Asymmetric Synthesis

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Organocatalytic Asymmetric Desymmetrization–Fragmentation of Cyclic Ketones**

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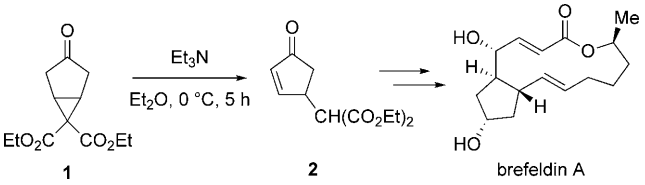
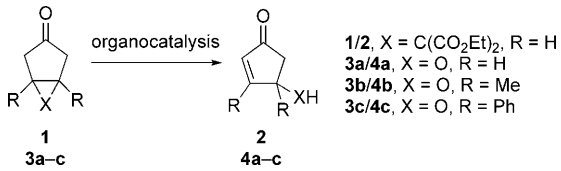
Within the last decade, the field of asymmetric organocatalysis has been the focus of immense interest and research.[1] A myriad of catalysts and reaction protocols have been developed to provide access to enantiomerically enriched compounds. However, despite the numerous successes in organocatalysis, the fundamental class of fragmentation reactions remains virtually unexplored. These reactions are useful synthetic tools, as exemplified by the synthesis of (±)-brefeldin A by Corey and Wollenberg:[2] In an initial step, the *meso* compound **1** fragments under base catalysis into chiral, racemic **2**, which is subsequently converted into the target compound (Scheme 1).



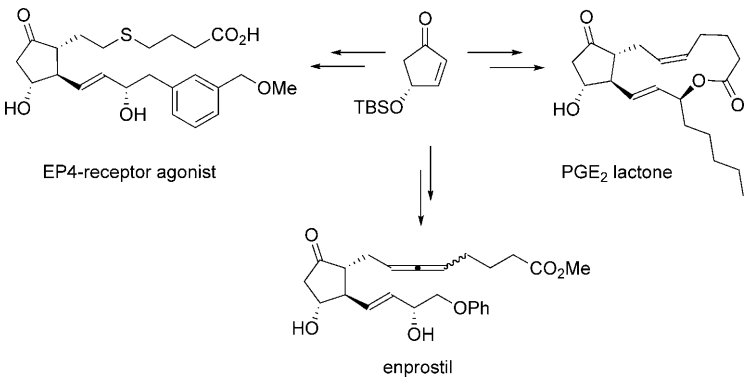
Scheme 1. Synthesis of (±)-brefeldin A by Corey and Wollenberg.

Considering the importance of optically active cyclopentenone derivatives as starting materials for the synthesis of biologically active compounds, we envisioned that a general asymmetric protocol for the desymmetrization of not only the *meso* compound **1**, but also of the related epoxides **3**, might be a highly attractive new fundamental chemical transformation. Herein we present the development of the organocatalytic asymmetric desymmetrization–fragmentation of *meso* compounds with a cyclopentanone skeleton (Scheme 2). In particular, the conversion of epoxycyclopentanones **3** into **4** is of great importance. For example, the *tert*-butyldimethylsilyl (TBS) ether derivative of **4a** has been used extensively as a starting material in the synthesis of prostaglandins and their analogues (Scheme 3).[3]



Scheme 2. Organocatalytic desymmetrization–fragmentation of *meso* cyclopentanones.

Although compound **4a** and derivatives in which the hydroxy group is protected have been approached previously by desymmetrization of the corresponding *meso* compounds,[4–6] the method described herein is the first example of an organocatalytic,[7] asymmetric synthesis of 4-hydroxycyclopent-2-enones **4** by the desymmetrization–fragmentation of epoxycyclopentanones **3**. Furthermore, various one-pot transformations of the optically active products are demonstrated, and the concept is extended to the kinetic resolution of a chiral, racemic epoxycyclohexanone. Finally, a simplified mechanistic model for the reaction is proposed.



Scheme 3. Examples of prostaglandins and analogues that have been synthesized from TBS-protected **4a**.

We selected the transformation of diethyl 3-oxobicyclo-[3.1.0]hexane-6,6-dicarboxylate (**1**) into diethyl 2-(4-oxocyclopent-2-enyl)malonate (**2**) as a model reaction for the organocatalytic asymmetric desymmetrization–fragmentation (Scheme 4). No enantioselective procedure had been described previously for the synthesis of this optically active

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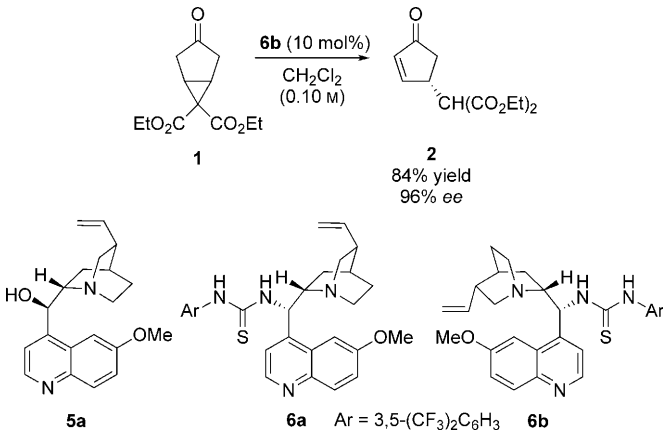


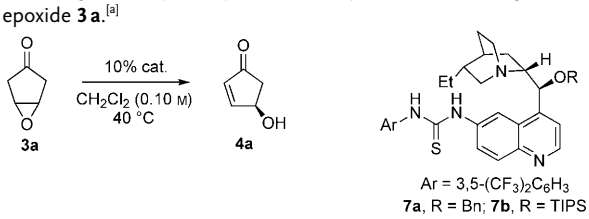
Scheme 4. Organocatalytic asymmetric desymmetrization–fragmentation of **1** as a model reaction.

compound. When we attempted the reaction with quinine (**5a**) as the organocatalyst, cyclopentenone **2** was obtained with 40% *ee*, which encouraged us to screen further catalysts and reaction conditions (see the Supporting Information). We found that bifunctional thiourea–cinchona alkaloid catalysts, such as **6a** and **6b**, afforded superior results.[8] Accordingly, when 10 mol% of the quinidine-derived thiourea catalyst **6b** was used, the product (*S*)-**2** was isolated in 84% yield and with 96% *ee* (Scheme 4), whereas (*R*)-**2** was obtained with 90% *ee* when **6a**, the quasienantiomer of **6b**, was used as the catalyst (see the Supporting Information).

Following the initial encouraging results, which confirmed the possibility of effectively desymmetrizing *meso* cyclopentanones, we focused our attention on the conversion of epoxides **3** into the very important 4-hydroxycyclopent-2-enone products **4**. However, when we carried out the desymmetrization–fragmentation of 6-oxabicyclo-[3.1.0]hexan-3-one (**3a**) under the conditions found suitable for **1**, racemic 4-hydroxycyclopent-2-enone **4a** was formed (Table 1, entry 1). Nevertheless, with catalyst **7a**, product **4a** was formed with 53% *ee* (Table 1, entry 2). Thus, the direct attachment of the thiourea moiety to the quinoline system in the catalyst appeared to provide selectivity.[9] The replacement of the benzyl group with the bulkier TIPS protecting group led to a satisfying improvement in the *ee* value of **4a** to 90% (Table 1, entry 3). Under these conditions, **4a** was isolated in excellent yield (93%) with 90% *ee* (Table 1, entry 4).

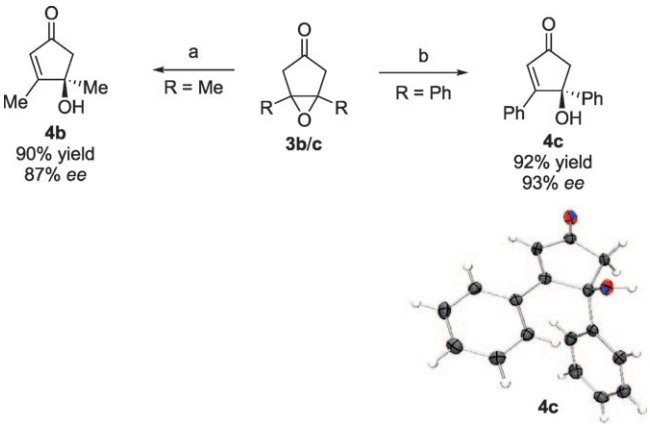
The protocol was then extended to epoxides **3b** and **3c**, which have aliphatic and aromatic substituents, respectively, in the 3- and 4-positions; the products **4b** and **4c** contain quaternary stereogenic centers (Scheme 5). When 1,5-dimethyl-6-oxabicyclo[3.1.0]hexan-3-one (**3b**) was treated with catalyst **7b** under the conditions identified for **3a**, optically active (*R*)-4-hydroxy-3,4-dimethylcyclopent-2-enone (**4b**)[11] was formed in 90% yield and with good enantioselectivity (87% *ee*). In the case of the phenyl-substituted analogue, 1,5-diphenyl-6-oxabicyclo[3.1.0]hexan-3-one (**3c**), excellent selectivity was observed with catalyst **6b**. Following a short optimization process (results not shown),

Table 1: Organocatalytic asymmetric desymmetrization–fragmentation of epoxide **3a**.[a]



Entry	Catalyst	*t* [h]	*ee* [%][b]
1	**6b**	24	racemic
2	**7a**	15	53 (*R*)
3	**7b**	48	90 (*R*)
4[c]	**7b**	15	90 (*R*)

[a] Reactions were carried out with 0.05 mmol of **3a**. All reactions proceeded to complete conversion, as determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] The *ee* value was determined by HPLC on a chiral stationary phase by using a Chiralpak OJ column after derivatization of the product as the corresponding dimethylphenylsilyl ether. The absolute configuration was determined by comparison of the optical rotation of **4a** with a literature value.[10] [c] The reaction was carried out with 0.4 mmol of **3a**. The product was obtained in 93% yield after flash chromatography. Bn = benzyl, TIPS = triisopropylsilyl.



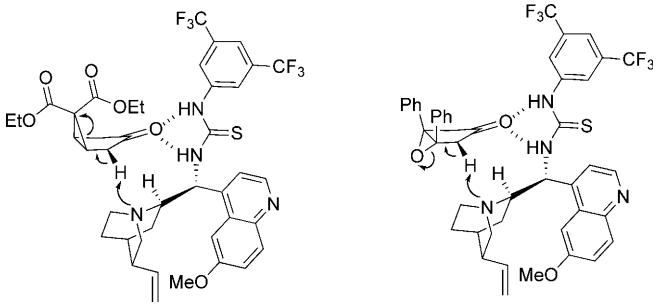
Scheme 5. Desymmetrization–fragmentation of substituted epoxides, and the X-ray crystal structure of product **4c**. Reagents and conditions: a) catalyst **7b** (10 mol%), CH_2Cl_2 (0.10 M), 40°C, 28 h, 90%, 87% *ee*; b) catalyst **6b** (10 mol%), CH_2Cl_2 (1.0 M), −20°C, 18 h, 92%, 93% *ee* (97% *ee* after recrystallization).

(*S*)-4-hydroxy-3,4-diphenylcyclopent-2-enone (**4c**) was synthesized in 92% yield and with 93% *ee*. The absolute configuration of **4c** was verified by X-ray crystallography[12] after recrystallization (Scheme 5).

To account for the selectivity of the asymmetric fragmentation, we propose a mechanism in which the thiourea part of the catalyst interacts with the carbonyl functionality of the cyclopentanone and thus increases the acidity of the α-hydrogen atoms. The quinuclidine moiety then removes one of the α-hydrogen atoms stereoselectively by deprotonation.

It is notable that the substrates **1** and **3c**, giving 96% and 93% *ee*, respectively, when being exposed to the same catalyst

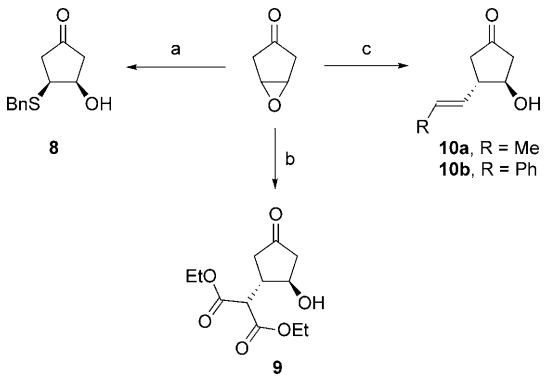
6b, show a reversed orientation of the C–X bond being cleaved. Accordingly, the leaving group of the bond-breaking process is opposite in the two products. A hypothesis for this observation is outlined in Scheme 6. The cyclopropane ring in



Scheme 6. Mechanistic proposal for the desymmetrization–fragmentation of **1** and **3c**.

1 and the phenyl substituents attached to the epoxide ring in **3c** are oriented away from the quinuclidine moiety of the catalyst to avoid steric repulsion. In this conformation, selective deprotonation yields the observed products, (*S*)-**2** and (*S*)-**4c**, by an E1cb-like mechanism.[13]

Having synthesized a variety of optically active α,β-unsaturated ketones with a cyclopentanone skeleton, we hoped to exploit this functionality in a tandem Michael addition reaction. Accordingly, the desymmetrization of **3a** in the presence of BnSH led to subsequent addition to give (3*S*,4*R*)-3-(benzylthio)-4-hydroxycyclopentanone (**8**; Scheme 7).[14] Remarkably, the presence of BnSH had a beneficial effect on the enantioselectivity: **8** was formed in 90% yield with 94% *ee* and d.r. 10:1.

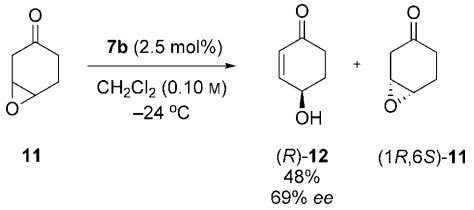


Scheme 7. Organocatalytic desymmetrization–Michael addition of **3a**. Reagents and conditions: a) BnSH (2 equiv), **7b** (10 mol%), CH_2Cl_2 (0.10 M), 40°C, 2 h, 90%, 94% *ee*; b) 1) **7b** (10 mol%), CH_2Cl_2 (0.10 M), 40°C, 45 min; 2) Cs_2CO_3 (1.1 equiv), $CH_2(CO_2Et)_2$ (1.5 equiv), room temperature, 30 min, 39%, 90% *ee*; c) 1) **7b** (10 mol%), CH_2Cl_2 (0.10 M), 40°C, 45 min; 2) filtration; 3) $RCH{=}CHB(OH)_2$ (1.2 equiv), $[\{Rh(cod)Cl\}_2]$ (3 mol%), Cs_2CO_3 (10 mol%), dioxane/H_2O (4:1; 0.33 M), room temperature; R = Me: 30 min, 84%, 90% *ee*; R = Ph: 2 h, 82%, 90% *ee*. cod = 1,5-cyclooctadiene.

The addition of a carbon nucleophile was also possible in a one-pot reaction. When diethyl malonate and a base were added after the consumption of the starting material, the *trans* adduct diethyl 2-((1*S*,2*R*)-2-hydroxy-4-oxocyclopentyl)malonate (**9**) was formed in 39% yield with 90% *ee* and d.r. > 95:5 (Scheme 7). The configuration of the newly constructed stereocenter was determined after the exposure of **9** to methanesulfonyl (Ms) chloride/NEt_3. Under these conditions, the hydroxy group was eliminated to yield (*R*)-**2**, the configuration of which had been determined earlier.

Owing to the mild conditions under which vinylic boronic acids undergo rhodium-catalyzed addition to α,β-unsaturated ketones, we finally chose to apply a highly diastereoselective protocol[15] to introduce propenyl (→**10a**) and styryl (→**10b**) substituents. Following opening of the epoxide under the previously determined conditions, the crude reaction mixture was filtered through silica gel and treated with the corresponding boronic acid in the presence of catalytic $[\{Rh(cod)Cl\}_2]$ and Cs_2CO_3. This procedure provided **10a** in two steps in 84% yield. An *ee* value of 90% and diastereomeric ratio of 98:2 were obtained. The structure of **10a** is closely related to the core of enprostil (Scheme 3) and other prostaglandin derivatives. Product **10b** was formed in 82% yield with 90% *ee* and d.r. 98:2 (Scheme 7). The relative configuration of **10b** was determined by elimination of the hydroxy group with MsCl/NEt_3, followed by standard hydrogenation with H_2 and catalytic Pd/C to yield (*S*)-3-phenethylcyclopentanone, a known compound.[16]

To elaborate the new reaction type in a conceptually different approach, we explored the possibility of using catalyst **7b** for the kinetic resolution of chiral, racemic 7-oxabicyclo[4.1.0]heptan-3-one (**11**; Scheme 8). We suspected that **7b** might show different catalytic activity towards the two enantiomers of **11**. Product **12** obtained in this reaction has been used as a starting material in a number of syntheses of biologically active compounds.[17] We were pleased to find that when racemic **11** was exposed to catalyst **7b** (2.5 mol%) at −20°C, enantiomerically enriched (*R*)-**12**[18] was formed in 48% yield and with 69% *ee*.



Scheme 8. Organocatalytic kinetic resolution of **11**.

In summary, we have developed a protocol for the high-yielding desymmetrization–fragmentation of a number of *meso* cyclopropane cyclopentanones and epoxycyclopentanones under the catalysis of thiourea-containing cinchona alkaloids to give optically active products with good to excellent enantioselectivities. Furthermore, we developed organocatalytic asymmetric one-pot and tandem desymmetrization–fragmentation–Michael addition reactions of an

epoxycyclopentanone by performing the desymmetrization–fragmentation in the presence of thiol and malonate nucleophiles; a rhodium-catalyzed vinylation was also possible. Finally, this organocatalytic concept was extended to the kinetic resolution of a racemic epoxycyclohexanone, which was converted into optically active 4-hydroxycyclohex-2-enone with promising enantioselectivity.

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