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Stereoselective Construction of Halogenated Quaternary Stereogenic Centers via Catalytic Asymmetric Diels−Alder Reaction

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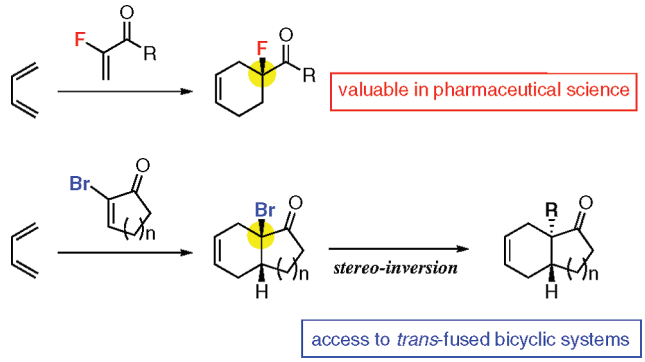
Stereoselective construction of halogenated chiral carbon centers is an important synthetic task because chiral fluorinated compounds are well-recognized as fascinating drug candidates[1] and chiral brominated compounds are useful synthetic intermediates for the synthesis of a range of optically active molecules. Asymmetric Diels−Alder reaction of halogenated olefins is an attractive approach for the stereoselective formation of halogenated quaternary stereogenic centers. However, to the best of our knowledge, only one report on the enantioselective Diels−Alder reaction of fluoroolefins has been published, and this reaction yielded fluorinated cycloadducts with up to 43% ee using a stoichiometric amount of a chiral titanium(IV) mediator;[2] however, significant efforts for this class of reaction without asymmetric induction have been made.[3,4] Additionally, in the case of bromoolefins, most of the successful enantioselective Diels−Alder reactions have been observed only when brominated enals are used as a dienophile.[5] Last year, Danishefsky reported an elegant method for the formation of trans-fused bicyclic systems by the radical isomerization of a cis-fused Diels−Alder adduct with a nitro function (the trans-DA paradigm).[6] We assumed that brominated bicyclic Diels−Alder adducts derived from α-bromo cyclic ketones could also be converted into trans-fused bicyclic systems by their reductive alkylation involving an inversion of the stereochemistry. In this paper, we describe the first highly enantioselective Diels−Alder reactions of α-halogenated α,β-unsaturated ketones; these reactions provide optically active cyclohexane derivatives with a halogenated quaternary stereogenic center (Scheme 1). Furthermore, a brominated cycloadduct was successfully converted to a trans-fused bicyclic system via reductive alkylation. This process is applicable to the asymmetric synthesis of natural steroid compounds.

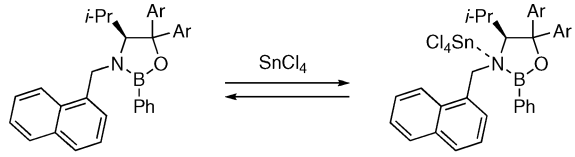
Our previous study revealed that Lewis acid-activated chiral oxazaborolidine (OXB) **1** acts as an efficient catalyst in the asymmetric Diels−Alder reaction (Scheme 2).[7] Initially, we examined the Diels−Alder reaction of 2-fluorohepten-1-en-3-one (**2**) with cyclopentadiene (**3a**) in the presence of 10 mol % **1a**. The reaction proceeded smoothly at −78 °C to yield product **4a** in 94% ee with good exo selectivity[8] (Scheme 3).[9] In contrast, the Diels−Alder reaction of ethyl vinyl ketone under the same conditions yielded a nonfluorinated product with high endo selectivity.[7a] This drastic difference in diastereoselectivity is in good agreement with the results of a previous study on titanium(IV)-mediated Diels−Alder reactions of α-fluoroenone.[2,3c]

We then used substituted cyclopentadienes as the diene. Recently, we demonstrated the highly regio- and enantioselective Diels−Alder reaction of 1- and 2-substituted cyclopentadienes (∼1:1 mixture)

Scheme 1. Stereoselective Construction of Halogenated Chiral Carbon Centers



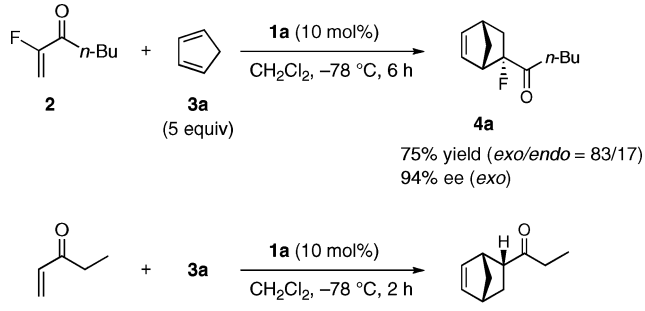
Scheme 2. Lewis Acid-Activated Chiral Oxazaborolidine (OXB)



Lewis acid activated OXB

1a: Ar = Ph
1b: Ar = 3,5-dimethoxyphenyl

Scheme 3. Enantioselective Diels−Alder Reactions Catalyzed by Lewis Acid-Activated Oxazaborolidine (OXB)



catalyzed by a Brønsted acid-activated chiral OXB.[10] Using this approach, we examined the Diels−Alder reaction of fluoroenone **2** and the functionalized monosubstituted cyclopentadienes **3b−d** catalyzed by **1a**. As Table 1 shows, all of the corresponding products were obtained in good yields with excellent diastereo- and enantioselectivity as single regioisomers (up to 94% ee; entries

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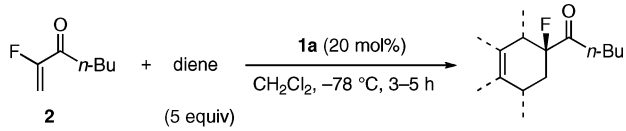
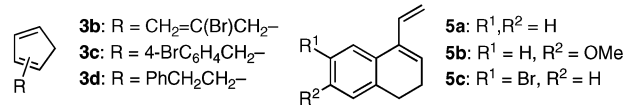
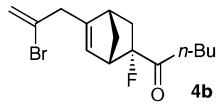
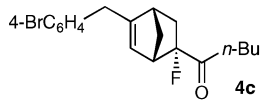
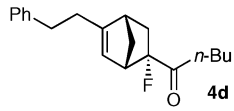
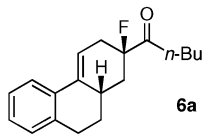
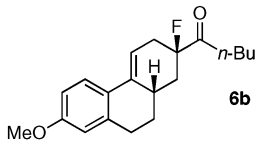
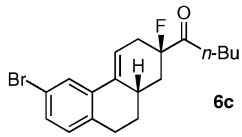
Table 1. Enantioselective Diels–Alder Reaction of α-Fluoroenone **2**[a]





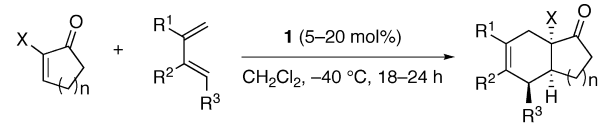
entry	diene	product	yield (%)[b]	*dr*	*ee* (%)[c]
1	**3b**	 **4b**	61	98/2	91
2	**3c**	 **4c**	83	95/5	94
3	**3d**	 **4d**	82	97/3	92
4[d]	**5a**	 **6a**	83	98/2	89
5[d]	**5b**	 **6b**	75	>99/1	94
6[d,e]	**5c**	 **6c**	85	>99/1	89

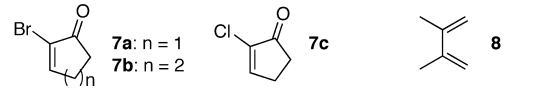
[a] See the Supporting Information for details. [b] Isolated yield. [c] Determined by chiral HPLC or GC analysis. [d] Reaction carried out with 30 mol % **1a**. [e] Both the relative and absolute stereochemistry were confirmed by X-ray crystallographic analysis of the corresponding oxime (see the Supporting Information for details).

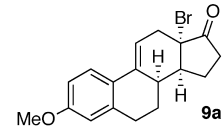
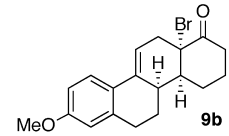
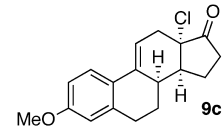
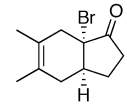
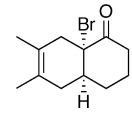
1–3).[9] These reactions showed exo selectivity similar to that of the reaction shown in Scheme 3. Subsequently, Dane's diene (**5b**) and its analogues **5a** and **5c** were also applied to the reaction with **2**. All of the reactions proceeded smoothly in the presence of 30 mol % catalyst, providing tricyclic products in high yields with excellent enantioselectivities as sole diastereoisomers (up to 94% ee; entries 4–6).[9] Thus, the present method enables the efficient synthesis of fluorocyclohexane derivatives having a fluorinated chiral quaternary stereogenic center with high optical purity.

Our next study focused on the enantioselective formation of halogenated bicyclic Diels–Alder adducts using 2-halocycloalken-1-ones.[11] To our delight, catalyst **1a** exhibited high reactivity toward this class of substrates (Table 2). The reaction of 2-bromocyclo-

Table 2. Asymmetric Diels–Alder Reaction of α-Halo Cyclic Enones[a]





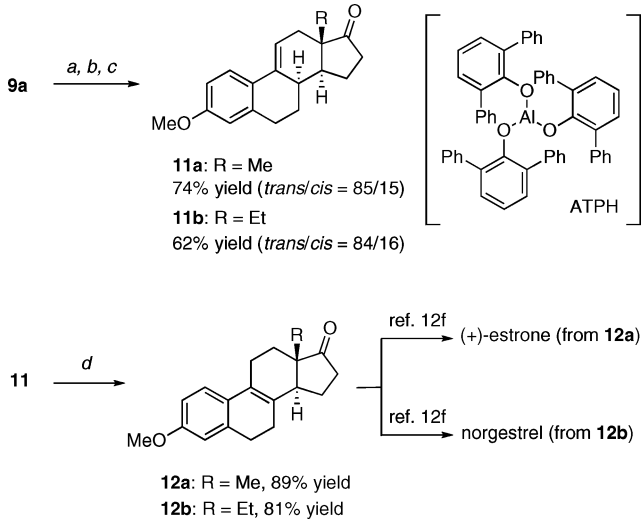
entry	enone	diene (equiv)	cat. (mol%)	product	yield[b] (%)	ee[c] (%)
1[d]	**7a**	**5b** (1.3)	**1a** (5)	 **9a**	73	94 (>99)[e]
2[d,f]	**7b**	**5b** (1.3)	**1a** (20)	 **9b**	56	95
3	**7c**	**5b** (1.3)	**1a** (5)	 **9c**	68	90
4	**7a**	**8** (15)	**1b** (20)	 **10a**	86	94
5	**7b**	**8** (15)	**1b** (20)	 **10b**	96	94

[a] See the Supporting Information for details. [b] Isolated yield. [c] Determined by chiral HPLC or GC analysis. [d] Both the relative and absolute stereochemistry were confirmed by X-ray crystallographic analysis. [e] After a single recrystallization. [f] Reaction was carried out at −78 °C.

penten-1-one (**7a**) with **5b** proceeded smoothly with high enantioselectivity in the presence of 5 mol % catalyst to provide a reasonable yield of the enantiomerically pure product **9a** after a single recrystallization (entry 1). The use of both 2-bromocyclohexen-1-one (**7b**) and 2-chlorocyclopenten-1-one (**7c**) also yielded the corresponding halogenated bicyclic adducts with excellent regio-, diastereo-, and enantioselectivities (entries 2 and 3). Catalyst **1b** with a 3,5-dimethoxyphenyl group was more reactive in the reaction with the simple and less reactive diene **8** while maintaining a high level of asymmetric induction (entries 4 and 5).

We then aimed to use the optically active brominated bicyclic adducts for asymmetric syntheses of estrone and norgestrel,[12] which have a trans-fused CD ring system, with the trans-selective reductive alkylation of **9a** as a key step. However, the general trend of diastereoselectivity in the alkylation of metal enolates favors undesired cis alkylation via 1,2-asymmetric induction.[13] We assumed that the use of the enolate species generated from the bulky aluminum reagent aluminum tris(2,6-diphenylphenoxide) (ATPH)[14]

Scheme 4. Formal Syntheses of Estrone and Norgestrel via Trans-Selective Reductive Alkylation of **9a**[a]



[a] Key: (a) ATPH (1.1 equiv), toluene, rt, 1 h; (b) MeLi (2.2 equiv), Et_2O, −78 °C, 15 min then 0 °C, 10 min; (c) R_3OBF_4 (3 equiv), 0 °C to rt, 24 h; (d) conc. HCl, CH_2Cl_2/MeOH, rt, 4 h

and a suitable reductant might reverse the substrate-controlled diastereoselectivity, leading to trans alkylation.

As shown in Scheme 4, the reductive alkylation was performed by precomplexation of 1.1 equiv of ATPH with **9a** and subsequent sequential treatment with 2.2 equiv of methyllithium and trimethyloxonium tetrafluoroborate. The corresponding methyl adduct was obtained in 74% yield with a trans/cis ratio of 85/15. In addition, the core structure of norgestrel was also synthesized using the same procedure with triethyloxonium tetrafluoroborate as the alkylating reagent. This reaction afforded a 63% yield of the ethyl adduct with a trans/cis ratio of 84/16. Pure trans adducts **11a** and **11b** were obtained after preparative HPLC. Finally, acid-mediated isomerization of the double bond afforded two key intermediates: **12a** leading to the formation of (+)-estrone by a known two-step sequence[12f] and **12b** leading to the formation of norgestrel by a known five-step sequence.[12f]

In conclusion, the first highly enantioselective Diels−Alder reactions of α-halo-α,β-unsaturated ketones with Lewis acid-activated chiral OXB as a catalyst have been demonstrated. The reaction of α-fluoroenones can be employed for the stereoselective construction of fluorinated quaternary stereogenic centers. In this study, a brominated cis-fused Diels−Alder adduct derived from an α-bromo cyclic enone was successfully converted to a trans-fused bicyclic system via reductive alkylation using the bulky aluminum reagent ATPH. With this process, remarkably short catalytic asymmetric syntheses of (+)-estrone and norgestrel have been realized.

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Note Added after ASAP Publication. A typographical error in the name of compound **7b** was corrected in the text on April 21, 2010.

Supporting Information Available: Experimental procedures, characterization of all new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Endo/exo nomenclature is related to the stereochemistry of the carbonyl substituent.
(9) We confirmed that the optical purities of cycloadducts **4a**, **4c**, and **6b** were not changed via chromatographic purifications on achiral silica gel or via evaporation of solvents. Therefore, we concluded that self-disproportionation of enantiomers is not involved in our purification process. For the enantiomer self-disproportionation effect of perfluorinated compounds, see: (a) Soloshonok, V. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 766. (b) Soloshonok, V. A.; Ueki, H.; Yasumoto, M.; Mekala, S.; Hirschi, J. S.; Singleton, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 12112.
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(13) We actually tried methylation of the lithium enolate generated from **9a** and lithium naphthalenide using methyl iodide. The reaction at −78 °C afforded predominantly the cis product (trans/cis = 3/97) in 56% yield.
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