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One-Pot Construction of Multi-Substituted Spiro-Cycloalkanediones by an Organocatalytic Asymmetric Epoxidation/Semipinacol Rearrangement

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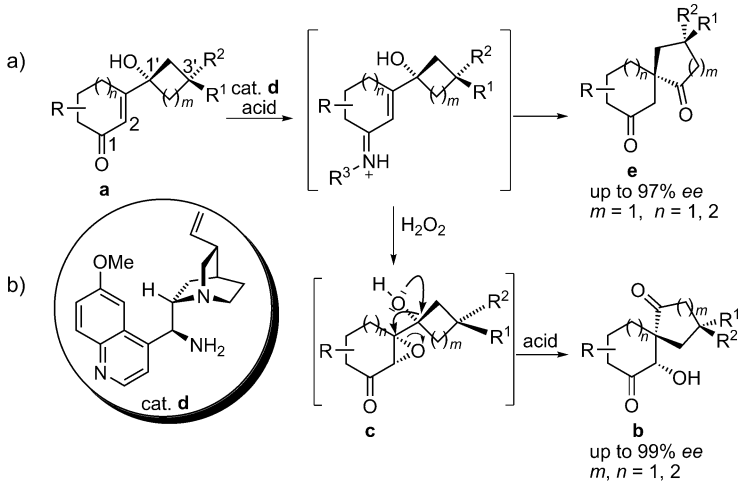
The construction of chiral spirocycloalkanedione cores,[1] which are key intermediates in the synthesis of natural spirocyclic compounds,[2] is an important task in organic synthesis. The semipinacol rearrangement has proven to be one of the most powerful procedures to access these units.[3] In recent years, tremendous effort has been made to investigate semipinacol rearrangements for this purpose and a series of novel methodologies have been developed, some of which have been applied efficiently to the synthesis of important natural products.[4] However, the catalytically effective asymmetric semipinacol rearrangement, used for constructing chiral units containing a quaternary carbon,[5] especially multi-substituted spirocycloalkanediones, still remains a challenge. Recently, we have reported two asymmetric semipinacol rearrangement reactions for the construction of spirocyclic ketones with high enantioselectivity.[6]

Organocatalysis has become a highly dynamic and rapidly expanding field in organic chemistry.[7] One of the most widely used organocatalysts over the past decade has been the cinchona-derived amine **d** (Scheme 1), which has been applied to a number of asymmetric reactions with high enantioselectivity.[8] For example, List and co-workers explored the asymmetric epoxidation of enones using amine **d**,[9] and Jørgensen and co-workers employed this **d**-promoted, one-pot reaction in the synthesis of chiral allylic alcohols.[10] In our previous work, we have also successfully used amine **d** to catalyze the semipinacol rearrangement of **a**, generating chiral spirocyclic 1,4-diketones of type **e** with up to 97% *ee* (Scheme 1a).[6b] We now present our studies on the use of this amine (**d**) to explore a new asymmetric epoxidation/semipinacol rearrangement in the efficient synthesis of more-complex tri-oxygenated spirocycloalkanediones **b**. We anticipated that the asymmetric epoxidation/semipinacol rearrangement of vinylogous α-ketol **a** might be carried out in a tandem or one-pot reaction (Scheme 1b) using amine **d** as a catalyst, to produce tri-oxygenated-spirocycloalkane-



Scheme 1. Strategy to complex chiral spirocycloalkanediones via an asymmetric epoxidation/semipinacol rearrangement.

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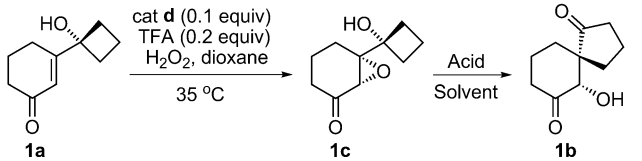
dione derivatives **b**. However, we were aware of some possible problems with this strategy. For example, the epoxidation of enone **a** to give **c** would not be easy owing to the presence of a bulky hydroxycycloalkyl substituent at the C-3 position. In addition, a mixture of two diastereoisomeric products of **b** might be formed if the rearrangement of epoxide **c** proceeded via competing S_N1 and S_N2-like processes (Scheme 1b). Furthermore, under weakly acidic conditions, a direct semipinacol rearrangement of enone **a** to form **e** (as in Scheme 1a) might take place before epoxidation occurred.[6b] Herein, we report the development of this process and its results.

We initially attempted to develop the tandem asymmetric epoxidation/semipinacol rearrangement of the vinylogous α-ketol **a**. However, the reaction of **1a** with 2.5 equivalents of H_2O_2 (30% w/w in H_2O), using amine **d** as the catalyst, in the presence of water-stable Lewis acids $Sc(OTf)_3$ and $Yb(OTf)_3$[11] failed to afford the expected product **1b** in various solvents at 35°C. Fortunately, the intermediate epoxide **1c** was produced with several solvents, such as 1,4-dioxane, tetrahydrofuran, or ethyl acetate. Among these solvents, 1,4-dioxane gave the highest *ee* (98%) and yield (68%).[12] In these cases, a trace amount of the competing semipinacol rearrangement product **e** was also observed.

Based on the experimental results above, we turned our attention to promoting the subsequent semipinacol rearrangement of epoxide **1c** into product **1b** so as to accomplish a one-pot procedure (Scheme 1b).[13] Thus, epoxide **1c** served as the substrate in a search for appropriate rearrangement conditions. We treated **1c** with a variety of Brønsted or Lewis acids in 1,4-dioxane,[14] and the results (Table 1) indicated that several Lewis acids, such as $Mg(ClO_4)_2$, $LiClO_4{\cdot}3H_2O$, $AlCl_3$, and $SnCl_4$, were ineffective in promoting this rearrangement at 50°C. Gratifyingly, when concentrated hydrochloric acid (4 equiv) was used; however, the reaction went to completion smoothly within 4 hours at room temperature to give the expected product **1b** with high stereoselectivity (99% *ee*) and in 30% yield (Table 1, entry 1). With this result in hand, our subsequent efforts were aimed at improving the yield of the rearrangement step by screening other Brønsted acids. However, neither trifluoroacetic acid (TFA) nor boric acid yielded the expected product **1b** (Table 1, entries 2 and 3). We considered the possibility that not only a Brønsted acid was required, but also the presence of water was important in effecting this rearrangement, because the presence of a large amount of water induced this reaction (Table 1, entries 2 and 3).

Table 1. Screening rearrangement conditions from **1c** to **1b**.[a]



entry	Solvent	Acid	Yield [%][e]	*ee* [%][f]
1	1,4-dioxane	HCl[b]	30	99
2	1,4-dioxane	TFA[c]	n.d.	–
3	1,4-dioxane	boric acid[c]	n.d.	–
4	1,4-dioxane/water	TFA[d]	60	96
5	1,4-dioxane/water	TFA[c]	84	99
6	THF/water	TFA[c]	69	99
7	1,4-dioxane/CH_2Cl_2	TFA[c]	n.d.	–
8	1,4-dioxane/MeOH	TFA[c]	n.d.	–

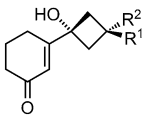
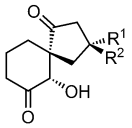
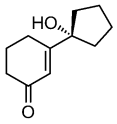
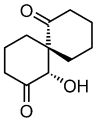
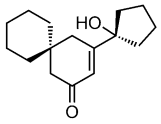
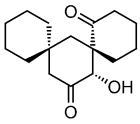
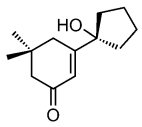
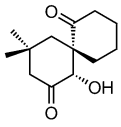
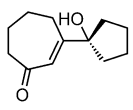
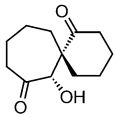
[a] All Reactions (except entry 1) were performed with 0.1 mmol of epoxide **1c** in 1 mL solvent at 50°C. [b] 4 equiv acid was added. [c] 10 equiv acid was added. [d] 0.02 equiv acid was added. [e] Yield of isolated product. [f] *ee* of product **1b** was determined by chiral HPLC analysis. THF = tetrahydrofuran, TFA = trifluoroacetic acid, n.d. = not detected.

As we anticipated, when dioxane and water (v/v 1:2) were used as a mixed solvent, rearrangement of epoxide **1c** proceeded sluggishly with 5% TFA at 50°C and gave the product **1b** in 60% yield after 36 hours (Table 1, entry 4). Increasing the amount of TFA to 10 equivalents reduced the reaction time to 6 hours and enhanced the yield of product **1b** to 84% (Table 1, entry 5). Likewise, the use of tetrahydrofuran and water as a mixed solvent also effected this rearrangement with 99% *ee*, and in 69% yield (Table 1, entry 6). Subsequently, we examined other mixed solvents, such as 1,4-dioxane with dichloromethane or methanol (Table 1, entries 7 and 8), but no product **1b** was observed. A survey of mixed solvents revealed that water as a co-solvent was essential to this rearrangement reaction. Furthermore, changing the ratio of dioxane/water from 1:1 to 1:3 was examined to find the optimal conditions, and dioxane/water in a ratio of 1:2 was found to give the best yield.

To further explore the substrate scope and generality of this one-pot procedure (Scheme 1b), a series of vinylogous α-ketol substrates, **a** (prepared through the coupling of various enones with cyclobutanone or cyclopentanone derivatives),[12] were subjected to asymmetric epoxidation with H_2O_2 followed by in situ acidification in the general process described below. The results are shown in Table 2. Substitution at the C-3′ position of the cyclobutanol moiety of substrate **1a** with both six- and seven-membered spiro-rings (Table 2, entries 2 and 3) were effectively converted into the desired product using this procedure, with comparable yields of 56% and 60%, respectively. The introduction of *cis*-mono-substituents 4-BrC_6H_4 and Ph at the C-3′ position (Table 2, entries 4 and 5) led to 3:1 diastereoisomeric mixtures of **4b/4b′** and **5b/5b′** in total yields of 55% and 57%, respectively.

Both major isomers, **4b** and **5b**, were produced in excellent optical purities (98% *ee* and 99% *ee*, respectively).The absolute configuration of (−)-**4b** was unambiguously confirmed by X-ray crystallography,[15] and, based on this information, the absolute configuration of other products **1b–3b** and **5b** in Table 2 were deduced. However, *trans*-mono-substitution with a phenyl group at the C-3′ position of **1a** resulted in poor 1:1 diastereoselectivity and a low total yield of 40% (Table 2, entry 6). When 3′,3′-diphenyl-substituted **1a** was subjected to the reaction conditions, we did not observe the expected product **b**, and **e** was the sole product, probably owing to steric hindrance caused by the bulky 3′,3′-diphenyl substitution during the initial epoxidation step.

Table 2. One-pot synthesis of asymmetric spirocycloalkanediones.[a]

Entry	Substrate	Product[c]	Yield [%][d]	*ee* [%][e]
				
1	**1a** R^1, R^2=H	**1b** R^1, R^2=H	66	99
2	**2a** R^1, R^2=$(CH_2)_5$	**2b** R^1, R^2=$(CH_2)_5$	56	99
3	**3a** R^1, R^2=$(CH_2)_6$	**3b** R^1, R^2=$(CH_2)_6$	60	99
4[b]	**4a** (R^1=H, R^2=4-BrC_6H_4)	**4b/4b′**	55(3:1)	98
5[b]	**5a** (R^1=H, R^2=C_6H_5)	**5b/5b′**	57(3:1)	99
6[b]	**6a** (R^1=C_6H_5, R^2=H)	**5b/5b′**	40(1:1)	94
7	 **7a**	 **7b**	75	99
8	 **8a**	 **8b**	51	99
9	 **9a**	 **9b**	46	99
10	 **10a**	 **10b**	70	93

[a] For experimental details, see the Supporting Information. [b] For entries 4–6, the *ee* values of **4b** and **5b** were described; The d.r. (given in parentheses) were determined by chiral HPLC. [c] Preparation of the racemates is described in the Supporting Information. [d] Total yield of isolated product. [e] *ee* values in parentheses were determined by chiral HPLC.

Enone **7a**, which has a larger C_3-cyclopentanol moiety, was examined using this procedure, and this substrate was found to give the highest yield (75%) of product **7b** obtained for any substrate in our study (Table 2, entry 7). Substitution on the ring of the cyclohexenone moiety with a six-membered spirocycle at the C-5 position was investigated and the desired product **8b** was produced in a moderate 51% yield (Table 2, entry 8). X-ray crystal structures of (−)-**4b** and (−)-**7b**[15] were obtained, and, based on this information and the absolute configuration of **4b**, the absolute configurations of products **7b**, **8b**, **9b**, and **10b** were elucidated. A C-5 dimethyl-substituted substrate gave only a low yield (46%) of product **9b** (Table 2, entry 9). Finally, the six-membered cyclohexenone ring of **7a** was expanded to a seven-membered ring in **10a** and used as a substrate in this protocol. Its reaction also gave a good yield (70%) of product **10b** with 93% *ee* (Table 2, entry 10).

The above results (Table 2) showed that the corresponding trioxygenated spirocycloalkanedione products **b** could be obtained with moderate total yields (40–75%) and excellent stereoselectivities (93–99% *ee*). In all cases, no other spiro-isomer was observed, indicating that the rearrangement step proceeded well in a concerted S_N2-type process. These types of multi-substituted spirocycloalkanediones, which contain tri-oxygenated functional groups and two adjacent chiral centers (including one all-carbon quaternary center), are versatile building blocks for the synthesis of many important molecules.[2] For example, the spirojatamol and erythrodiene-type natural products would be readily synthesized through conversion of the hydroxy and carbonyl groups adjacent to the spirocenter into fully reduced alkyl groups.[2]

In summary, a new and efficient one-pot procedure for the synthesis of various trioxygenated-spirocycloalkanedione cores has been developed based on an asymmetric epoxidation/semipinacol rearrangement. The significant features of this transformation include the excellent stereoselectivity and high efficiency in an aqueous medium.

Experimental Section

Experimental Details

A mixture of substrate **a** (0.15–0.51 mmol, 0.1 M in 1,4-dioxane), catalyst **d** (0.1 equiv) and TFA (0.2 equiv) was stirred in 1,4-dioxane at RT for 10 min, and then H_2O_2 (30% w/w in H_2O, 2.5 equiv) was added. The reaction was heated to 35–50 °C for 20–72 h. After completed conversion of enone into the epoxide had been established by TLC analysis, TFA (10 equiv) and water was added at 50 °C. The reaction was stirred for 6–36 h, cooled to RT, and a saturated solution of $NaHCO_3$ (4 mL) was added. The reaction mixture was extracted with Et_2O (15 mL × 3), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

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Keywords: asymmetric synthesis · chiral quaternary carbon · epoxidation · semipinacol rearrangement · spiro compounds

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[15] For ORTEPs of (−)-**4b** and (−)-**7b**, please see the Supporting Information. CCDC 800896 (−)-**4b** and CCDC 814514 (−)-**7b** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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