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A Simple and Practical Synthesis of (+)-2-Bromobicyclo[2.2.1]hept-5-ene-2-carboxaldehyde via Chiral Lewis Acid Catalyzed [4+2] Cycloaddition

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A SIMPLE AND PRACTICAL SYNTHESIS OF (+)-2-BROMOBICYCLO[2.2.1]HEPT-5-ENE-2-CARBOXALDEHYDE VIA CHIRAL LEWIS ACID CATALYZED [4+2] CYCLOADDITION

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Abstract: A chiral titanium complex derived from BINOL and Ti(O-*i*-Pr)4 catalyzes the Diels-Alder reaction of 2-bromoacrolein and cyclopentadiene with 97:3 enantioselectivity. Lower enantioselectivity was observed using other dienes or with methacrolein as dienophile.

The Diels-Alder reaction is widely regarded as one of the most powerful synthetic processes available to the organic chemist due to its connective nature, the formation of the ubiquitous six-membered ring as product, high potential for the generation of stereogenic centers (up to six) from achiral reactants, and a manifold of opportunities for ring scission of the products to yield highly functionalized acyclic materials. The development of Lewis acid catalysis has greatly extended the scope of this reaction, permitting the use of more highly

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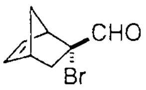
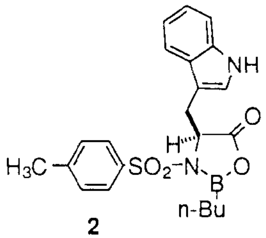
substituted and delicate reaction partners. In recent years, the development of asymmetric Lewis acid catalysis of the Diels-Alder reaction has been rapid and dramatic, and many catalysts have been reported which afford excellent enantioselectivity in both bimolecular and intramolecular examples.[1]

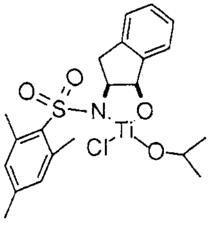
In addition to obvious utility in the construction of six-membered rings, the power of the Diels-Alder process in the synthesis of highly functionalized five-membered rings has been amply documented by the evolution of the Harvard bicycloheptane approach to prostaglandins.[2] In this context, Corey has explicitly noted[3b] the very diverse synthetic potential of bromo-aldehyde **1** and has reported two preparations of **1** using catalysts **2**[3] and **3**[4] below.



1



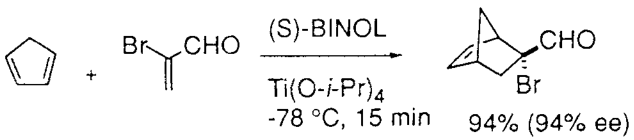
2



3

Use of 5 mol % of the borane **2** provided spectacular results, allowing the formation of **1** in 99% ee (95% yield); while the titanium based catalyst **3** gave 93% ee (94% yield) at the 10 mol % level.[5]

It occurred to us that the chiral Lewis acid catalysts recently employed by us for carbonyl allylation[6] might prove useful in this instance. Indeed, using the procedure detailed below, **1** could be prepared in 94 % ee, (94% yield) as shown in Eq 1 below.



(1)

Although the exo/endo selectivity (17:1) obtained was considerably lower than that realized using **2**, this is of little practical import since the small amount of endo isomer is trivially removed by stirring a solution of the crude product with aqueous silver nitrate as described by Corey.[4]

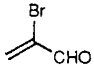
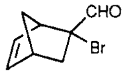
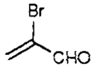
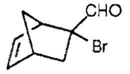
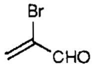
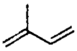
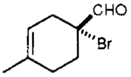
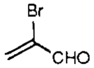
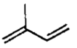
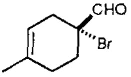
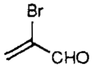
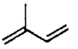
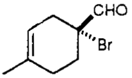
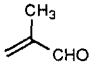
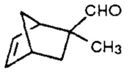
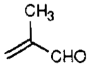
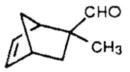
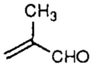
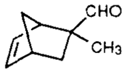
This very simple protocol using only commercially available reagents provides results essentially identical to those obtained with the more difficultly accessible catalyst **3**, but is clearly not competitive with those observed using catalyst **2**. However, the simplicity of the procedure may make it very useful in many circumstances.

A brief survey of other substrates indicated that the yield and enantiomeric excess obtained for **1** is probably not general. Results for other products obtained by the Diels-Alder process catalyzed precisely as described for **1** are given below. The highest yields and enantioselectivity were generally obtained using dichloromethane as solvent; however, in one case (entry 5), ether gave better results than dichloromethane.

We are continuing our studies of Diels-Alder reactions catalyzed as described herein in hopes of identifying those structural elements of diene and dienophile which give good results using this very simple protocol.

Representative Experimental Procedure. Preparation of 2-Bromobicyclo[2.2.1]hept-5-ene-2-carboxaldehyde. A mixture of (S)-(-)-1,1'-bi-2-naphthol (85.8 mg, 0.30 mmol), 1M Ti(O-i-Pr)$_4$ in CH_2Cl_2 (0.30 mL, 0.30 mmol), and oven dried powdered 4Å molecular sieves (1.2 g) in CH_2Cl_2 (10 mL) was heated at reflux for 1 h. The red brown mixture was cooled to -78 °C and 2-bromoacrolein (0.40 g, 0.24 mL, 3.0 mmol) was added followed by cyclopentadiene (0.99 g, 1.0 mL, 15.0 mmol). The mixture was stirred for 15 min at -78 °C and then quenched with saturated aqueous $NaHCO_3$ solution. The

Table I

Entry[a]	a,b-Enal	Diene	BINOL:Ti	T(t) °C	Product	% Yield[b] (exo : endo)[c]	% ee
1			1 : 1[d]	-78 (5 min)		94 (17 : 1)	94[e]
2			2 : 1[f]	-78 (5 min)		90 (40 : 1)	80
3			1 : 1	-20 (12 h)		75 (10 : 1)[g]	80[h]
4			2 : 1	-20 (12 h)		75 (10 : 1)[g]	80
5[i]			1 : 1	-20 (12 h)		90 (10 : 1)[g]	87
6			1 : 1	-20 (12 h)		75 (10 : 1)	58[j]
7			2 : 1	-78 (22 h)		81 (12:1)	56
8[k]			2 : 1	-78 (24 h)		70 (10 : 1)	50

[a] Unless otherwise noted, reactions were carried out in CH_2Cl_2 using 10 mol % of catalyst and 5 equivalent of diene per aldehyde. [b] All yields are isolated yields. [c] Exo/endo ratio or regioselectivity was determined using ^{1}H NMR. [d] Catalyst prepared from (S)-BINOL and Ti(O-i-Pr)$_4$ at 1:1 stoichiometry in presence of 4Å MS as given in the representative experimental procedure. [e] Enantiomeric purity was determined by reduction with $NaBH_4$, conversion to the Mosher MTPA ester, and ^{19}F NMR measurement. [f] Catalyst prepared from (R)-BINOL and Ti(O-i-Pr)$_4$ at 2:1 stoichiometry in CH_2Cl_2 solution at 23 °C for

(continued)

Table I Continued

1 h as previously described.[6b] [g] Ratio corresponds to regioselectivity. [h] Enantiomeric purity was determined by reduction with $NaBH_4$ and ^1H NMR measurement using the chiral shift reagent $Eu(hfc)_3$ in $CDCl_3$. [i] This entry was conducted using ether instead of CH_2Cl_2. [j] Enantiomeric purity was determined by ^1H NMR of the corresponding (-)-(2R,4R)-2,4-pentanediol acetal. [k] This entry was conducted using toluene instead of CH_2Cl_2.

mixture was stirred at ambient temperature for 1 h, then filtered using Celite. The organic layer was dried ($MgSO_4$), and the solvent was evaporated. Chromatography on silica gel (4:1 hexanes:ethyl acetate) afforded 0.567 g (94 %) of the adduct.[1d] The minor, *endo* CHO, diastereomer was removed using Corey's procedure. Thus a mixture of compound **1** (40.0 mg, 0.20 mmol), H_2O (1 mL), and $AgNO_3$ (1.0 mg, 0.007 mmol) was stirred at 23 °C for 2 h. The mixture was extracted with ether and the organic layer was dried ($MgSO_4$) and concentrated. Chromatography on silica gel (9:1; hexane:acetone) afforded 0.032 g (80%) of the *exo* isomer. The enantiomeric purity was determined to be 94% by reduction with $NaBH_4$, conversion to the Mosher MTPA ester, and ^{19}F NMR measurement.

The three known Diels-Alder adducts described herein were characterized by ^1H NMR spectroscopy, which were in excellent agreement with the literature data.[1d,5]

<u>2-Bromobicyclo[2.2.1]hept-5-ene-2-carboxaldehyde</u>: ^1H NMR ($CDCl_3$) δ 9.54 (s, 1H), 6.48 (dd, J=3.0, 5.6 Hz, 1H), 6.15 (dd, J=3.0, 5.6 Hz, 1H), 3.26 (br s, 1H), 2.98 (br s, 1H), 2.64 (dd, J=3.5, 13.4 Hz, 1H), 1.44-1.58 (m, 2H), 1.30 (d, J=9.0 Hz, 1H)

<u>1-Bromo-4-methyl-3-cyclohexene-1-carboxaldehyde</u>: ^1H NMR ($CDCl_3$) δ 9.38 (s, 1H), 5.29 - 5.34 (m, 1H), 2.76-2.81 (m, 1H), 2.54-2.60 (m, 1H), 2.10-2.29 (m, 4H), 1.67 (s, 3H).

2-Methylbicyclo [2.2.1] hept-5-ene-2-carboxaldehyde: ^{1}H NMR ($CDCl_3$) δ 9.64 (s,1H), 6.28 (dd, *J*=5.5, 3.0 Hz, 1H) 6.10 (dd, *J*=5.5, 3.0 Hz, 1H), 2.88 (br s, 1H), 2.80 (br s, 1H) , 2.22 (dd, *J*=11.5, 3.5 Hz, 1H) 1.39 (m, 2H), 1.00 (s, 3H) 0.75 (d, *J*=11.5 Hz ,1H) .

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