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Lewis Acid Catalyzed Inverse-Electron-Demand Diels−Alder Reaction of Tropones

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Tropone and related compounds in the troponoid family were initially well-known for having nonbenzenoid aromaticity.[1] Since the pioneering work of Tetsuo Nozoe in the 1930s,[2] interest on such a theoretical aspect has stimulated extensive studies of the synthesis, structure, and reactivity of troponoids,[3] which has continued until the present time. Some noteworthy examples in recent years include the following: the phosphoramidite−palladium complex catalyzed asymmetric [6+3] cycloaddition with trimethylenemethane and applications to welwitindolinone core synthesis by Trost, et al.;[4a,b] the phosphine catalyzed [6+3] cycloaddition with allylic compounds by Lu, et al.;[4c] the N-heterocyclic carbene catalyzed [8+3] cycloaddition with enals by Nair, et al.;[4d] the [8+2] cycloaddition with ketenes by Yamabe, Machiguchi, et al.;[4e] the construction of ingenane core through Lewis acid catalyzed/thermal intramolecular [6+4] cycloaddition by Rigby, et al.;[4f,g] the synthesis of CP-225,917 core through Lewis acid catalyzed intermolecular [6+4] cycloaddition by Gleason, et al.;[4h] and the [8+2] cycloaddition with 1,3-dipoles by Ishar, et al.[4i]
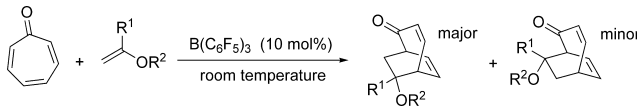
From the synthetic point of view, Diels−Alder reactions of tropone can provide direct access to bicyclo[3.2.2] ring structures, which could be further elaborated into more complex molecular architectures through selective manipulation of their pre-existing functional groups. Under thermal conditions, tropone, as a diene, participates in not only normal-Diels−Alder reactions with electron-deficient dienophiles[5] but also inverse-electron-demand Diels−Alder reactions with electron-rich dienophiles.[6,7] However, neither the Lewis acid catalyzed nor asymmetric version has been studied.

As a continuation of our interest in developing Lewis acid catalyzed reactions, especially their asymmetric versions,[8] we initiated the current investigation of the tropone Diels−Alder reaction, which could constitute a rare example of all-carbon based catalytic enantioselective inverse-electron-demand Diels−Alder reactions. To the best of our knowledge, the only previous case on such a scenario was the study on 2-pyrone Diels−Alder chemistry by Markó, et al. and Posner, et al.[9]

We began the trials with tris(pentafluoro)phenylborane[10,11] to catalyze this Diels−Alder reaction between tropone and ethyl vinyl ether. Gratifyingly, desired [4+2] adducts were obtained as a mixture of regio- and diastereoisomers under ambient temperature and pressure, while the previous report[6a] required high temperature and ultrahigh pressure in the absence of a Lewis acid catalyst. The scope of this reaction was briefly explored as shown in Table 1.

To improve the reaction's efficiency and selectivity, a screening of various typical achiral and chiral Lewis acid catalysts was undertaken for the reaction between tropone and ethyl vinyl ether. However, we soon realized that most of these catalysts were ineffective, with no conversion of tropone and significant decomposition of ethyl vinyl ether, perhaps through either cationic or coordinative polymerization. Thus, the important role of tris(pentafluoro)phenylborane as an active, yet mild Lewis acid catalyst is noteworthy.[11] Since ketene acetals are considerably more electron-
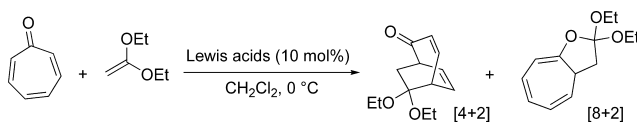
Table 1. B(C$_6$F$_5$)$_3$ Catalyzed Diels−Alder Reactions of Tropone[a]

entry	R^1	R^2	solvents	yield, %[b]	regioselectivity, (major/minor)[c]
1	H	Et	THF	76	7/1
2	H	Bn	THF	80	6/1
3	H	^{n}Bu	THF	78	12/1
4	H	^{t}Bu	Me-THF	39	8/1
5	Me	Bn	THF	27	4/1
6	Me	Me	neat	73	20/1

[a] See Supporting Information for details. [b] Isolated yield of all four regio- and diastereomers. [c] Estimated by crude ^{1}H NMR, the endo/exo ratio of the major regioisomers range from 1:1 to 5:1.

Table 2. Lewis Acid Catalyzed Cycloaddition Reactions between Tropone and Ketene Diethyl Acetal

entry	Lewis acid	[4+2]/[8+2][a]	entry	Lewis acid	[4+2]/[8+2][a]
1	B(C$_6$F$_5$)$_3$	>99:1	5	BPh$_3$	<1:99
2	Me$_3$Al	2:1	6	Me$_2$AlCl	<1:99
3	Et$_2$Zn	1:1	7	BF$_3$·OEt$_2$	<1:99
4	Ti(OiPr)$_4$	1:2	8	TiCl$_4$	<1:99

[a] Estimated by crude ^{1}H NMR, see Supporting Information for details.

rich than vinyl ethers, they could be more likely to participate in the inverse-electron-demand Diels−Alder reaction with tropone. Indeed, the reaction between ketene diethyl acetal and tropone catalyzed by tris(pentafluoro)phenylborane can proceed at 0 °C to give the Diels−Alder adduct (Table 2, entry 1); other Lewis acid catalysts can also promote this reaction, but to give the [4+2] adduct along with some [8+2] adduct (Table 2, entry 2−4) or to give [8+2] adduct only. Such divergence in the behavior of different Lewis acid catalysts is of great mechanistic interest to us; at this moment, however, we decided to leave that puzzle for future studies and focus on the development of the asymmetric Diels−Alder reaction of tropone, which we believe could lead to numerous applications for natural product syntheses.

After a number of failures using various chiral catalysts, a breakthrough for the asymmetric version came as we applied BINOL−aluminum type catalysts[12] to the cycloaddition between tropone and ketene diethyl acetal. The best results were obtained with the dinucleus BINOL−aluminum complex,[13] a Lewis acid assisted Lewis acid catalyst[14] prepared from the tris(m-xylyl)silyl substituted BINOL ligand and 2 equiv of diisobutylaluminum

Scheme 1. Dinucleus BINOL–Aluminum Complex Catalyzed Asymmetric Diels–Alder Reaction between Tropone Derivatives and Ketene Diethyl Acetal
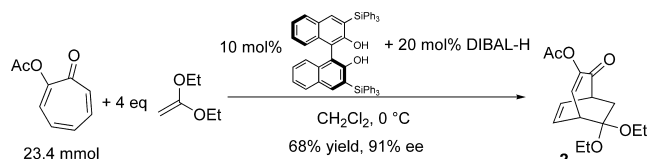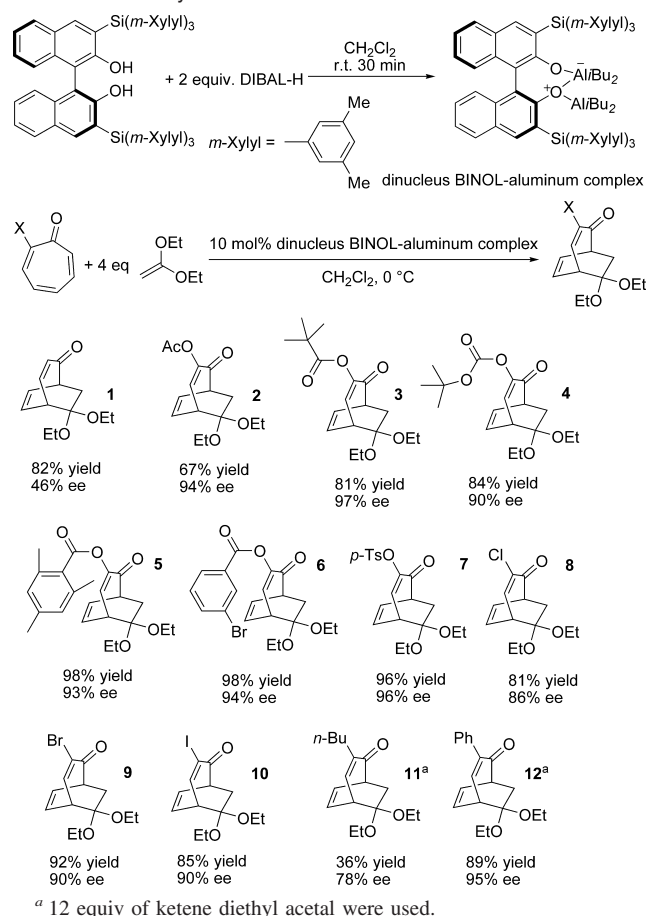

Figure 1. Gram-Scale Synthesis of Diels–Alder Adduct **2**

aluminum catalyst to give functionalized bicyclo[3.2.2] ring structures with high enantioselectivities. Since the starting materials and catalysts are all readily available, this reaction should be widely applicable for asymmetric synthesis of highly substituted chiral seven-membered rings. Future work is directed toward expanding the scope of this reaction and applications to natural product total synthesis.

Supporting Information Available: Experimental procedures, spectral and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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hydride at room temperature in dichloromethane, to give the Diels–Alder adducts exclusively without other types of cycloadducts.[15] Although only modest enantioselectivity (**1**, 46% ee) was obtained for tropone itself, substituted tropone derivatives generally gave excellent results: up to 97% ee was obtained as shown in Scheme 1. The acetate (**2**), pivalate (**3**), *tert*-butoxycarbonate (**4**), benzoates (**5** and **6**), and *p*-toluenesulfonate (**7**) substituted adducts were all obtained in over 90% ee's. Halogenated tropones were also suitable substrates for this reaction, giving adducts **8**, **9**, and **10** with good enantioselectivities. While *n*-butyl substituted adduct **11** was obtained in lower yield and ee, results of phenyl substituted adducts **12** were much better. To correlate the absolute configurations, iodide **10** was arylated under Suzuki coupling conditions[16] to give compound **12** in 88% yield without loss of optical purity. To demonstrate the synthetic utility of this methodology, we conducted a gram-scale reaction using the more easily available triphenylsilyl substituted BINOL ligand to deliver the Diels–Alder adduct **2** in 68% yield and 91% ee (Figure 1).

In summary, we have identified tris(pentafluoro)phenylborane as a good achiral Lewis acid for promoting tropone Diels–Alder reactions; second, we have developed an asymmetric version using chiral