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SHORT COMMUNICATION

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The Effect of Lewis Acids on the Cycloaddition of 3,3,6-Trimethylcyclohex-5-ene-1,2,4-trione: Hydrogen Transfer versus Cycloaddition with Cyclopentadiene

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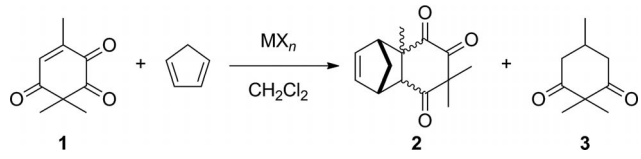
Exposure of 3,3,6-trimethylcyclohex-5-ene-1,2,4-trione to catalytic amounts of Lewis acids revealed two disparate reactions in the presence of cyclopentadiene. The expected cycloaddition was found to be reversible for the title compound, and transfer hydrogenation was the preferred pathway over long periods of time. Other tested substrates were able to undergo facile cycloaddition with considerable yields and without the parallel reduction.

Introduction

Cyclohex-5-ene-1,2,4-triones present an understudied class of molecules, which offer an interesting scaffold for diversity-oriented synthesis. Substituents on the cyclic ring, compatible with the use of Bobbitt's salt,[1] can lead to fundamental building blocks for further transformation. Theoretically, the alkene, ketone, and diketone moieties could be targeted through selective reactions to give a wide array of compounds, which would lead to further elaboration toward the synthesis of natural products or other biologically relevant targets. In a recent publication, we detailed a one-step reaction to generate these substrates and further showed their use in the Diels–Alder cycloaddition with cyclopentadiene to give adducts in good yields.[2] Addition of a methyl or phenyl substituent on the alkene moiety led to markedly diminished reactivity, which was overcome through the use of Lewis acid catalysis. The action of Lewis acids on cyclohex-5-ene-1,2,4-triones has been unexplored. Herein, we present the twofold reactivity of Lewis acids on 3,3,6-trimethylcyclohex-5-ene-1,2,4-trione (**1**), and this leads to both cycloadduct **2** and reduction to dione **3** (Scheme 1).

Lewis acid catalysis is a well regarded tool in organic chemistry. Although these species affect many reactions (e.g., Friedel–Crafts,[3] Nazarov,[4] Meerwein–Pondorf–Verley, and Oppenauer reactions[5]), the Diels–Alder cycloaddition[6] is the most widely recognized as benefitting from the addition of Lewis acids.[7] In a typical $[\pi_{4s}+\pi_{2s}]$ cycloaddition, the catalyst has been shown to lessen the energy difference between the diene HOMO and dienophile LUMO energies through complexation to Lewis basic sites in the dienophile.[8] Additionally, a higher selectivity for *endo* and *exo* diastereomers can also be achieved, especially at lower temperatures.[9] Ligating species also afford a secondary mode of tuning the reactivity profile.[10] Predominantly, this lies in the realm of chiral modifiers, which form a complex with the metal catalyst to provide an environment about the dienophile that allows for enrichment in enantiomers.[11]



Scheme 1. Reaction between **1** and cyclopentadiene catalyzed by Lewis acids.

Results and Discussion

En route to optimizing the diastereoselectivity of the reaction to **2**, we discovered that **1** was thermally unstable and decomposed to a complex mixture of products. This compelled the use of $TiCl_4$, which has been used previously as a catalyst, to diminish the cycloaddition energy barrier in preference to the side products. At room temperature, a good yield (63%) of **2** was found with a diastereomeric ratio (*dr*) of 2:1 (*endo*/*exo*). Yields diminished at lower temperatures, but the *endo*/*exo* ratio remained largely unchanged. Other Lewis acids were screened to determine the effect of the catalyst on the cycloaddition, and the results are presented in Table 1. All of the screened catalysts gave a near-equimolar distribution of *endo* and *exo* adducts, and the conversions ranged from 5 to 30%. The best conversions were found with $TiCl_4$, but $AlCl_3$ provided adequate conversion to use for optimization later. The highest diastereo-

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selectivity was found with $(NH_4)_2ZnCl_4$ (Table 1, entry 7), although the diminished conversions precluded its viability as a catalyst.

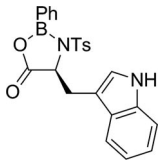
Table 1. Screen of Lewis acids for conversion and diastereoselectivity.[a]

Entry	Lewis acid	*T* [°C]	Conv.[b] [%]	*dr* (*endo*/*exo*)[c]
1	$TiCl_4$	22	100 (63[d])	2:1
2	$TiCl_4$	0	79 (25[d])	3:2
3	$TiCl_4$	–78	72 (21[d])	3:2
4	$AlCl_3$	22	30	1:1.6
5	$AlCl_3$	0	30	1:1
6	$AlCl_3$	–78	10	1:1
7	$(NH_4)_2ZnCl_4$	22	20	4.4:1
8	$Cu(acac)_2$	22	5	1:1
9	$BF_3{\cdot}OEt_2$	22	–[e]	–[e]
10	$BF_3{\cdot}OEt_2$	–78	25	2:1

[a] Reactions were performed with ene-triketone (0.05 mmol) and cyclopentadiene (3 equiv.) at the specified temperature for 1.5 h. acac = acetylacetonate. [b] Analyzed by HPLC with a MeOH/H_2O gradient (30 to 100% over 15 min, total run time = 30 min). [c] Determined by ^1H NMR spectroscopy and HPLC. [d] Isolated yield [%] from a 1 mmol-scale reaction. [e] Polymerized.

The reaction with aluminum chloride was performed at a higher scale (1 mmol), and upon isolation and characterization, **3** was found as the major product (22%), along with 59% recovery of the starting material. This paradoxical reaction piqued our interest, as the reversible reaction was largely unknown. We felt it necessary to assess the effect of the catalyst on both pathways. The results are presented in Table 2.

Table 2. Lewis acid screen for the reaction between **1** and cyclopentadiene.[a]

Entry	Lewis acid	% Yield[b]	**2**/**3**[c]
1	$TiCl_4$	63	3:1
2	$AlCl_3$	22	1:99
3	$AlCl_3$	63[d]	1:99
4		54 (1:3 *dr*, 4:1 *er*)	2:1
5	$InCl_3$	20 (1:2.5 *dr*)	1:9
6	$CeCl_3{\cdot}7H_2O$	8 (1:2 *dr*)	1:4
7	$RuCl_3$	10 (1:2 *dr*)	1:9
8	$ZnCl_2$	4 (1:3 *dr*)	1:6
9	$NiCl_2{\cdot}6H_2O$	34 (1:2 *dr*)	1:3
10	$PdCl_2$	40 (1:2 *dr*)	1:4
11	$ZrCl_4$	67 (1:3 *dr*)	1:1
12	camphorsulfonic acid	quant. (1:1 *dr*)	1:2
13	LiBr	44 (1:2 *dr*)	1:9
14	$MgCl_2$	51 (1:2.7 *dr*)	1:10
15	TMSCl	81 (1:3 *dr*)	1:2

[a] Reaction performed at 1 mmol scale with 20 mol-% catalyst and at 0.5 M in CH_2Cl_2 for 24 h at room temperature. [b] Combined yield. [c] Determined by ^1H NMR integrations. [d] 20 mol-% galvinoxyl added.

Across the Lewis acid series, yields and ratios between **2** and **3** were variable, and the yields ranged from 8% to quantitative. Low amounts of product were found with $InCl_3$ (Table 2, entry 5), $CeCl_3$ (Table 2, entry 6), $RuCl_3$ (Table 2, entry 7), and $ZnCl_2$ (Table 2, entry 8). It was further found that these specific catalysts gave predominately **3**. Increased yields were found for the remaining Lewis acids. The latter cases seemed to give roughly identical amounts of **2** and **3**, except for the cases of Li^+ and Mg^{2+}, which gave almost complete conversion to **3** in fair amounts. No discernible pattern is apparent from these results. Our goal of increasing the selectivity of the cycloaddition was realized through the use of an oxaborazolidinone (Table 2, entry 4; Ts = *para*-toluenesulfonyl), which gave **2** and **3** in a 2:1 ratio and the cycloadduct with good selectivity (1:3 *dr*, 4:1 *er*).[12]

The low yields and high proportion of the *exo* diastereomer found in **2** led us to believe the reaction was reversible under all of the catalysts studied. Titanium rapidly produced **2** in 1.5 h at room temperature. Longer exposure to $TiCl_4$ (16 h) showed that **3** formed as the major product. This confirmed that the reaction was reversible over longer time periods and that **3** was the preferred product. A pronounced concentration of *exo* found in all of the species could be attributed to the steric interference between the methylene and the C-6 methyl group, as presented by the Alder–Stein principle (Figure 1).[13]

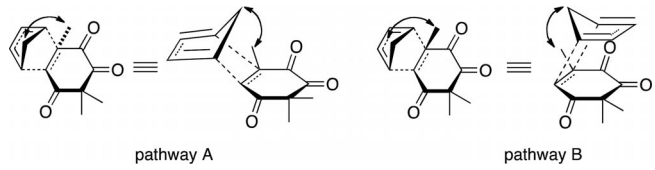


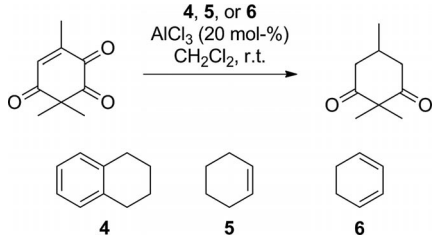
Figure 1. Transition states for *endo* and *exo* cycloadducts.

Understanding that the cycloaddition was reversible and led to the formation of the *exo* adduct, we turned our attention to the production of **3**. A source of hydrogen must be present in the system for **3** to be produced, which means that the solvent, catalyst, or cyclopentadiene must act in such a fashion to liberate hydrogen for the reduction, none of which were precedented to undergo this sort of reaction. It was found that under the same conditions as those for the cycloaddition (20 mol-% catalyst and 0.5 M solution), **3** was not produced over 24 h in the absence of cyclopentadiene. In the presence of cyclopentadiene, the reaction occurred rapidly. Isolated yields of **3** were identical to the yields obtained in Table 2. This strongly suggests that cyclopentadiene was acting as the source of hydrogen for this system. This is the first case of cyclopentadiene acting in such a manner.

As cyclopentadiene would be unable to act as a hydride source, we felt that a radical pathway may be involved in the formation of **3**. The addition of the radical scavenger galvinoxyl in a loading equivalent to that of the catalyst led to **3** in 63% yield (Table 2, entry 3). This increased the yield almost threefold and suggested that a radical was involved; however; it was most likely involved in a manner that prohibits the progress of the reaction. Further support through deuterium labeling of cyclopentadiene[14] found no deuter-

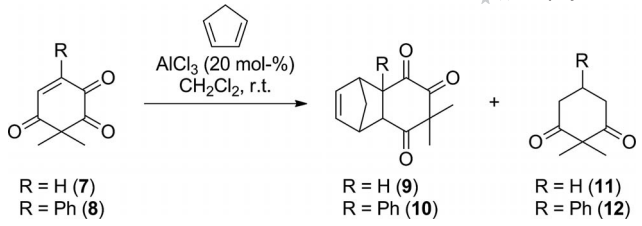
ium incorporation into **3**, although the high excess and low level of label could be reasons for this.

There was no directly comparable reaction present in the literature as noted here. The closest relative would be transfer hydrogenation, which, as the name suggests, is the transfer of hydrogen from one molecule to another.[15,16] Usually, Hantzsch's ester is used,[17] although tetralin (**4**), cyclohexene (**5**), 1,3-cyclohexadiene (**6**), and 1,4-cyclohexadiene have been shown to be able to undergo transfer hydrogenation.[16] In terms of selectivity, this type of reduction would target the alkene moiety, although the Meerwein–Pondorf–Verley (MPV) reduction selectively reduces carbonyl groups.[5] Under the conditions for MPV reduction, **3** was undetected. With this result, we explored the use of known transfer-hydrogenation agents to ascertain if they would give the same product under our conditions. This was found to be the case; **4** provided **3** in 33% yield, whereas **5** gave **3** in 29% yield, and **6** was found to give **3** in 48% yield (Scheme 2). No cycloadduct was found with **6**.



Scheme 2. Transfer hydrogenation of **2** to **3** with tetralin, cyclohexene, and cyclohexadiene.

Analogous systems were also exposed to the Lewis acid conditions to explore the generality of the reaction (Scheme 3). The reduction was solely noted with **1**. Alternative ene-triketones such as 3,3-dimethylcyclohex-5-ene-1,2,4-trione (**7**) and 3,3-dimethyl-6-phenylcyclohex-5-ene-1,2,4-trione (**8**) showed predominately the cycloadducts (i.e., **9** and **10**, respectively) with a diminished amount of their corresponding reduced products (i.e., **11** and **12**, respectively). Exposure of **7** to $AlCl_3$ led to the rapid formation of **9** over 30 min with no discernible formation of reduced product **11**. Over 24 h, **11** was formed in trace amounts. During this time period, no change in the diastereoselectivity was noticed for **9**. This suggests that adduct formation was irreversible, which contrasts the reversibility of **2**. Although a small amount of **12** was present, the Diels–Alder adduct was the major product if **8** was treated with cyclopentadiene. Presumably, the planarity of the phenyl ring allows for a more stable adduct and irreversible cycloaddition. In the absence of the catalyst, **8** will undergo cycloaddition at elevated temperatures (refluxing toluene); however, both **10** and **12** are present in an approximately equimolar distribution. The data support the conclusion that reduction is a thermodynamic preference that can be disfavored by irreversible adduct formation. The reversibility is most likely due to the steric hindrance between the *syn*-facial methyl group and the methylene unit of **2**.



Scheme 3. Reaction of hydrogen and phenyl-substituted ene-triketones and cyclopentadiene with aluminum chloride.

Conclusions

The action of Lewis acids on cyclohex-5-ene-1,2,4-triones and cyclopentadiene exhibits twofold reactivity. The simplest reactant, **7**, showed the expected irreversible formation of **9** without the formation of parent dione **11**. Substitution at C-6, that is, both **1** and **8**, showed disparate ratios of the cycloadducts, **2** and **10**, and diones, **3** and **12**. This can be attributed to two ideas: (1) steric interference between the substituent allows reversible cycloaddition; (2) a thermodynamically favored product. With the observed diastereoselectivities, the former idea seems justified. The latter idea stems from the degree of unsaturation contained in **1** and its congeners. Because of the quinone-like structure, it would be a simple matter of aromatization, if not for the quaternary carbon. We believe this disrupts the aromaticity, which leads to a "frustrated aromatic" compound. Under the catalytic conditions for cyclization, **1** undergoes reduction to the parent 1,3-dione, whereas **7** and **8** are able to condense with cyclopentadiene. The major reactivity difference between the three substrates is the fluxional nature of **2** versus **9** and **10**. The pathway leading to the diones, **3**, **11**, and **12**, is a convoluted problem that we have only begun to explore, and it is the first case of cyclopentadiene acting as a hydrogen source.

Experimental Section

General Procedure for Cycloaddition: A vial was charged with the Lewis acid (0.2 mmol), **1** (1 mmol), and CH_2Cl_2 (3 mL). Freshly distilled cyclopentadiene was added, and the solution was stirred at ambient temperature for 24 h. The solution was then separated by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford a mixture of **2** and **3**. HPLC traces and NMR integrations were used to determine molar ratios of the sample.

(4*S*)-4-(Methylindole)-*B*-phenyl-*N*-tosyl-1,2,3-oxaborazolidinone: The procedure of Corey was used with minor modification.[18] Tryptophan (10.54 g, 51.7 mmol) was dissolved in THF/H_2O (1:9, 150 mL), followed by the addition of Et_3N (18.0 mL, 129.1 mmol), and the resulting solution was cooled to 0 °C. *p*-Toluenesulfonyl chloride (10.905 g, 57.2 mmol) was added in a single portion. The mixture was allowed to stir for 1 h at 0 °C, and then warmed to room temperature and stirred for an additional 3 h. The solution was extracted with CH_2Cl_2 (3× 50 mL), dried with Na_2SO_4, and concentrated in vacuo. The material was sufficiently pure to carry forward. The residue was dissolved in toluene, and phenylboronic acid (6.15 g, 50.8 mmol) was added. The suspension was then heated at reflux through a Soxhlet extraction apparatus with CaH_2 for 6 h, and then concentrated under reduced pressure and redis-

solved in toluene (120 mL, 0.43 M theoretical). A small sample for analysis was separated by flash column chromatography on silica gel (1% MeOH/CH_2Cl_2) to afford the oxazoboralidinone as a white powder (m.p. 131–134 °C). R_f = 0.26 (1% MeOH/CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.8 (s, 1 H, indole NH), 8.13 (d, J = 8.44 Hz, 1 H, indole CH), 7.47 (d, J = 8.25 Hz, 2 H, aryl CH), 7.23–7.31 (m, 4 H, aryl CH), 7.17 (m, 3 H, aryl CH), 7.06 (m, 2 H, aryl CH), 6.92 (t, J = 7.87 Hz, 1 H, aryl CH), 3.89 (q, J = 6.99 Hz, 1 H, CH), 3.07 (m, 2 H, CH_2), 2.85 (dd, J = 14.49, 7.78 Hz, 1 H, CH), 2.31 (s, 3 H, Ar-CH_3), 2.29 (s, 3 H) ppm. ^{13}C (125 MHz, [D$_6$]DMSO): δ = 172.6 (C=O), 142.2 (C), 138.0 (C), 136.1 (C), 129.1 (CH), 128.9 (CH), 128.2 (CH), 126.9 (CH), 126.2 (C), 123.9 (CH), 120.8 (CH), 118.3 (CH), 117.8 (CH), 111.4 (CH), 108.8 (CH), 56.5 (CH), 28.3 (CH_2), 21.0 (CH_3) ppm. ^{11}B (160 MHz, [D$_6$]DMSO): δ = 20.0 ppm. HRMS (ESI+): calcd. for $C_{24}H_{22}BN_2O_4S$ [M + H]$^+$ 445.1393; found 445.1431. $[\alpha]_D$ = +16.3585 (c = 0.119, CH_2Cl_2).

Supporting Information (see footnote on the first page of this article): Spectra of the oxazoboralidinone catalyst.

Acknowledgments

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[1] J. M. Bobbitt, *J. Org. Chem.* **1998**, *63*, 9367–9374.
[2] N. A. Eddy, C. B. Kelly, M. A. Mercandante, N. E. Leadbeater, G. Fenteany, *Org. Lett.* **2012**, *14*, 498–501.
[3] N. O. Calloway, *Chem. Rev.* **1935**, *17*, 327–392.
[4] C. Santelli-Rouvier, M. Santelli, *Synthesis* **1983**, 429–442.
[5] T. Ooi, T. Miura, Y. Itagaki, H. Ichikawa, K. Maruoka, *Synthesis* **2002**, 279–291.
[6] O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1928**, *460*, 98–122.
[7] a) T. Inukai, T. Kojima, *J. Org. Chem.* **1967**, *32*, 869–871; b) T. Inukai, T. Kojima, *J. Org. Chem.* **1967**, *32*, 872–875; c) H. B. Kagan, O. Riant, *Chem. Rev.* **1992**, *92*, 1007–1019; d) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49–92; e) P. Yates, P. Eaton, *J. Am. Chem. Soc.* **1960**, *82*, 4436–4437.
[8] G. I. Fray, R. Robinson, *J. Am. Chem. Soc.* **1961**, *83*, 249.
[9] a) J. M. Coxon, R. D. J. Froese, B. Ganguly, A. P. Marchand, K. Morokuma, *Synlett* **1999**, 1681–1703; b) R. Gleiter, M. C. Bohm, *Pure Appl. Chem.* **1983**, *55*, 237–244.
[10] T. J. Davis, J. Balsells, P. J. Carroll, P. J. Walsh, *Org. Lett.* **2001**, *3*, 2161–2164.
[11] a) H.-U. Blaser, *Chem. Rev.* **1992**, *92*, 935–952; b) J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857–897; c) E. Corey, T. Shibata, T. Lee, *J. Am. Chem. Soc.* **2002**, *124*, 3808–3809; d) L. Dias, *J. Braz. Chem. Soc.* **1997**, *8*, 289–332.
[12] The adduct formed had $[\alpha]_D$ = –8.3667 (c = 0.2, CH_2Cl_2).
[13] K. Alder, G. Stein, *Angew. Chem.* **1937**, *50*, 510–519.
[14] B. A. Lyons, J. Pfeifer, T. H. Peterson, B. K. Carpenter, *J. Am. Chem. Soc.* **1993**, *115*, 2427–2437.
[15] a) T. Nishiguchi, K. Tachi, K. Fukuzumi, *J. Am. Chem. Soc.* **1972**, *94*, 8916–8917; b) G. Brieger, T. J. Nestrick, *Chem. Rev.* **1973**, *73*, 567–580; c) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *Angew. Chem.* **2004**, *116*, 6829–6832; *Angew. Chem. Int. Ed.* **2004**, *43*, 6660–6662; d) D. Xue, Y.-C. Chen, X. Cui, Q.-W. Wang, J. Zhu, J.-G. Deng, *J. Org. Chem.* **2005**, *70*, 3584–3591; e) C. Wang, X. Wu, J. Xiao, *Chem. Asian J.* **2008**, *3*, 1750–1770; f) K. Fujita, R. Yamaguchi, *Synlett* **2005**, 560–571; g) T. Naoto, H. Takaya, S. Murahasi, *Chem. Rev.* **1998**, *98*, 2599–2660; h) G. Zassinovich, G. Mestroni, S. Giadiali, *Chem. Rev.* **1992**, *92*, 1051–1069.
[16] a) A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, J. Meienhofer, *J. Org. Chem.* **1978**, *43*, 4194–4196; b) T. Nishiguchi, K. Tachi, K. Fukuzumi, *J. Org. Chem.* **1974**, *40*, 237–240.
[17] For reviews on the use of Hanztsch's ester in Synthesis see: a) S.-L. You, *Chem. Asian J.* **2007**, *2*, 820–827; b) S. G. Ouellet, A. M. Walji, D. W. C. MacMillan, *Acc. Chem. Res.* **2007**, *40*, 1327–1339.
[18] E. J. Corey, K. Ishihara, *Tetrahedron Lett.* **1992**, *33*, 6807–6810.

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