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A New Approach to Promoting Sluggish Diels−Alder Reactions: Dihapto-Coordination of the Diene

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Metals have played an important role in the development and refinement of Diels−Alder reactions.[1] From diverse parts of the periodic table, often in conjunction with chiral auxiliary ligands, they have been used to enhance both the rate and stereoselectivity of this venerable reaction of organic synthesis. While most methods involve the metal assuming the role of Lewis acid in the activation of the dienophile (Figure 1),[1−7] an alternative strategy is to activate the diene with a metal complex. Most commonly, this approach has been used in the context of inverse-electron-demand Diels−Alder reactions, but not universally so. For instance, seminal research by Welker et al. has shown that cobalt-substituted dienes show dramatically enhanced reactivity and stereoselectivity with conventional (i.e., electron-poor) dienophiles.[8] Herein we explore an alternative approach to promoting a classical Diels−Alder reaction in which the reactivity of the diene is enhanced by its coordination to a π-base (Figure 1). While disruption of the diene π-system may seem counterintuitive for promoting a Diels−Alder reaction, for a nonconcerted (i.e., ionic) mechanism,[9] the metal could facilitate the conjugate addition by stabilizing the allyl cation intermediate as shown in Figure 1.

We chose as our test case the reaction of ethyl vinyl ketone with cyclohexadiene, a reaction which is reported to have a 90% completion period of >100 000 h at 25 °C.[6]

The fragment {TpMo(NO)(MeIm)} (where Tp = hydridotris(pyrazolyl)borate and MeIm = 1-methylimidazole) was chosen as the π-base because of its exceptionally low reduction potential, which renders it a powerful π-base that can be easily air-oxidized to obtain the desired organic product.[10,11] Previously, we have shown that this system can form robust dihapto-coordinated complexes with conjugated dienes and that it resists conversion to the more pedestrian tetrahapto coordination.[12,13] Furthermore, {TpMo(NO)(MeIm)} has been shown to both protect the bound C=C bond and to activate the uncoordinated alkene toward protonation.[10] Preparation of TpMo(NO)(MeIm)(η^2-cyclohexadiene) **1** is achieved by reduction of TpMo(NO)(MeIm)Br (THF, sodium dispersion) in the presence of 1,3-cyclohexadiene. Two coordination diastereomers (**1A** and **1B)** are isolated in a kinetic ratio of 1.5:1, differing only by which face of the diene is coordinated by the metal.[11]

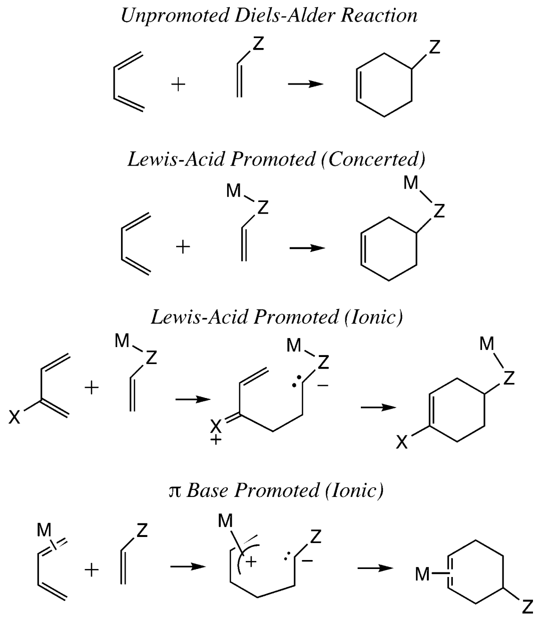
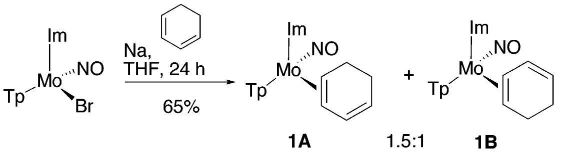


Figure 1. Metal-promoted Diels−Alder reactions.



(1)

When a solution of **1** is treated with ethyl vinyl ketone in CH$_2$Cl$_2$, no reaction occurs after 3 days (25 °C). However, when the experiment is repeated at −40 °C with the addition of 25 mol % of BF$_3$·OEt$_2$, a molybdenum-bound 1-bicyclo[2.2.2]oct-5-en-2-ylpropan-1-one complex **2** can be isolated (after basic workup) in 80% yield. Repeating the reaction in methanol at 25 °C also delivered the complex **2** in 60% yield, *without the aid of a Lewis acid*. For comparison, a similar solution of 1,3-cyclohexadiene and EVK, in CH$_2$Cl$_2$ with BF$_3$·OEt$_2$ at −40 °C or in methanol alone at 25 °C, failed to give any trace of cycloadduct over a similar time frame.

Key spectroscopic features for the bicyclooctene complex **2** include an anodic wave in a cyclic voltammogram of **2** at $E_{p,a} = -0.280$ V (NHE; 100 mV/s) and a ν(NO) of 1560 cm^{-1}, each indicative of a TpMo(MeIm)(NO)(alkene) complex.[10] In addition, the absence of any olefinic signals in the ^{1}H or ^{13}C NMR spectrum of **2** confirms that this species does not contain an uncoordinated alkene. 1-Methylimidizole signals at 3.77 and 3.76 ppm point to a mixture of two dominant diastereomers in a 1.5:1 ratio.[14] Exposure of a solution of **2** (prepared in situ from **1**) to air for 3 h affords 1-bicyclo[2.2.2]oct-5-en-2-ylpropan-1-one **3** in >95% yield from the metal complex after isolation via thin-layer chromatography (Scheme 1).[6] The bicyclooctene **3** can also be demetalated by treatment with AgOTf. The product is isolated as a 6:1 ratio of endo/exo isomers, and ^{1}H NMR data of **3** are consistent with those of previous reports.[6]

Other α,β-unsaturated ketones were screened for reactivity with the molybdenum-bound cyclohexadiene; methyl vinyl ketone, 3-penten-2-one, mesityl oxide, methacrolein, and methyl acrylate all gave products similar to that of ethyl vinyl ketone as shown in Table 1. The reactions were all carried out under two sets of conditions, methanol at 25 °C or CH$_2$Cl$_2$ at −40 °C with the addition of BF$_3$·OEt$_2$. Due to the reduced electrophilicity of an ester

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Scheme 1

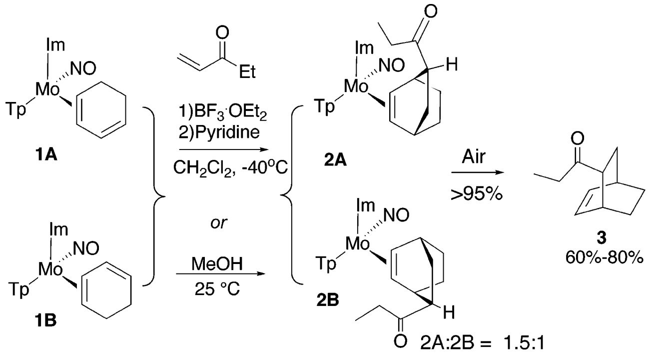
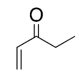
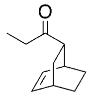
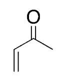
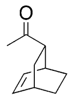
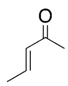
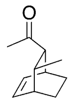
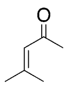
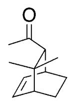
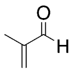
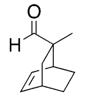
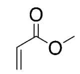
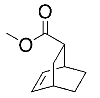


Table 1

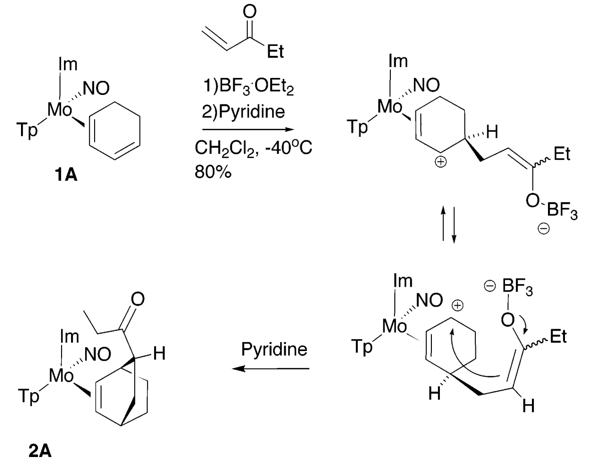
Dienophile	Product	#	Yield from **1**		$[O]^d$	endo:exo
			a	b		
		**3**[6]	80%	51%	Air	6:1
		**4**[6]	60%	64%	AgOTf	3:1
		**5**[7]	35%	nr	AgOTf	3:1[c]
		**6**	30%	nr	AgOTf	3:1
		**7**[6]	15%	68%	Air	6:1
		**8**[5]	17%	nr	AgOTf	6:1

[a] CH_2Cl_2 + 25 mol % $BF_3{\cdot}OEt_2$, −40 °C. [b] MeOH, 25 °C. Yields determined from proton NMR data using durene as an integration standard. [c] Methyl is trans to acetyl in both isomers. [d] Best results.

group (cf. aldehyde or ketone), methyl acrylate required several equivalents of $BF_3{\cdot}OEt_2$ and a longer reaction period for the starting material to be consumed. In methanol, 3-penten-2-one, mesityl oxide, and methyl acrylate failed to yield cycloadducts. Dimethyl fumarate, dimethyl maleate, and acrylamide were also tested, but failed to give the intended product for either set of reaction conditions. These results are outlined in Table 1.

In earlier work, we demonstrated that diene complex **1** can be protonated to form the allyl species $[TpMo(NO)(MeIm)(\eta^3\text{-}C_6H_9)]^+$, which has been spectroscopically and structurally characterized.[11] We hypothesize that the net [4 + 2] cycloaddition is proceeding through a conjugate addition to the unbound olefin to afford an "η^2" cyclohexadienium intermediate,[10] which subsequently isomerizes and closes to afford the six-membered ring according to Scheme 2. The TBS-promoted reaction of an η^2-naphthalene complex and acrylonitrile has been reported to operate by a similar reaction mechanism.[15]

Scheme 2



While there appear to be no other reports of η^2-diene complexes participating in [4 + 2] cycloaddition reactions, this concept is similar to an elegant methodology developed by Arrayas and Liebeskind, in which η^3-bound pyranyl and pyridinyl complexes of $TpMo(CO)_2$ undergo electrophile-led [4 + 2] and [5 + 3] cyclizations.[16]

In conclusion, a [4 + 2] cyclization between cyclohexadiene and various dienophiles is promoted by the η^2-coordination of the diene to a π-basic transition metal complex. While the present system may have its practical limitations, it demonstrates a novel approach to facilitating the Diels−Alder reaction without Lewis acids, microwave reactors,[5] or high pressures.[7] Efforts are currently underway in our group to use an α-pinene-resolved[17] form of **1** to access enantioenriched cycloadducts.

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Supporting Information Available: Full synthetic details for the preparation of cycloadducts **3**−**8** and characterization of compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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