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Enantioselective Cationic Polyene Cyclization vs Enantioselective Intramolecular Carbonyl−Ene Reaction

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Abstract: This paper describes highly efficient catalytic enantioselective cationic polyene cyclization and catalytic enantioselective intramolecular carbonyl−ene reaction in good to high yields with high enantioselectivities. The intimate relationship and mechanistic differences between the two enantioselective reactions were studied in detail. In addition, the cyclization products are versatile and useful building blocks for natural products and pharmaceuticals syntheses.

Both cationic polyene cyclization[1] and intramolecular carbonyl−ene reaction[2] are powerful methods for construction of cyclic and polycyclic carbocycles and heterocycles. Recently, Ishihara, MacMillan, and Jacobsen and their co-workers have elegantly demonstrated enantioselective polyene cyclization reactions catalyzed by organocatalysts.[3] On the other hand, despite the pioneering work on metal-catalyzed enantioselective polyene cyclizations by the groups of Yamamoto, Yang, Corey, and Gagné,[4] catalytic versions with high enantioselectivity are still few, as are catalytic *intramolecular* carbonyl−ene reactions.[5] In addition, the intimate relationship and mechanistic differences between the intramolecular cationic polyene cyclization reaction and the carbonyl−ene reaction, as depicted in eq 1, are not well studied.[6] Continuing our ongoing interest in enantioselective polyene cyclization,[7] in this paper we present our findings on the interplay between the two reactions of 1,5-keto−olefin substrates (eq 1), which are prone to cyclize via either polyene cyclization[8] or a carbonyl−ene pathway.[6] Both cationic polyene cyclization products and carbonyl−ene cyclization products could be obtained selectively in good yields and with high enantioselectivities.

(1)

Our study began with promoting cyclization of keto−olefin **1** using various conditions (Table 1; see Supporting Information for condition screening). The best conditions found to effectively catalyze the enantioselective cyclization of **1** used 0.20 equiv of $Sc(OTf)_3$[2,9] and 0.20 equiv of Pybox ligand **A**[2,9] with $(CH_2Cl)_2$ as solvent. A single isomer of 6-*exo* carbonyl−ene cyclization product **2** was obtained in 87% yield and with 95% ee. In addition, **2** was readily converted to polyene cyclization product **3** in 85% yield without significantly loss of enantiomeric purity (Table 1, entry 1) with the aid of 4.0 equiv of $TiCl_4$. Similar results were also obtained with analogous substrates **1a**−**c** (entries 2−4). In all cases, good yields and high enantioselectivities were achieved for both carbonyl−ene products and polyene cyclization products.

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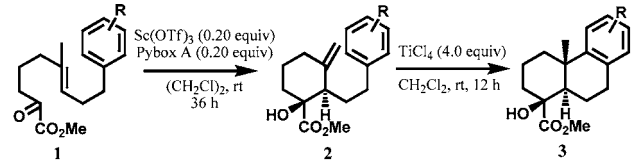
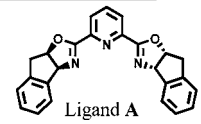
Table 1. Enantioselective Carbonyl−Ene Reaction of 1,5-Keto−Olefin and Cyclization of Ene Product to Polycyclic Adduct[a]



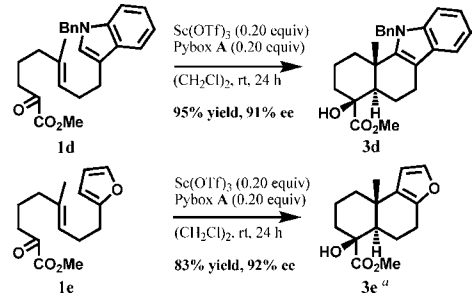
Entry	R	Substrate	2 Yield[b,c] (%)	2 Ee[d] (%)	3 Yield[b,c] (%)	3 Ee[d] (%)
1	2-OMe	**1**	87	95	85	93
2	4-OMe	**1a**	81	92	75	86
3	——	**1b**	60	93	90	88
4	**4**-Cl	**1c**	83	91	53[e]	87



Ligand **A**

[a] Standard procedure: $Sc(OTf)_3$ (0.02 mmol), ligand **A** (0.02 mmol), MS 4 Å (0.15 g), and $(CH_2Cl)_2$ (2 mL) were stirred at room temperature for 2 h prior to addition of substrate (0.1 mmol in 1 mL of $ClCH_2CH_2Cl$). The reaction was stirred for 36 h before workup. [b] A single isomer was isolated. [c] Isolated yields. [d] Values of ee were determined by chiral HPLC analyses (Supporting Information). [e] TfOH used instead of $TiCl_4$.

Scheme 1



[a] Ene cyclization product was obtained in 12% yield, 90% ee.

On the other hand, under the optimized reaction conditions, polyene cyclization products instead of ene products were obtained when cyclization substrates bore terminators such as furan and indole rings (Scheme 1, **3d**, 95% yield, 91% ee; **3e**, 83% yield, 92% ee). Mechanistically, the polyene cyclization prevailed over the ene cyclization because furan and indole heterocyclic rings are more nucleophilic than the phenol ether ring in **1** and **1a**.[10] By the

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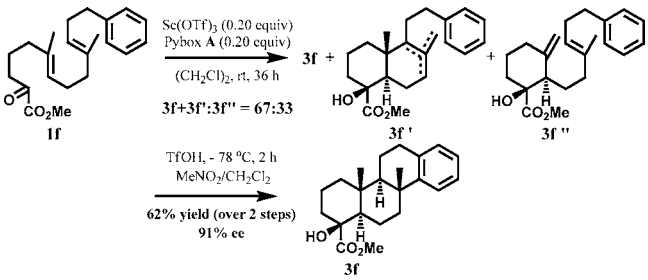
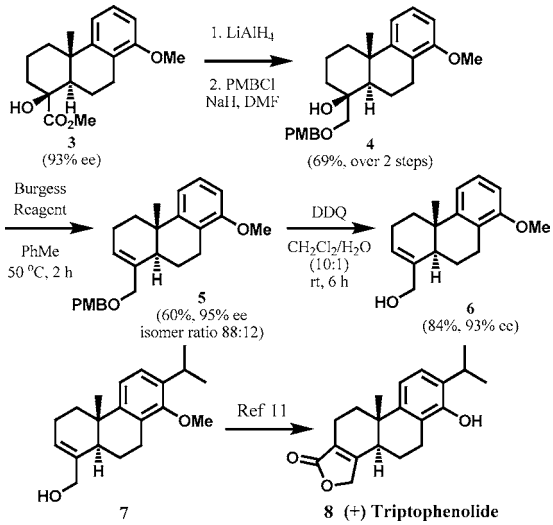
Scheme 2



same token, polyene cyclization products were also isolated when the terminator was a trisubstituted olefin[7b] (Scheme 2, **1f**), although the product was a mixture of isomers (Supporting Information). For ease of synthesis and analysis, the cyclization product mixture of **1f** was subjected to TfOH[7b] to facilitate complete tetracycle formation. The tetracyclic product **3f** was obtained in 62% yield and with 91% ee over two steps.

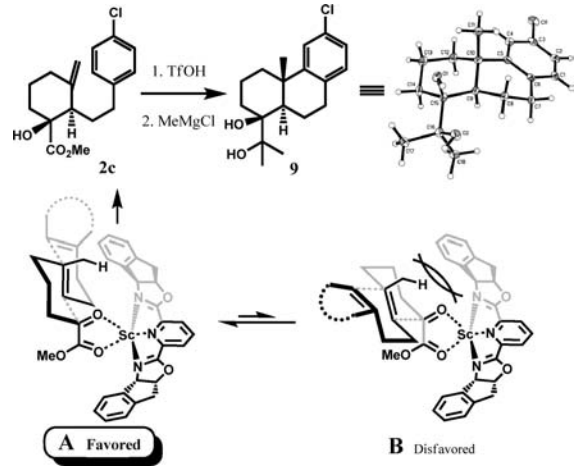
This enantioselective cyclization protocol provides an efficient access to diverse, highly enantiomeric polycyclic terpenoids. To demonstrate the powerful capability of this method, the cyclization product **3** was transformed to allylic alcohol **6** in 35% yield and with 93% ee over four steps (Scheme 3). Alcohol **6** shares the tricyclic core of **7**, which is the key intermediate of van Tamelen's total synthesis of (±)-triptophenolide **8**.[11] We believe that this approach will provide a rapid and enantioselective synthesis of (+)-triptophenolide **8**.

Scheme 3. Synthesis of Tricyclic Core of (+)-Triptophenolide



The absolute stereochemistries of the cyclization product **3** and one derivative **9** were determined via X-ray analyses (Scheme 4 and Supporting Information). On the basis of the observed stereochemistries of the cyclized adducts and the previous reported chiral induction of Pybox−Lewis acid catalysts,[2e−j,12] we propose the following mechanism to rationalize the origin of enantioselectivity (Scheme 4). The $Sc(OTf)_3$−Pybox catalyst is believed to chelate the carbonyl oxygen atoms of the α-keto−ester moiety to form a catalyst−substrate binding complex. The keto−olefin substrate adopts a chair−chair conformation[6,13] with the ester group occupying a pseudoequatorial position to lower the transition-state energy.[7a] Carbonyl−ene reaction favors transition state **A**, affording **2c**.[6] Transition state **B** is disfavored because of the steric repulsion between the phenyl moiety of the catalyst and the alkyl chain of the substrates. For the same reason, cationic polyene cyclization also favors transition state **A** and undergoes cascade bicylization or tricyclization, affording fused polycyclic rings of **3d**−**f**, showing *trans* or *trans-anti-trans*[13] conformation (Schemes 1 and 2).

Scheme 4. Determination of Absolute Stereochemistry of Cyclization Products and Proposed Mechanism



In conclusion, we have demonstrated that both catalytic enantioselective cationic polyene cyclization and catalytic intramolecular carbonyl−ene reaction were achieved in good to high yields and with high enantioselectivities by tuning the substrates or using forcing reaction conditions. To the best of our knowledge, this is the first time that an α-keto−ester was demonstrated to initiate enantioselective cationic polyene cyclization catalyzed by a Lewis acid. The cyclization products are versatile and useful building blocks for natural terpenoids and pharmaceuticals[14] syntheses. Efforts focusing on the total synthesis of (+)-triptophenolide are currently in progress and will be reported in due course.

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Supporting Information Available: Additional experimental procedures, spectral data for reactions products, and two CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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