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# Challenge toward Structural Complexity Using Asymmetric Catalysis: Target-Oriented Development of Catalytic Enantioselective Diels–Alder Reaction

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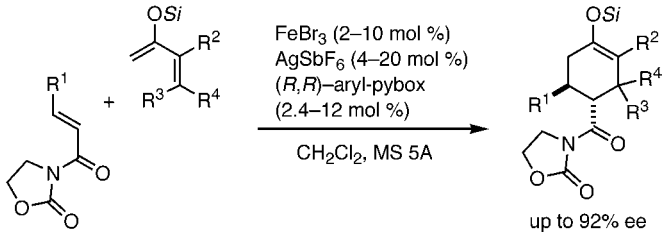
## ABSTRACT




**A new method for the catalytic enantioselective Diels–Alder reaction using polysubstituted silyl enol ethers as dienes is described. High enantioselectivity (up to 92% ee) was produced using a catalyst generated from $FeBr_3$ and $AgSbF_6$ in a 1:2 ratio and aryl-pybox (aryl = Ph or *p*-ethoxyphenyl). This reaction should facilitate the enantioselective synthesis of polycyclic acylphloroglucinols such as hyperforin or garsubellin A, which are currently of interest from synthetic and medicinal points of view.**

Polycyclic polyprenylated acylphloroglucinols have attracted recent attention from synthetic and medicinal points of view due to their structural complexity and interesting biological activities.[1] Among them, hyperforin (Figure 1, **1**)[2] is a mild antidepressant element of St. John's wort, and nemorosone (**2**) has strong cytotoxic activity against several cancer cell lines.[3] Another interesting compound is garsubellin A (**3**), which has neurotrophic activity through choline acetyltransferase (ChAT) induction.[4] Although many studies toward the synthesis of this group of compounds have been reported,[5] including ours,[6] there are no approaches using catalytic asymmetric reaction. This is presumably due to the difficulty

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(1) Recent review: Verotta, L. *Phytochem. Rev.* **2002**, *1*, 389−407.

(2) Gurevich, A. I.; Dobrynin, V. N.; Kolosov, M. N.; Popravko, S. A.; Ryabova, I. D.; Chernov, B. K.; Derbentseva, N. A.; Aizenman, B. E.; Garagulya, A. D. *Antibiotiki (Moscow)* **1971**, *16*, 510−513.

(3) Cuesta-Rubio, O.; Frontana-Uribe, B. A.; Ramirez-Apan, T.; Cardenas, J. *Z. Naturforsch.* **2002**, *57c*, 372−378 and reference cited therein.

(4) (a) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947−949. (b) Fukuyama, Y.; Minami, H.; Kuwayama, A. *Phytochemistry* **1998**, *49*, 853−857.

(5) (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Soc. Chem.* **1999**, *121*, 4724−4725. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q.; Kim, S.; Kessabi, J. *Org. Lett.* **1999**, *1*, 807−810. (c) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943. (d) Young, D. G. J.; Zeng, D. *J. Org. Chem.* **2002**, *67*, 3134−3147. (e) Kraus, G. A.; Nguyen, T. H.; Jeon, I. *Tetrahedron Lett.* **2003**, *44*, 659−661. (f) Krause, G. A.; Dneprovskaia, E.; Nguyen, T. H.; Jeon, I. *Tetrahedron* **2003**, *59*, 8975−8978. (g) Klein, A.; Miesch, M. *Tetrahedron Lett.* **2003**, *44*, 4483−4485. (h) Ciochina, R.; Grossman, R. B. *Org. Lett.* **2003**, *5*, 4619−4621. (i) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2004**, *45*, 1113−1116.

(6) (a) Usuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2002**, *4*, 859−862. (b) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621−3624.

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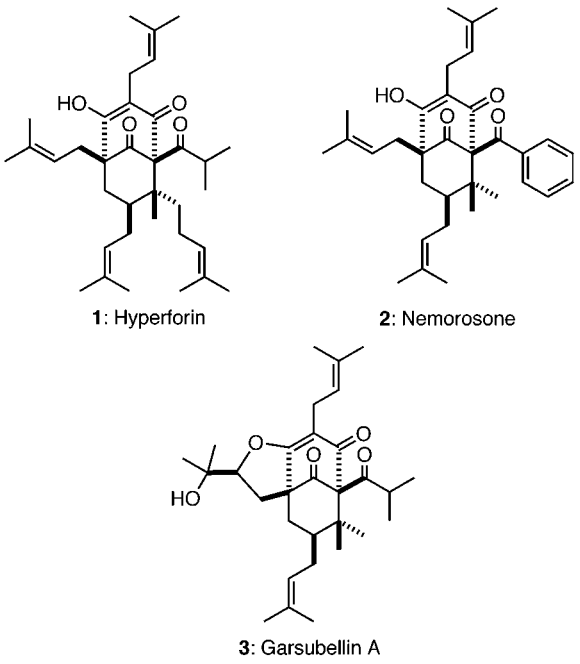
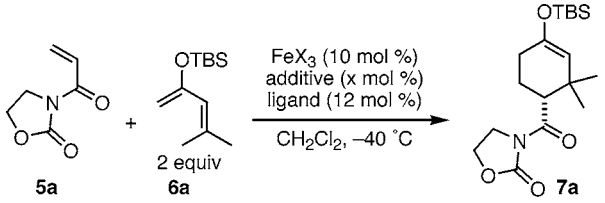



**Figure 1.** Examples of polycyclic acylphloroglucinols.

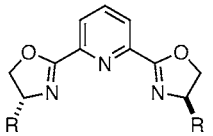
in constructing polysubstituted cyclohexanones in a stereoselective manner. Herein, we report a novel catalytic enantioselective intermolecular Diels−Alder reaction using polysubstituted dienes, which should facilitate the asymmetric synthesis of acylphloroglucinols.

On the basis of our previous synthetic studies of **3**,[6] we selected chiral cyclohexanones generally depicted as **7** (Table 2), which contain a quaternary carbon at the 3-position, as a key intermediate in the initial stage of synthesis. Although the catalytic enantioselective Diels−Alder reaction is a powerful synthetic methodology for constructing chiral six-membered rings,[7] simple dienes and/or dienophiles are normally used as substrates.[8] Thus, we first investigated the reaction between **5a** and **6a**, giving the product **7a**. Screening of chiral ligands and Lewis acid metals revealed that the combination of Ph-pybox[9] and cationic $Fe^{3+}$ salt[10] [$Fe(ClO_4)_3$] produced promising enantioselectivity (76% ee; Table 1, entry 1), although the chemical yield was moderate. On the other hand, other Lewis acid metals such as $Sc(OTf)_3$, $Cu(OTf)_2$, and $Zn(OTf)_2$ and cationic $Fe^{2+}$ salt gave much worse results.[11] $FeBr_3$−Ph-pybox did not promote the reaction even at room temperature.

**Table 1.** Optimization of the Reaction Conditions




| entry | $FeX_3$ | additive (x mol %) | ligand | time[a] (h) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | $Fe(ClO_4)_3$ | none | **4a** | 21 | 35 | 76 |
| 2 | $FeBr_3$ | $AgClO_4$ (30) | **4a** | 23 | 71 | 64 |
| 3 | $FeBr_3$ | $AgSbF_6$ (10) | **4a** | 16 | 36 | 82 |
| 4 | $FeBr_3$ | $AgSbF_6$ (20) | **4a** | 16 | 64 | 86 |
| 5 | $FeBr_3$ | $AgSbF_6$ (30) | **4a** | 16 | 42 | 80 |
| 6[d] | $FeBr_3$ | $AgSbF_6$ (4) | **4a** | 7 | 75 | 92[e] |
| 7 | $FeBr_3$ | $AgSbF_6$ (20) | **4b** | 16 | 12 | 22 |
| 8 | $FeBr_3$ | $AgSbF_6$ (20) | **4c** | 16 | 11 | 8 |



(*R*,*R*)-Ph-pybox (**4a**) : R = Ph
(*R*,*R*)-$^{i}$Pr-pybox (**4b**) : R = $^{i}$Pr
(*R*,*R*)-$^{t}$Bu-pybox (**4c**) : R = $^{t}$Bu

[a] Not optimized. [b] Isolated yield. [c] Enantiomeric excess (ee) was determined by chiral HPLC using chiral stationary phases. See Supporting Information for details. [d] Performed with 2 mol % $FeBr_3$ and 2.4 mol % (*R*,*R*)-Ph-pybox at −50 degrees. The reaction was performed at −50 °C. [e] Absolute configuration was determined to be *R*.

To improve the results, anhydrous cationic $Fe^{3+}$ complexes generated in situ in the presence of $Ag^+$ salts were studied (Table 1, entries 2−5) as catalysts.[12] High enantioselectivity (86% ee) was obtained when the catalyst was prepared from $FeBr_3$ and $AgSbF_6$ in a 1:2 ratio (Table 1, entry 4). Because similar results were obtained using the $Ag^+$ salt-free filtered catalyst solution, AgBr does not participate in the catalyst system. The phenyl group of the ligand is crucial for both catalyst activity and enantioselectivity; employing $^{i}$Pr-pybox (**4b**) or $^{t}$Bu-pybox (**4c**) as a chiral ligand gave the product with low yield and enantioselectivity (entries 7 and 8). These results might suggest the importance of the $\pi$-electronic interaction between the dienophile and the phenyl groups of the ligand.[13] Finally, product **7a** was obtained in 75% yield

(7) For recent reviews on catalytic asymmetric Diels−Alder reaction, see: (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667. (b) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg; Vol. III, pp 1178−1235. For a recent review on the Diels−Alder reaction in total synthesis, see: (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698.

(8) Examples of the catalytic asymmetric intermolecular Diels−Alder reaction with complex dienes: (a) Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611−3612. (b) Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120−14125. For intramolecular reactions, see: (c) Narasaka, K.; Saitou, M.; Iwasawa, N. *Tetrahedron: Asymmetry* **1991**, *2*, 1305. (d) Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786. An example of the catalytic diastereoselective Diels−Alder reaction that produces quaternary stereocenters on a cyclohexane structure: (e) Roush, W. R.; Barda, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 7402−7403. (f) Roush, W. R.; Limberakis, C.; Kunz, R. K.; Barda, D. A. *Org. Lett.* **2002**, *4*, 1543−1546 (asymmetric version using a stoichiometric amount of chiral auxiliary).

(9) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119−3154.

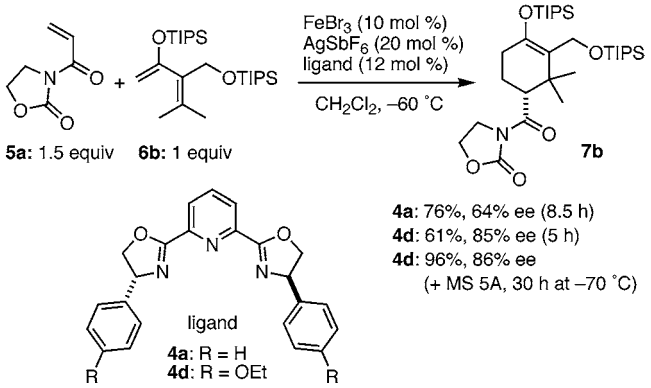
(10) Examples of catalytic asymmetric Diels−Alder reaction using a chiral iron complex: (a) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728−729. (b) Kündig, E. P.; Bourdin, B.; Bernardineli, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1856−1858.

(11) See Supporting Information for details.

(12) Commercially available $Fe(ClO_4)_3$ contains crystal constitutional water, which has adverse effects on the reaction.

(13) For a discussion of the importance of the $\pi-\pi$ interaction between an asymmetric catalyst and a substrate in the catalytic enantioselective Diels−Alder reaction, see ref 7a.

**Scheme 1.** Modification of Ph-Pybox Ligand

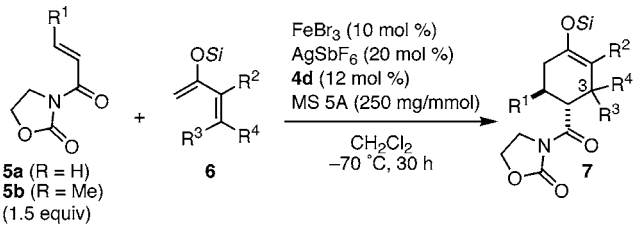


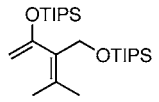
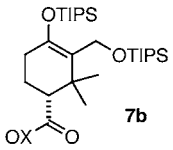
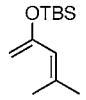
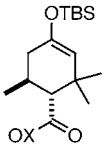
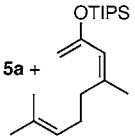
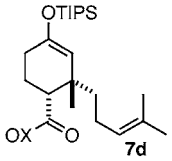
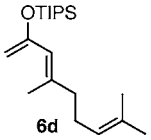
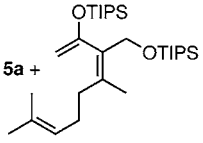
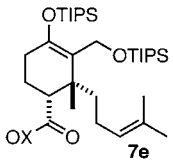
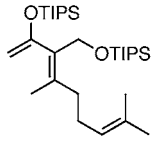
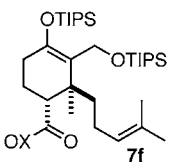

with 92% ee when the reaction was performed at −50 °C for 7 h in the presence of 2 mol % catalyst (entry 6).

Next, we investigated a more challenging reaction using tetrasubstituted diene **6b**, which might lead to the synthetic intermediate of **2** or **3**.[14] Using a catalyst prepared under the above optimized conditions, however, afforded product **7b** in only 64% ee (Scheme 1). To improve the results, we modified the Ph-pybox ligand. Specifically, we investigated the electronic effects of the pybox phenyl rings, on the basis of the finding that the phenyl groups were crucial for both reactivity and enantioselectivity.[13] Using the catalyst derived from ligand **4d**[15] possessing *p*-ethoxyphenyl groups, the enantiomeric excess increased to 85% ee. Finally, in the presence of 5 Å MS,[16] the reaction proceeded smoothly even at −70 °C to afford **7b** in 96% yield with 86% ee (Table 2, entry 1).[17]

The optimized reaction conditions were applied to other substrates that afford polysubstituted cyclohexanones (Table 2). High reactivity and enantioselectivity were produced even from 3-methyl acryloxazolidione (**5b**; entry 2), which is much less reactive than **5a**. Reaction characteristics differed depending on the geometry of the dienes when prenylmethyl-substituted dienes (**6c** and **6d**) were used (entries 3 and 4). From (*Z*)-diene **6c**, *exo* addition was the major reaction pathway (1:6), and the product **7d** was obtained with 80% ee (entry 3). From (*E*)-diene **6d**, *endo*/*exo* selectivity was only moderate (2.7:1); however, both diastereomers were obtained with high enantioselectivity (86 and 88% ee; entry 4). Furthermore, this reaction was applicable to more complex dienes **6e** and **6f**, which afford potential key intermediates for hyperforin (**1**) synthesis (entries 5 and 6). The reaction proceeded with excellent *exo* selectivity in both cases, presumably due to the existence of sterically bulky TIPS-oxymethyl groups in the dienes. Thus, chiral cyclohexanones containing contiguous tertiary and quaternary stereocenters with a functional group ($R^2$) for further manipulation were constructed with high enantio- and diastereoselectivity. This reaction was scalable and can be used in the initial stage of the total synthesis to introduce the first chirality into a molecule.

**Table 2.** Catalytic Enantioselective Diels−Alder Reaction[a]




| entry | substrates | product | yield (%)[b] (*endo* : *exo*)[c] | ee (%)[d] (*endo*, *exo*) |
|---|---|---|---|---|
| 1 | **5a** +  **6b** |  **7b** | 96 | 86 |
| 2 | **5b** +  **6a** |  **7c** | 96 | 85 |
| 3 | **5a** +  **6c** |  **7d** | 70 (1:6) | 41, 80 |
| 4 | **5a** +  **6d** | **7d** | 83 (2.7:1) | 86, 88 |
| 5 | **5a** +  **6e** |  **7e** | 61 (1: >33) | 76[e] |
| 6 | **5a** +  **6f** |  **7f** | 99 (1: >33) | 87[e] |

[a] For a representative procedure, see ref 17. The absolute configurations were temporarily assigned by analogy to **7a**. The relative configurations were determined on the basis of NMR analysis. [b] Isolated yield. [c] Determined by $^1$H NMR. [d] Determined by chiral HPLC after appropriate conversions. [e] Ee of *exo* product.

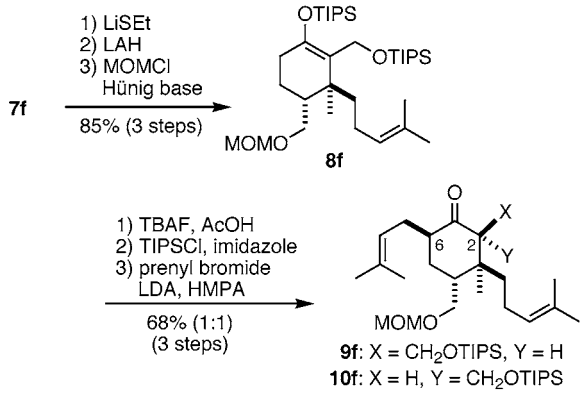
(14) **7a** could not be used as a synthetic intermediate for **2** or **3**. All attempts to introduce a side chain at the C-2 position failed due to the steric hindrance.

(15) Nesper, R.; Pregosin, P.; Püntener, K.; Worle, M.; Albinati, A. *J. Organomet. Chem.* **1996**, *507*, 85−101. There was no significant difference in reactivity or enantioselectivity between Ph-pybox (**4a**) and **4d** in the reaction of **5a** and a relatively simple diene **6a**: **7a** was obtained in 67% yield with 90% ee under the conditions shown in Table 2. For results using other Ar-pybox ligands, see Supporting Information.

(16) Use of 5 Å MS prevents undesired hydrolysis and polymerization of the diene.

(17) **General Procedure.** A suspension of ligand **4d** (55.0 mg, 0.12 mmol), $FeBr_3$ (29.6 mg, 0.10 mmol), $AgSbF_6$ (68.8 mg, 0.20 mmol), and 5 Å MS (250 mg) in $CH_2Cl_2$ (2.5 mL) was stirred at ambient temperature for 8 h in the dark before dienophile **5a** (212 mg, 1.5 mmol) in $CH_2Cl_2$ (17.5 mL) was added. After 15 min, diene **6f** (509 mg, 1.0 mmol) was added dropwise to the mixture at −70 °C to start the reaction. After 30 h, reaction was quenched by the addition of $Et_3N$ and water.

**Scheme 2.** Conversion of Diels−Alder Product




The synthetic utility of the catalytic enantioselective Diels−Alder reaction using structurally complex dienes was clearly demonstrated by the application to a short-step synthesis of initial stage key intermediates **9f** and **10f** for hyperforin (**1**) (Scheme 2). The oxazolidione moiety of **7f** was reduced via a thiol ester to the corresponding primary alcohol, which was protected with MOM group to afford **8f**. The enol silyl ether **8f** was converted to the ketone in the presence of TBAF/AcOH. In this step, partial (ca. 50%) cleavage of the TIPS ether also proceeded giving a mixture of the TIPS ether and the primary alcohol, which was reprotected by the treatment with TIPSCl. α-Prenylation of the cyclohexanone gave a separable diastereomixture of **9f** and **10f**. Both **9f** and **10f** can be utilized for further transformations, because the stereochemistry at C-2 and C-6 disappears in the formation of the bicyclic skeleton.[6]

In summary, we developed a catalytic enantioselective Diels−Alder reaction using a cationic $Fe^{3+}$−Ar-pybox complex as a catalyst. This reaction is the first catalytic enantioselective Diels−Alder reaction of acylic 4,4-disubstituted 1,3-dienes. It allowed for an efficient and rapid synthesis of chiral polysubstituted cyclohexanones, which is difficult to access using other methods. Based on this methodology, further studies toward the total synthesis of acylphloroglucinols are currently ongoing.

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

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