J|A|C|S COMMUNICATIONS

Published on Web 09/28/2009

Organocatalytic Asymmetric Vinylogous α-Ketol Rearrangement: Enantioselective Construction of Chiral All-Carbon Quaternary Stereocenters in Spirocyclic Diketones via Semipinacol-Type 1,2-Carbon Migration

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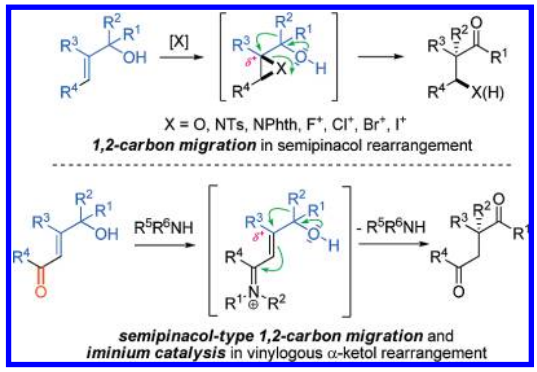
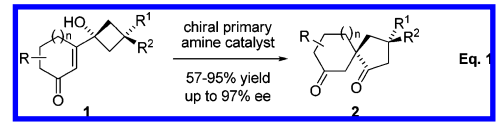
Received July 27, 2009; E-mail: tuyq@lzu.edu.cn

Asymmetric construction of chiral quaternary carbon stereocenters is one of the most challenging subjects in modern organic synthesis,[1] and the development of synthetic methodologies in this area of research has always been in high demand. Over the past several decades, tremendous efforts have been made in the asymmetric formation of quaternary carbon centers;[2] however, catalytic enantioselective synthesis, especially of stereogenic all-carbon quaternary centers, still remains a major challenge for synthetic chemists. In the context of our interest in the stereoselective construction of 1,3-diheteroatom units with 2-quaternary carbon centers, a series of synthetic protocols based on the semipinacol rearrangement has been developed in our group to effectively achieve the quaternary carbon stereocenters.[3] However, the asymmetric versions of our previous protocols using the semipinacol rearrangement strategy were limited to utilizing kinetic resolution[3b] or stoichiometric chiral reagents,[3c] and the catalytic enantioselective semipinacol rearrangement still remains elusive.[4,5] Encompassing the development of catalytic asymmetric synthesis of all-carbon quaternary stereogenic centers, we envisioned that the 1,2-sigmatropic migration in the semipinacol rearrangement might be extended to vinylogous α-hydroxy ketones, which could analogously result in an electron-deficient electrophilic center next to the tertiary hydroxyl moiety (Scheme 1), leading to the generation

Scheme 1. Semipinacol and Related Rearrangements for the Synthesis of All-Carbon Quaternary Stereocenters



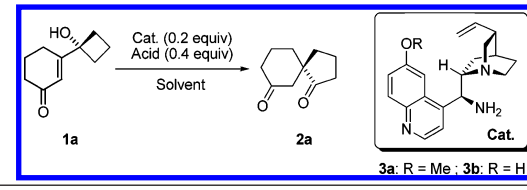
of an all-carbon quaternary stereogenic center. In light of the aforementioned semipinacol-type 1,2-carbon migration and inspired by the chiral iminium catalysis of enones,[6] we recently discovered the first organocatalytic asymmetric vinylogous α-ketol rearrangement via semipinacol-type 1,2-carbon migration for the construction of chiral all-carbon quaternary stereocenters in spirocyclic diketones,[7] which are versatile building blocks in the synthesis of natural products and pharmaceutical molecules (eq 1). To our knowledge, there is no precedent for the catalytic enantioselective vinylogous α-ketol rearrangement, and the current protocol provides an



alternative asymmetric access to chiral all-carbon quaternary centers through semipinacol-type 1,2-carbon migration.[5] Herein, we present our preliminary results on this topic.

During the initial elaboration of standard conditions, cinchona-based primary amine **3a** was examined as a promising catalyst.[8] As indicated in Table 1, the hydroxy enone **1a** as a model substrate was subjected

Table 1. Optimization Studies on Asymmetric Rearrangement[a]



Entry	Cat.	Acid[b]	Solvent	*t* (h)	Yield (%)[c]	ee (%)[d]
1	**3a**	CF_3CO_2H	THF	18	75	34
2	**3a**	*o*-NBA	THF	48	60	39
3	**3a**	*o*-NBA	CCl_4	3	59	53
4	**3a**	D-CSA	CCl_4	59	62	31
5	**3a**	L-CSA	CCl_4	59	65	24
6	**3a**	PTS	CCl_4	39	91	14
7	**3a**	CF_3CO_2H	CCl_4	5	55	38
8	**3a**	AcOH	CCl_4	21	67	48
9	**3a**	NBLP	CCl_4	15	52	62
10	**3a**	NBDP	CCl_4	6	55	43
11	**3b**	NBLP	CCl_4	4	41	75
12[e]	**3b**	**NBLP**	**CCl_4**	**32**	**84**	**77**

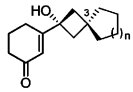
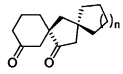
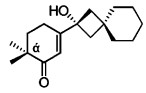
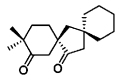
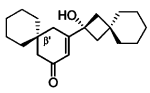
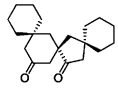
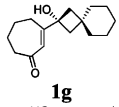
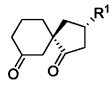
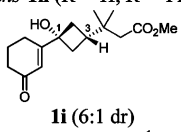
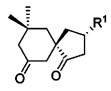
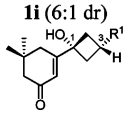
[a] All reactions were performed with 0.1 mmol of **1a**, 0.02 mmol of catalyst, and 0.04 mmol of acid in 2 mL of solvent at 40 °C. [b] Abbreviations: *o*-NBA, 2-nitrobenzoic acid; CSA, camphor-10-sulfonic acid; NBLP, *N*-Boc-L-phenylglycine; NBDP = *N*-Boc-D-phenylglycine; PTS = *p*-Toluenesulfonic acid. [c] Isolated yield. [d] Determined by chiral HPLC. [e] With addition of 4 Å molecular sieves.

to the combination of **3a** and CF_3CO_2H in THF at 40 °C, and the spirocyclic diketone **2a** was obtained in good yield but with a low ee of 34% (entry 1). By variation of the solvents and acids (entries 2−10), it was found that the combination of *N*-Boc-L-phenylglycine (NBLP) as the acid[9a] and CCl_4 as the solvent could increase the reaction enantioselectivity to 62% ee (entry 9). Gratifyingly, when further optimizations were conducted with multifunctional cinchona-derived catalyst **3b**[9b] (entries 11 and 12), the enantiocontrol of this vinylogous α-ketol rearrangement was ultimately improved to 77% ee in the presence of 4 Å molecular sieves (entry 12).

With the optimal conditions established above, the scope and generality of this reaction were then investigated with various cyclic hydroxy enones (**1b**−**k**) bearing a substituted cyclobutanol motif. From Table 2, it can be seen that all-carbon quaternary stereogenic

10.1021/ja906291n CCC: $40.75

Table 2. Enantioselective Vinylogous α-Ketol Rearrangement Catalyzed by the **3b**/NBLP Catalyst System[a]

Entry	Substrate[b]	Product[c]	*t* (h)	Yield (%)[d]	ee (%)[e]
1	**1a** 	**2a** 	32	84	77
2	**1b** (n=1)	**2b**	36	76	86
3	**1c** (n=2)	**2c**	22	66	92
4	**1d** (n=3)	**2d**	57	87	93
5	**1e** 	**2e** 	190	57 (99)[f]	82
6	**1f** 	**2f** 	36	95	88
7	**1g** 	**2g** 	24	83	87
8	*cis*-**1h**/*trans*-**1h** (7:1 dr)	**2h**	48	80 (17:1)[g]	91[i,j]
9	*cis*-**1h** (R^1 = Ph, R^2 = H)	**2h**	24	92 (29:1)[g]	97[i,k]
10	*trans*-**1h** (R^1 = H, R^2 = Ph)	**2h**	17	80 (2.3:1)[g]	48[i,l]
11	**1i** (6:1 dr) 	**2i** 	21	87 (8:1)[h]	94[i]
12	**1j** (R^1 = Ph, 25:1 dr) 	**2j**	41	80 (17:1)[h]	97[i]
13	**1k** (R^1 = 4-BrC_6H_4, 7:1 dr)	**2k**	65	80 (26:1)[h]	96[i]

[a] For experimental details, see the Supporting Information. [b] For entries 11−13, the major cis isomer is described. [c] For entries 8−13, the absolute configuration of major diastereoisomer is given. [d] Isolated yield. [e] Determined by chiral HPLC. [f] The yield in parentheses was based on the recovered starting material. [g] The dr value in parentheses was determined by chiral HPLC. [h] The dr value in parentheses was determined by ^{1}H NMR. [i] The ee value of the major isomer. [j] 57% ee for the minor isomer. [k] 41% ee for the minor isomer. [l] 77% ee for the minor isomer.

centers in spirocycles could be effectively constructed by this semipinacol-type 1,2-carbon migration in the enantioselective vinylogous α-ketol rearrangement, and a wide range of spirocyclic 1,4-diketones **2b**−**k** were obtained with good to excellent enantioselectivities (82−97% ee) in moderate to high yields (57−95% yield). Compared with the model substrate **1a** (entry 1), hydroxy enones disubstituted at the C3 position of the cyclobutanol moiety (**1b**−**d**, entries 2−4) underwent the molecular rearrangement with increased asymmetric induction. When substrates disubstituted at the α′ and β′ positions of the cyclohexenone moiety (**1e** and **1f**, respectively, entries 5 and 6) were used, slightly decreased enantiocontrol was observed, and α′-substitution caused a dramatic decrease in the reactivity of this rearrangement reaction (entry 5). One substrate with a cycloheptenone motif instead of the cyclohexenone unit (**1g**, entry 7) was also explored and certainly showed good ee and yield. In addition, some C3-monosubstituted examples (**1h**−**k**, entries 8 and 11−13), in which cis-1,1,3-trisubstituted cyclobutanes were the major or predominant components of the starting material, were examined in this catalytic system. Interestingly, highly enantioselective rearrangement reactions were carried out with 91−97% ee and 80−87% yield (entries 8 and 11−13), and good diastereoselectivities (8:1 to 26:1 dr) in the products were also demonstrated. Notably, control experiments with decreased catalyst loading (**1j**) and enlarged reaction scale (*cis*/*trans*-**1h**)[10a] indicated little influence on the stereoselectivity and yields, but some effect on the reactivity was found in the former case. To further clarify the influence of the diastereomeric ratio of the reactants on the reaction diastereo- and enantioselectivity, *cis*-**1h** (entry 9) and *trans*-**1h** (entry 10) were independently subjected to the current standard conditions. Interestingly, improved and decreased stereoselectivity, respectively, for the major isomer product were observed. This fact clearly demonstrates that the cis isomer is the matched substrate for the diastereo- and enantioselectivity of this asymmetric vinylogous α-ketol rearrangement under the current organocatalysis, while the trans isomer is the unmatched one. It should be noted that the absolute configuration of the product **2k** was unambiguously assigned by X-ray crystallography.[10b]

In conclusion, an unprecedented organocatalytic enantioselective vinylogous α-ketol rearrangement reaction via a semipinacol-type 1,2-carbon migration was discovered for the first time, and chiral all-carbon quaternary stereocenters in spirocyclic diketones were constructed with good to excellent enantiocontrol. Our current methodology for the asymmetric synthesis of quaternary stereogenic centers constitutes an alternative strategy to classical semipinacol rearrangement. Further studies of the detailed mechanism and synthetic applications are under investigation.

Acknowledgment. We gratefully acknowledge financial support from the NSFC (20621091, 20672048, and 20732002) and the Chang Jiang Scholars Program.

Supporting Information Available: Experimental details, compound characterization, and X-ray crystallographic data (CIF) for **1j** and **2k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA906291N