ORGANIC LETTERS

2012
Vol. 14, No. 24
6178–6181

Hydrolytic Enantioselective Protonation of Cyclic Dienyl Esters and a β-Diketone with Chiral Phase-Transfer Catalysts

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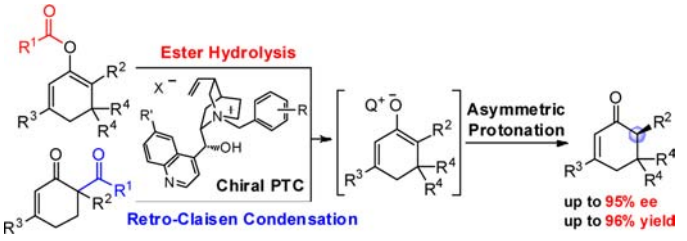
Received October 20, 2012

ABSTRACT



Hydrolytic enantioselective protonation of dienyl esters and a β-diketone catalyzed by phase-transfer catalysts are described. The latter reaction is the first example of an enantio-convergent retro-Claisen condensation. Corresponding various optically active α,β-unsaturated ketones having tertiary chiral centers adjacent to carbonyl groups were obtained in good to excellent yields and enantiomeric ratios (83−99%, up to 97.5:2.5 er).

Asymmetric ester hydrolysis is one of the most important biocatalytic reactions.[1] In general, enzymes have been employed for asymmetric ester hydrolysis because of their high enantioselectivity under mild conditions.[1] Although the reactions have several drawbacks such as high cost and low stability of enzymes,[2] no practical asymmetric ester hydrolysis with an artificial catalyst has been achieved so far.

In this context, we recently reported the first hydrolytic enantioselective protonation (EP) of cyclic alkenyl esters catalyzed by phase-transfer catalysts (PTC).[3] In this study, we attempted to apply our catalytic system to the enantioselective synthesis of cyclic α,β-unsaturated enones containing tertiary chiral centers adjacent to carbonyl groups as a further application.

Optically active α,β-unsaturated enones are ubiquitous units of various natural products.[4] In particular, enantioenriched 6-tertiary chiral cyclohexenones are considered as useful synthetic intermediates since they can be transformed to 4-tertiary chiral enones, which have often been

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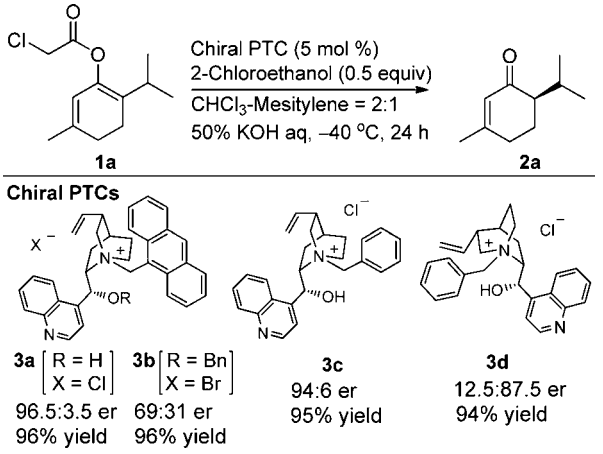
10.1021/ol3027363
Published on Web 12/03/2012

Scheme 1. Catalyst Screening[a,b]

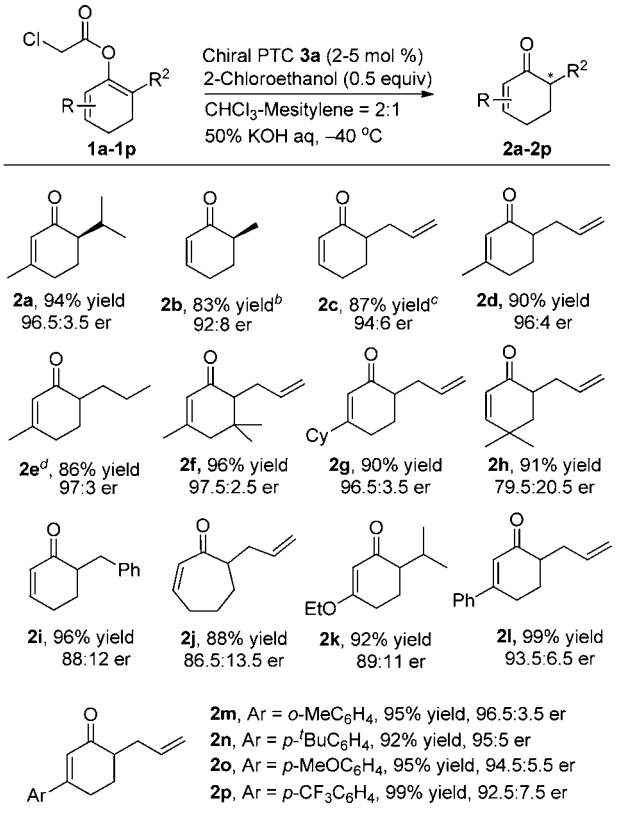


[a] A screw cap vial was charged with Chiral PTC (5 mol %), $CHCl_3$-mesitylene (2:l, 400 μL), 2-chloroethanol (0.5 equiv), and 50% KOH aq (100 μL). The mixture was cooled to −40 °C, dienyl ester (0.1 mmol) was added, and the mixture was stirred for 24 h. [b] GC yield.

used for the synthesis of biologically active compounds.[5] In addition, other transformations are also available.[6−9] However, conventional approaches are limited to stoichiometric reactions[5a−d,f,h−k,10] and catalytic reactions that lack generality.[5e,11,12] Therefore, asymmetric synthesis of the enones is regarded as an important subject.

EP is one of the potent reactions for the preparation of the enones. To date, several distinct catalytic EP reactions have been developed.[12−16] However, only a few examples were applied to the synthesis of the enones with limited scopes.[12] Herein, we report a highly enantioselective, general catalytic method for the synthesis of the cyclic enones bearing tertiary chiral centers neighboring to carbonyl groups by asymmetric hydrolytic protonation of dienyl

Scheme 2. Scope of Dienyl Esters: Phase-Transfer Catalytic Hydrolytic Enantioselective Protonation[a]



[a] A screw cap vial was charged with **3a** (2 mol %), $CHCl_3$-mesitylene (2 1, 400, μL), 2-chloroethanol (0.5 equiv), and 50% KOH aq (100 μL). The mixture was cooled to −40 °C, dienyl ester (0.1 mmol) was added, and the mixture was stirred for 24 h. Full conversion of substrates was confirmed by TLC before the reactions were quenched. Isolated yields are shown unless otherwise noted. [b] GC yield. [c] 5 mol % of catalyst was used. [d] 2.5 mmol scale.

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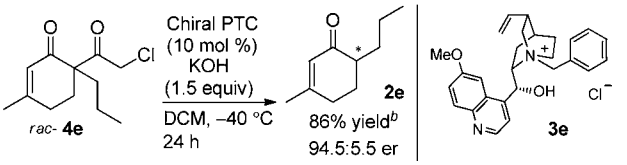
Scheme 3. Enantio-convergent Retro-Claisen Reaction of a Racemic β-Diketone[a,b]



[a] A screw cap vial was charged with chiral PTC (0.01 mmol), CH_2Cl_2 (200 μL), and KOH (solid, 1.5 equiv). The mixture was cooled to −40 °C, β-diketone (0.1 mmol) was added, and the mixture was stirred for 24 h. [b] Isolated yield.

esters and a racemic β-diketone. In addition, the preliminary mechanistic studies including DFT calculation suggested a possibility that the EP step of this reaction proceed regardless of water.

First, we examined the reaction of dienyl ester **1a**, and the reaction gave the product in high yields and enantioselectivities (Scheme 1). PTC **3a** showed the highest enantioselectivity as well as the reaction of enol esters, which we previously reported.[3] Next, we screened the substrate scope. Dienyl esters having different aliphatic groups at the C2-position underwent the hydrolysis in high yields and good to high enantioselectivities (Scheme 2). In addition, results of the substrates **1b** and **1c** indicated that modest bulkiness at the C2-position of dienyl esters was necessary for effective asymmetric induction. The reactions with 3- and/or 5-alkylated dienyl esters also proceeded without loss of enantioselectivities (**1a**, **1d**−**g**). However, the substrates bearing a 4,4-dimethyl, 2-benzyl, or seven-membered ring backbone gave the products in lower enantiomeric ratios (er) (**1h**−**j**). The substrate **1k**, which has 5-ethoxy group, afforded the product in lower er compared with 5-methyl substrate **1a**. δ-Arylated substrates provided the products in good to high enantioselectivities (**1l**−**p**). Electron-deficient or -rich aryl substituents on the δ-position of the substrates were also tolerant. In considering further applications of this catalytic system, we came up with an application to the asymmetric

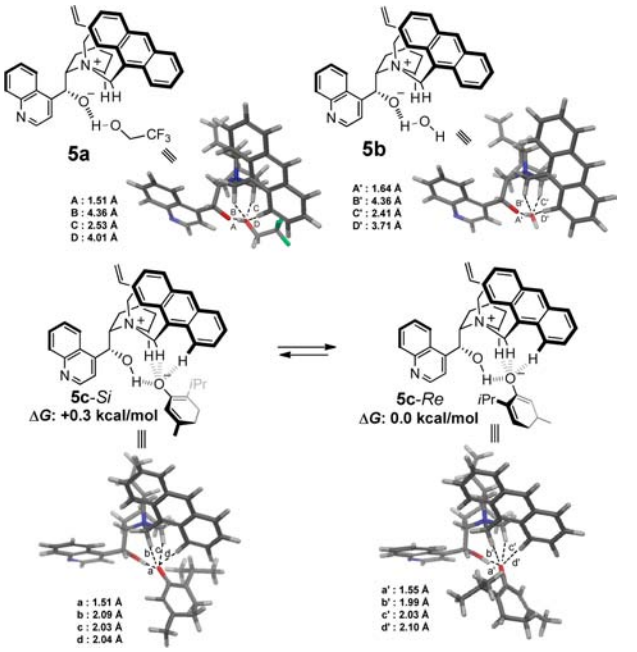


Figure 1. Calculated structures of the ammonium 2,2,2-trifluoroethoxide (**5a**), hydroxide (**5b**), and enolates (**5c**-*Si*, **5c**-*Re*) at the MPWB1K/6-31G* level of theory.

retro-Claisen condensation of racemic β-diketones because the reaction proceeds via the same ammonium enolate intermediate. Recently, the transformations accompanying C−C bond cleavage have drawn much attention due to the direct construction of new skeletons.[17] Additionally, to the best of our knowledge, asymmetric retro-Claisen condensation with artificial catalysts has not been reported.[18] Therefore, we performed the investigation of stereoablative enantio-convergent protonation of a racemic β-diketone via retro-Claisen condensation.

First, we applied the reaction condition of the hydrolytic protonation of dienyl esters to the reaction, which resulted in low selectivities. Further investigation proved the solid−liquid biphasic condition was more suitable for the reaction. Additional screening of the solvents, reaction temperatures, and catalysts were performed (see the Supporting Information). The best result was obtained when the reaction with solid KOH and the catalyst **3e** was performed in CH_2Cl_2 at −40 °C (Scheme 3, 94.5:5.5 er). With reference to the reaction mechanism, we previously reported an NOE experiment of *N*-(9-anthracenylmethyl)cinchonidinium 2,2,2-trifluoroethoxide. In this case, only one signal of the interionic NOE was observed between the methylene protons of the anion and the proton of quinoline ring, which is located near the 9-hydroxy group. In order to obtain

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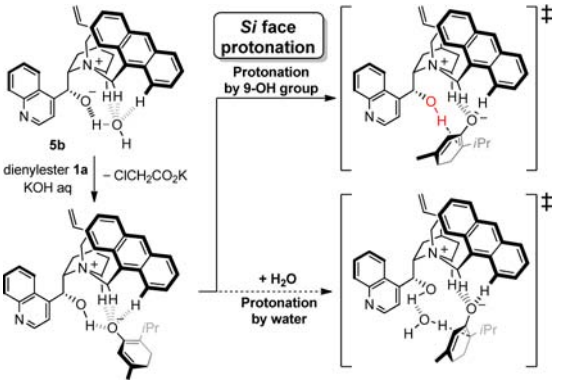
further mechanistic insights, we carried out a DFT optimization of *N*-(9-anthracenylmethyl)cinchonidinium salts, and the optimized structures are shown in Figure 1.[19] In regard to the important features of the calculated structures **5c** in Figure 1, hydrogen-bonding interactions between three C−H groups of the ammonium cation including C−H bonds of anthracenyl moiety and the oxygen atom of the enolate were observed on the basis of their C−H···O bond lengths.[20] As for the structure of the ammonium salt **5a**, the proton of 9-OH group of the ammonium cation was abstracted by 2,2,2-trifluoroethoxide. This result indicated that 9-hydroxy group was more acidic than 2,2,2-trifluoroethanol of which pK_a is 12.4 in water.[21] In addition, the proton of the 9-OH group of the ammonium hydroxide **5b** was also abstracted by hydroxide anion. In contrast to the ammonium salts **5a** and **5b**, deprotonation of the 9-OH group of ammonium dienolates (**5c**-*Si* and **5c**-*Re*), which are subjected to the following EP, was not observed. Given the pK_a of cyclohexenol (pK_a = 11.7 in water)[22] as a representative of cyclic enol derivatives, the results of DFT optimization of ammonium salts suggested that the acidic nature of the 9-OH group reinforced the stability of the ammonium dienolate from nonselective protonation pathways by reducing the electron density of the carbon atom of the dienolate. In addition, there was little energetic difference between **5c**-*Si* and **5c**-*Re*, which directed the *Si* and *Re* faces of the enolate toward the outside, respectively. These results indicated that the role of the ammonium cation in the enantioselective protonation step is not preferentially protecting one enantioface from nonselective protonation, although extra evidence is necessary for supporting this speculation because the energetic differences may be enhanced in the corresponding transition states of the external protonation. In order to support the above hypothesis, the reaction with the stoichiometric ammonium alkoxide **5a** in the presence of a small amount of water was carried out to give the product in 72% yield and 93.5:6.5 er (the water content in the reaction mixture is 17 mol %; see the Supporting Information). These results suggested that bulk water as an external proton source is not necessary and support the above hypothesis, although there is a possibility that a small amount of water has an effect on the yield and er; additional evidence is required to prove this hypothesis. One possible mechanism of enantioselective step is a protonation from an acidic 9-hydroxy group or water after the dissociation of the hydrogen bond between the 9-hydroxy group and the enolate (Scheme 4). Further mechanistic studies will be presented in an upcoming paper.

Scheme 4. Proposed Mechanism of Enantioselective Protonation of the Ammonium Dienolate



In summary, we report a highly enantioselective, catalytic hydrolytic protonation of dienyl esters via phase-transfer catalytic base hydrolysis. We also present an unprecedented enantio-convergent hydrolytic protonation of a racemic β-diketone. These reactions provide rapid access to the 6-tertiary chiral cyclohexenones.

Acknowledgment. We thank Prof. T. Katsuki and Prof. T. Uchida, Kyushu University, for the use of the Karl Fischer titrator. The present work is supported by the Grant-in-Aid for Global-COE program, "Science for Future Molecular Systems", Challenging Exploratory Research (No. 23655087), and Scientific Research on Innovative Areas, Organocatalysts (No. 24105524), from the Ministry of Education, Culture, Science, Sports and Technology of Japan.

Supporting Information Available. Experimental procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(19) The candidates of the ground-state structures shown in Figure 1 were generated with the MacroModel program.[23] The initial structure for the conformational search was inferred from the NOE experimental data[3] (see the Supporting Information). The candidate structures are fully optimized at the MPWB1K/6-31G* level of calculation, which was developed for the calculation of weak interactions.[24]

(20) Similar interactions were previously observed in the mechanistic studies of phase-transfer catalytic reactions. See: (a) Gomez-Bengoa, E.; Linden, A.; López, R.; Múgica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955. (b) Cannizaro, C. E.; Houk, K. N. *J. Am. Chem. Soc.* **2002**, *124*, 7163.

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