.

showed that the solvent-dependent stereo-discrimination is controlled by the enthalpy–entropy compensation mode switching. The stereoselectivities of (*S*)-selective Mannich-type reactions in non-polar solvents are governed by the differences in the entropies of activation ($\Delta\Delta S^\ddagger_{S-R}$), while the stereo-discrimination processes of (*R*)-selective reactions are based on differences in the enthalpies of activation ($\Delta\Delta H^\ddagger_{R-S}$). Since not only solvents but also substrate concentration and pressure are well known to affect entropies of activation ($\Delta\Delta S^\ddagger$), multidimensional tuning by exploiting combinations of these entropy-related factors is also potentially attractive for designing other classes of dynamic asymmetric organocatalysis.¹⁸

Programmed Organocascades

The stereodivergent catalysis described in the previous sections clearly demonstrated that stereoselectivity of a single chiral source is tunable by suitably altering the reaction conditions with single-flask operation. An obvious drawback from the

viewpoint of synthetic practicality is that purification is necessary to isolate each stereoisomer. In 2011, Sohtome and Nagasawa expanded the concept of dynamic asymmetric organocatalysis to a programmed organocascade (cycle-specific organocascade),¹² which allows discrete control of individual bond-forming processes by suitably selecting the reaction conditions.¹⁹⁻²¹ A specific focus of their investigation is to control the reactivity and selectivity of phenols **14**, because multiple reactive sites are available in the aromatic moiety (*i.e.*, *ortho*- and *para*-positions), in addition to the oxygen function. Inspired by the early work by Chen,²³ they initially developed the Friedel-Crafts (FC) reaction of **14** with **15** using (*S,S*)-**16**, as shown in the first process in Scheme 1.^{22,24} The chemo-, regio-, and enantioselectivity achieved even in the presence of multiple reactive sites in the FC-adduct **17** is remarkable (66-99% yield, 82-94% ee). The selectivity may be a consequence of synergistic proximity effects controlled by guanidine/bisthiourea catalyst (*S,S*)-**16**; chemoselective interactions of electron-deficient thiourea with the nitro group in **15** and of guanidinium cation with phenolate generated from



Scheme 4 Programmed-organocascade for the synthesis of (*S,S*)-**16** from **14** and **15**.

14 were proposed.²⁴ Specifically, the stereo-discrimination in the FC reaction is governed by the differential activation entropy ($\Delta\Delta S^\ddagger = 25.4 \text{ J mol}^{-1}\text{K}^{-1}$), rather than by the differential activation enthalpy ($\Delta\Delta H^\ddagger = \sim 0 \text{ kJ mol}^{-1}$); this is an unusual example that is in contrast with the general “reactivity and selectivity principle”, in which the maximum enantioselectivity can be attained over a wide reaction temperature range.²⁵ After completion of the first FC reaction, subsequent addition of potassium carbonate (50 mol%) as an external trigger promotes the dimer-forming reaction of **17**, giving the corresponding dihydrofuranyl-hydroxyamines (*S,S*)-**18** in single-flask operation (51-99% yield, 83/17-95/5 dr, 90-99% ee).¹² Because kinetic resolution occurs to increase the ee value of (*S,S*)-**18** over that of (*S*)-**17**, potassium carbonate results in cooperative activation of the FC product **17** together with guanidine/bisthiourea (*S,S*)-**16**. Control experiments in the absence of the catalyst (*S,S*)-**16** also support this idea; in the reaction of FC adduct (*S*)-**17aa** (88% ee), which can be synthesized from 2-naphthol (**14a**) with **15a** (R = Ph) using the guanidine/bisthiourea (*S,S*)-**16**, a significant decline of the reactivity (34%, 20/1 dr, 87% ee) was observed in the absence of (*S,S*)-**16**, resulting in recovery of (*S*)-**17aa** (65%, 89% ee), while full conversion occurred in the presence of catalyst (*S,S*)-**16** to give (*S,S*)-**18** (99% yield, 8/1 dr, 98% ee). It is noteworthy that the chirality in the second reaction is also controlled by (*S,S*)-**16**. This observation contrasts with typical diastereoselective cascades, in which the chirality in the second reaction is governed by chiral information in the first adduct.¹⁹⁻²¹ Thus, this example teaches us that chiral libraries involving distinct molecular frameworks can be efficiently constructed from a simple starting material having multiple reactive sites under the control of a single chiral catalyst.

Conclusions

In this Perspective, we have focused on three recent topics, i.e., sequential diastereodivergent and enantiodivergent organocatalysis and organocascades, in order to showcase the potent utility of sequential dynamic asymmetric organocatalysis. Exploring such sequences requires considerable work, because two optimization processes for different types of asymmetric catalytic transformations with a single chiral source are needed. Since it is still difficult to take a snapshot of the dynamic structural change of the catalyst and/or the transition state by means of spectroscopy, conceptualizing the stereo-switching principle with mechanistic studies may be the key to further accelerate the development of sequential dynamic asymmetric organocatalytic reactions with high predictability of products.

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†Dedicated to Professor Tadashi Nakata on the occasion of his 70th birthday.

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