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Catalytic Asymmetric Construction of α-Quaternary Cyclopentanones and Its Application to the Syntheses of (−)-1,14-Herbertenediol and (−)-Aphanorphine

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Abstract: A novel and efficient strategy to build α-benzylic quaternary cyclopentanones with excellent enantioselectivities (up to 96% *ee*) and high yields (up to 99% yield) has been developed, and its application demonstrated by the first catalytic asymmetric total synthesis of (−)-1,14-herbertenediol and the formal synthesis of (−)-aphanorphine.

Quaternary stereocenters are sterically hindered structural units extensively found in a variety of natural products and bioactive molecules, and their efficiently construction is generally a key step for organic synthesis.[1,2] For example, the phenyl-substituted quaternary center at the α-position to the carbonyl in cyclopentanone is a highly strained structural motif, which is similar to groups found in herbertane-type sesquiterpenes,[3] such as (−)-herbertene,[4] (−)-1,14-herbertenediol,[5] and (−)-herbertenoid[6] (Figure 1). These molecules exhibit special biological activities, such as anti-lipid-oxidation and antifungal properties, and also share two unique contiguous quaternary carbon centers on the cyclopentane ring with one attached to a phenyl group. Since the 1990s, development of strategies toward the synthesis of these natural products with an all-carbon quaternary center has attracted much attention from organic chemists.[7] However, among the reported strategies approaching these sesquiterpenes, most afford the final products in racemic forms,[7e] and only few are catalytic and asymmetric, such as the Pd-catalyzed asymmetric α-arylation of alkyl-substituted cyclopentanones developed by Buchwald,[8] and the asymmetric chlorination/ring expansion cascade published by You.[9] Therefore, it is still highly desirable to develop more efficient methodologies approaching the synthesis of this kind of natural product.

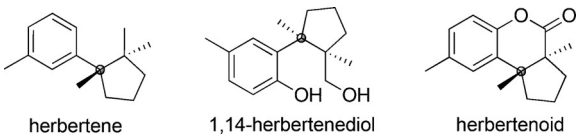

Figure 1. Selected herbertane-type sesquiterpenes.

In connection with our long-standing interest in the asymmetric construction of highly strained quaternary centers,[10] we previously developed an organocatalytic asymmetric rearrangement of vinylogous γ-ketol, which is efficient for the construction of a series of chiral spirocyclic quaternary centers.[10f] Thus we hypothesize that if such a reaction is effective for a substrate with an acyclic and phenyl-substituted vinylogous γ-aldol, such as **1a** (Scheme 1), a new and more efficient synthesis of the herbertane-type sesquiterpenes might be achievable. Herein we present our efforts toward this methodology development and its application to the first catalytic asymmetric synthesis of (−)-1,14-herbertenediol and formal synthesis of (−)-aphanorphine.

Our initial investigation focused on screening catalysis systems. Firstly, our previously well recognized cinchona alkaloid-based organocatalyst[10f] Cat. **A1** (Scheme 1), was used to promote the rearrangement of **1a** with an *E* double bond, which was readily prepared from a known method (for details, see the Supporting Information).[11] However, both the enantioselectivity (16%) and yield (46%) of the reaction were unsatisfactory (Scheme 1). Furthermore, in the presence of some other secondary amine catalysts (Cat. **A2**–**A4**; Scheme 1),[12] only racemic product was obtained.[13] The results might be attributed to the presence of a less hindered carbonyl group, which would affect the enantioselectivity during the rearrangement step. On the basis of the above results and considerations, we envisioned that such a disadvantage might be overcome through the use of a catalyst such as chiral silver phosphates (CSPs), which could interact with the substrate through a dual activation mode.[14]

Following above assumption, we carried out the reaction under the catalysis of three typical CSPs. Fortunately, when we

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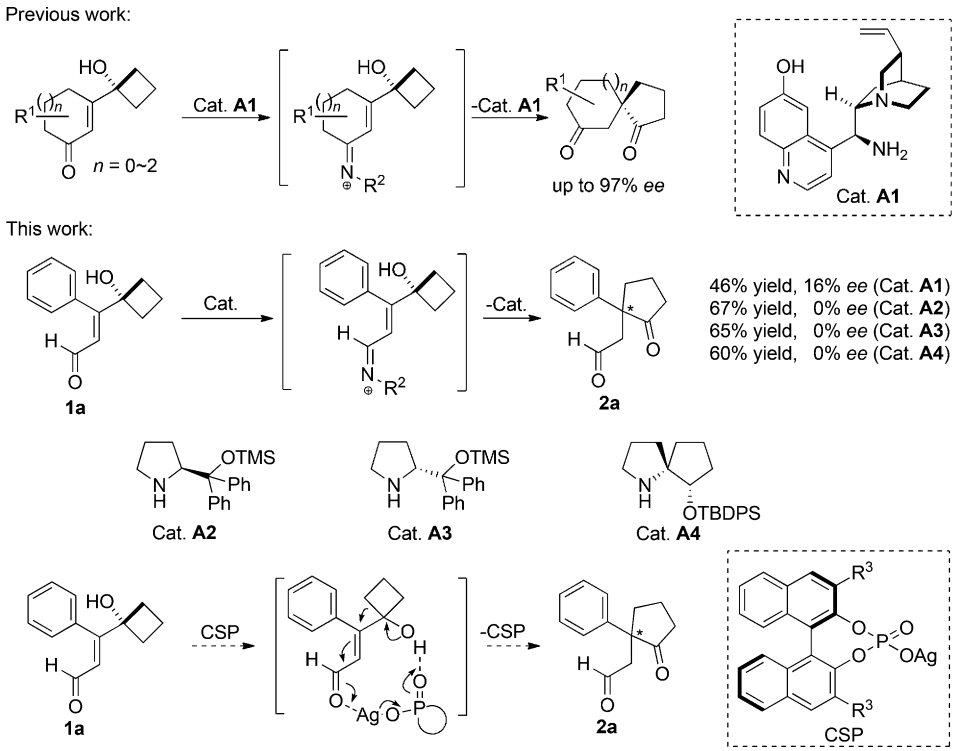


Scheme 1. Design of the catalytic asymmetric reaction.

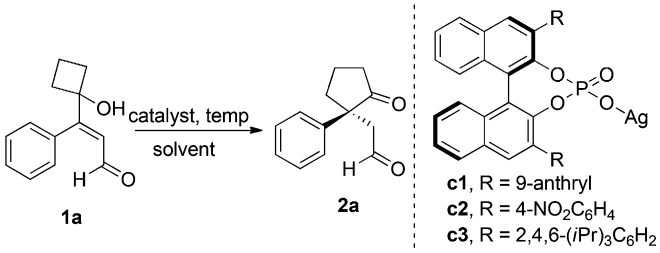
substituents on the phenyl ring showed some influence on the enantioselectivity of the reaction. In the case of substrates with substituents at the *para* or *meta* position of the phenyl ring, the *ee* values of the corresponding products were usually excellent (**2b**–**g**, **2i**, **2j**). In contrast, the *ee* values were much lower for substrates with a substituent at the *ortho* position of the phenyl ring (**2h** and **2l**). To further quantify the utility of such a method, we also carried out the reaction of **1f** on 2 mmol scale and the product **2f** was readily obtained in 92% yield and 90% *ee*.

Encouraged by above experimental results, the utility of this method was further demonstrated with the synthesis of herbertane-type sesquiterpenes by using it as a key step (Scheme 2).[3] For example, 1,14-

tested the reaction of **1a** in the presence of CSP catalyst **c1**, the reaction could proceed successfully in toluene at room temperature to give the desired product **2a** in 40% yield and 45% *ee* (Table 1, entry 1). Further screening of another two common CSPs, **c2** and **c3**, did not give better results (Table 1, entries 1 and 2). Next, screening of different solvents with **c1** as catalyst indicated that $CHCl_3$ was the best choice, giving the desired product **2a** in 91% yield and 82% *ee* (Table 1, entry 6). We also attempted to improve the enantioselectivity of this reaction by lowering the temperature of the reaction system; the desired product **2a** could be obtained in 93% *ee* at −25 °C (Table 1, entries 9–12). The influence of molecular sieves on this transformation was also tested, and the use of 5 Å MS slightly increased the *ee* value to 95% (Table 1, entry 15).

With the optimized reaction conditions in hand (Table 1, entry 15), the substrate scope of the asymmetric semipinacol rearrangement reaction was explored. A series of olefin aldehydes with different aryl substituents at the β-position was tested as substrates in this reaction (Table 2), giving the expected products in good to excellent yields and *ee* values. Among the substrates screened, the electronic effect of the substituents on the phenyl ring did not clearly affect the enantioselectivity; substrates with either an electron-donating or an electron-withdrawing group at the *para* position of the phenyl ring (**1b**–**e**) could afford the desired products in excellent *ee* values. However, with regards to reaction yield and rate, it was clear that the more electron-withdrawing the substituent was, the lower the yield and longer the reaction time were (Table 2, **1b**–**e**). Interestingly, the position of

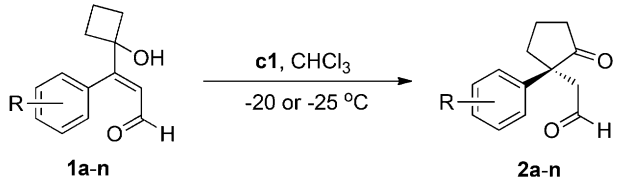
Table 1. Optimization of the reaction conditions.[a]

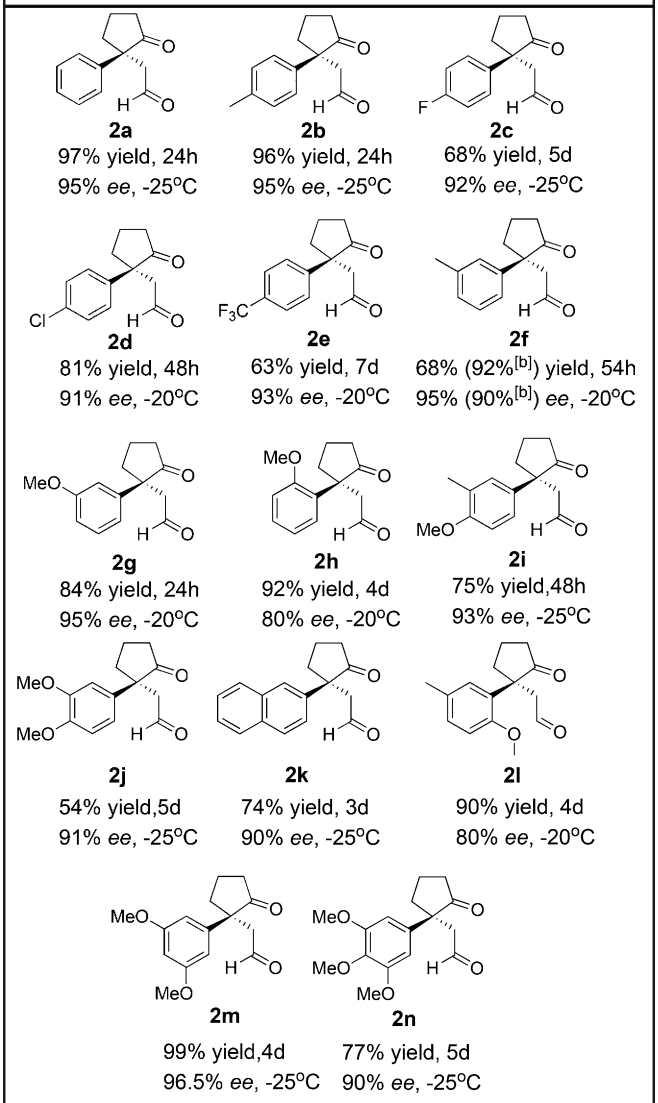


Entry	Cat.	Solvent	T [°C]	t [h]	Yield [%][b]	*ee* [%][c]
1	**c1**	toluene	25	6	40	45
2	**c2**	toluene	25	6	33	14
3	**c3**	toluene	25	6	trace	NA
4	**c1**	CH_2Cl_2	25	2	92	70
5	**c1**	DCE	25	2	90	70
6	**c1**	$CHCl_3$	25	2	91	82
7	**c1**	CCl_4	25	2	90	55
8	**c1**	CH_2Cl_2	0	12	90	76
9	**c1**	$CHCl_3$	0	12	95	86
10	**c1**	$CHCl_3$	−10	18	95	89
11	**c1**	$CHCl_3$	−20	18	95	92
12	**c1**	$CHCl_3$	−25	24	97	93
13[d]	**c1**	$CHCl_3$	−25	24	97	93
14[e]	**c1**	$CHCl_3$	−25	24	97	93
15[f]	**c1**	$CHCl_3$	−25	24	97	95

[a] Reaction conditions: **1a** (0.1 mmol), catalyst (0.005 mmol), and solvent (1.0 mL) stirred at a given temperature under argon atmosphere for 24 h. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] 40 mg of 3 Å molecular sieves were added. [e] 40 mg of 4 Å molecular sieves were added. [f] 40 mg of 5 Å molecular sieves were added. DCE = 1,2-dichloroethane.

Table 2. Substrate scope of the catalytic asymmetric semipinacol rearrangement.[a]





[a] Reaction conditions (unless otherwise stated): **1** (0.1 mmol), **c1** (0.005 mmol), and $CHCl_3$ (1.0 mL) stirred at −25 or −20 °C under argon atmosphere for 24 h; the *ee* values of compounds **2a**–**n** were determined from the corresponding compounds **3a**–**n** (for details, see the Supporting Information). [b] The reaction was carried out on 2 mmol scale.

herbertenediol[5] could be synthesized asymmetrically in seven steps from compound **2l**. Firstly, in the presence of Wilkinson's catalyst, decarbonylation of the aldehyde **2l** could give compound **3l** in moderate yield. Then the ketone **3l** was treated with sodium hexamethyldisilazide (NaHMDS) and $PhNTf_2$ to afford corresponding vinyl triflate **4**, which was converted into ester **5** through a carbomethoxylation catalyzed by $[Pd(PPh_3)_4]$ in a THF/methanol solvent mixture. Next, hydrogenation of ester **5** with 10% Pd/C followed by demethylation of the phenyl ring by boron tribromide furnished the tricyclic intermediate **6** as a single product in nearly quantitative yield. Finally, *syn*-methylation of compound **6** followed by lithium aluminum hydride reduction led to (−)-1,14-herbertenediol,[5] which also confirmed the absolute configuration of the product **2l**. The absolute configurations of other products (**2a**–**k**, **2m**, **2n**) could also be deduced from this result. Furthermore, the formal synthesis of (−)-aphanorphine was also carried out through a simple decarbonylation of the aldehyde **2g**, which gave Ogasawara's intermediate **8** in 60% yield.[15]

In conclusion, a novel and efficient asymmetric semipinacol rearrangement of olefin aldehyde was developed, which could afford a series of cycloalkanones with an all-carbon quaternary stereocenter in excellent enantioselectivity (up 96% *ee*). The application of the methodology was well demonstrated by the first catalytic asymmetric total synthesis of (−)-1,14-herbertenediol and the formal synthesis of (−)-aphanorphine.

Experimental Section

General procedure: To a solution of compound **1** (0.1 mmol) in anhydrous $CHCl_3$ (1.0 mL) at −20 °C or −25 °C under argon was added 5 Å molecular sieves (40 mg) and catalyst (0.05 mmol, 3.6 mg). The reaction mixture was stirred until the disappearance of compound **1** by TLC monitoring. The mixture concentrated under vacuum and purification of the residue by column chromatography on silica gel to afford product **2**.

Acknowledgements

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Keywords: asymmetric synthesis · enantioselectivity · organocatalysis · quaternary stereocenters · sesquiterpenes

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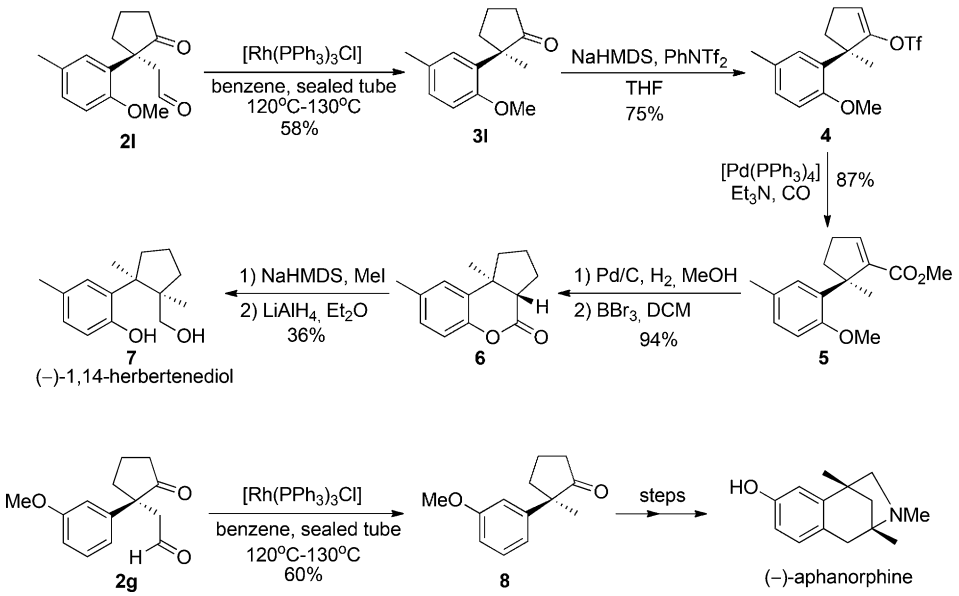

Scheme 2. Syntheses of (−)-1,14-herbertenediol and (−)-aphanorphine.

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