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Hetero Diels−Alder Reactions Catalyzed by the Metallocenium Complex [Cp*$_2$Ce][BPh$_4$]

Gary A. Molander* and Robert M. Rzasa

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

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Introduction

Lewis acid promoted processes represent one of the most useful families of reactions available to synthetic chemists. As a testament to the importance of this class of transformations, literally hundreds of different promoters have been synthesized and utilized in diverse organic reactions. As a class, cationic metallocene complexes appear underrepresented in terms of their development as potentially useful Lewis acid catalysts. Reetz and co-workers were among the first to recognize the potential of this group of complexes in selective organic synthesis. In preliminary studies, his group described the use of a cationic iron complex to promote a Mukaiyama aldol reaction.[1] More recently, cationic zirconium complexes[2] have been employed to promote Diels−Alder reactions,[3] a cationic ruthenium complex has been developed as an asymmetric Diels−Alder catalyst,[4] and cationic palladium(II) and platinum(II) species have been employed in asymmetric hetero Diels−Alder processes.[5]

Cationic lanthanocenes[6] have been utilized in polymerization reactions and related processes,[6c,g] but they have not been employed as Lewis acid catalysts for the selective synthesis of small organic molecules. This class of Lewis acids possesses several features that would appear to make them extremely attractive for this purpose. In particular, one should be able to tune the reactivity of the complexes to match the chemical conversion desired. Diverse ligands with various steric properties, including chiral nonracemic platforms, might be utilized to control reactivity and stereoselectivity.[7] The counterion might also be adjusted to modulate the catalytic activity of these complexes.[8] Perhaps most importantly, the metals themselves can be interchanged to adjust the Lewis acidity. Ligand exchange phenomena provide ample evidence that the early lanthanides, with a lower charge-to-radius ratio, are less Lewis acidic than the late lanthanides.[6a−e]

Our interest in studying these complexes as Lewis acid catalysts for organic transformations was piqued by the report from the Evans group detailing the facile and high-yielding synthesis of lanthanide metallocene cations.[6h] Although the extreme Lewis acidity of these complexes created some concern about turnover in highly functionalized substrates that might contain an array of Lewis basic sites, we reasoned that the ability to tune the complexes would afford sufficient adaptability to design a suitable catalyst system. Herein, we report initial results achieved in the application of lanthanocenium cations to the synthesis of 4-pyranones via the hetero Diels−Alder reaction.

Results and Discussion

The hetero Diels−Alder reaction between a diene and an aldehyde was first demonstrated in the preparation of 2,3-dihydropyran-4-ones.[9] This method has provided a useful strategy for the synthesis of saccharides[10] and complex natural products.[11] Recent investigations[12] have led to the development of asymmetric[13] and immobilized catalysts.[14]

As a first step toward the development of novel asymmetric catalysts for the hetero Diels−Alder reaction, we report our results using achiral cationic lanthanide

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(1) Bach, T.; Fox, D. N. A.; Reetz, M. T. *J. Chem. Soc., Chem. Commun.* **1992**, 1634.

(2) Jordan, R. F.; Dasher, W. E.; Echols, S. F. *J. Am. Chem. Soc.* **1986**, *108*, 1718.

(3) (a) Wipf, P.; Xu, W. *Tetrahedron* **1995**, *51*, 4551. (b) Collins, S.; Koene, B. E.; Ramachandran, R.; Taylor, N. J. *Organometallics* **1991**, *10*, 2092. (c) For an asymmetric cationic catalyst, see: Hong, Y.; Kuntz, B. A.; Collins, S. *Organometallics* **1993**, *12*, 964.

(4) Kundig, E. P.; Saudan, C. M.; Bernardinelli, G. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1220.

(5) Oi, S.; Terada, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 8660.

(6) (a) Hazin, P. N.; Bruno, J. W.; Schulte, G. K. *Organometallics* **1990**, *9*, 416. (b) Evans, W. J.; Ulibarri, T. A.; Chamberlain, L. R.; Alvarez, J. W., Jr. *Organometallics* **1990**, *9*, 2124. (c) Heeres, H. J.; Meetsma, A.; Teuben, J. H. *J. Organomet. Chem.* **1991**, *414*, 351. (d) Schaverien, C. J. *Organometallics* **1992**, *11*, 3476. (e) Deng, D.; Zheng, X.; Qian, C.; Sun, J.; Dormand, A.; Baudry, D.; Visseaux, M. *J. Chem. Soc., Dalton Trans.* **1994**, 1665. (f) Schumann, H.; Winterfeld, J.; Keitsch, M. R.; Herrmann, K.; Demtschuk, J. *Z. Anorg. Allg. Chem.* **1996**, *622*, 1457. (g) Yuan, F.; Shen, Q.; Sun, J. *J. Organomet. Chem.* **1997**, *538*, 241. (h) Evans, W. J.; Seibel, C. A.; Ziller, J. W. *J. Am. Chem. Soc.* **1998**, *120*, 6745. (i) Cendrowski-Guillaume, S. M.; Nierlich, M.; Lance, M.; Ephritikhine, M. *Organometallics* **1998**, *17*, 786. (j) Song, X.; Thornton-Pett, M.; Bochmann, M. *Organometallics* **1998**, *17*, 1004.

(7) (a) Evans, W. J. In *The Chemistry of the Metal−Carbon Bond*; Hartley, F. R., Patai, S., Eds.; John Wiley & Sons: Chichester, 1982. (b) Schumann, H.; Genthe, W. In *Handbook on the Chemistry and Physics of Rare Earths*; Gschneidner, K. A., Jr., Eyring, L., Eds.; Elsevier: Amsterdam, 1984. (c) Schumann, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 474. (d) Evans, W. J. *Adv. Organomet. Chem.* **1985**, *24*, 131. (e) Marks, T. J.; Ernst, R. D. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982; Vol. 3. (f) Schumann, H.; Meese-Marktscheffel, J. A.; Esser, L. *Chem. Rev.* **1995**, *95*, 865. (g) Schaverien, C. J. *Adv. Organomet. Chem.* **1994**, *36*, 283. (h) *Metallocenes*; Togni, A., Halterman, R. L., Eds.; Wiley-VCH: Weinheim, 1998.

(8) (a) Strauss, S. H. *Chem. Rev.* **1993**, *93*, 927. (b) Chen, Y.-X.; Stern, C. L.; Yang, S.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 12451. (c) Jia, L.; Yang, X.; Stern, C. L.; Marks, T. J. *Organometallics* **1997**, *16*, 842. (d) Li, L.; Marks, T. J. *Organometallics* **1998**, *17*, 7, 3996. (e) Chen, Y.-X.; Metz, M. V.; Li, L.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 6287. (f) Lanza, G.; Fragalà, I. L.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 8257. (g) Luo, L.; Marks, T. J. *Top. Catal.* **1999**, *7*, 97.

(9) (a) Danishefsky, A.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (b) Danishefsky, A.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 3183.

(10) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060.

(11) (a) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1. (b) Danishefsky, S. J. *Chemtracts-Org. Chem.* **1989**, *2*, 273. (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987; p 94. (d) Schaus, S. E.; Brenalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876. (e) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427.

(12) Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* **1994**, *35*, 2545.

(13) (a) Schaus S. E.; Branalt, J.; Jacobsen E. N. *J. Org. Chem.* **1998**, *63*, 403. (b) Hanamoto, T.; Furuno, H.; Sugimoto, Y.; Inanaga, J. *Synlett* **1997**, 79. (c) Ghosh, A. K.; Mathivanan, P.; Cappiello, J.; Krishnan, K. *Tetrahedron Asymmetry* **1996**, *7*, 2165. (d) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998. (e) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907.

(14) Gerstberger, G.; Palm, C.; Anwander, R. *Chem. Eur. J.* **1999**, *5*, 997.

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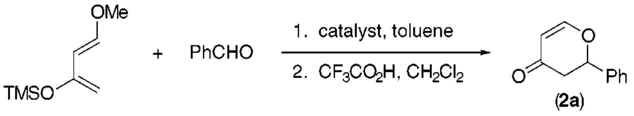
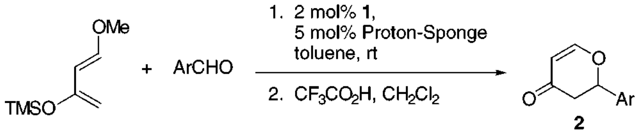
Table 1. Yields for Catalyzed Reaction of Benzaldehyde with Danishefsky's Diene



entry	catalyst	mol % catalyst	T (°C), time (h)	% isoltd yield
1	Eu(fod)$_3$	10	−25, 69	87
2	[Cp*$_2$La][BPh$_4$]	10	−25, 25	73
3	[Cp*$_2$Ce][BPh$_4$] (**1**)	10	−25, 69	63
4	[Cp*$_2$La][BPh$_4$]	1	25, 23	89
5	**1**	1	25, 23	93
6	[Cp*$_2$Sm][BPh$_4$]	1	25, 19	88
7	[Cp*$_2$Ce(THF)$_2$][BPh$_4$]	1	25, 26	90
8	[Cp*$_2$Ce][B(C$_6$F$_5$)$_4$]	1	25, 24	15
9	No catalyst		25, 72	
10	**1**	0.1	25, 92	91

Table 2. Reactions of Substituted Benzaldehydes and Danishefsky's Diene



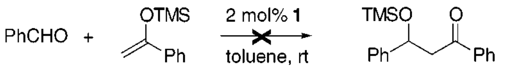
entry	Ar	time (h)	% isoltd yield
1[a]	p-MeOC$_6$H$_4$	24	62 (**2b**)
2	p-MeC$_6$H$_4$	15	89 (**2c**)
3	C$_6$H$_5$	20	91 (**2a**)
4	p-FC$_6$H$_5$	50	83 (**2d**)
5	p-O$_2$NC$_6$H$_4$	24	71 (**2e**)
6	2-pyridyl	18	65 (**2f**)

[a] Reaction performed at 55 °C.

complexes. To assess whether this class of cationic complexes could catalyze the hetero Diels−Alder reaction, we evaluated the reactivity of a series of cationic lanthanide complexes. First, we examined the catalyst activity in the reaction of benzaldehyde with Danishefsky's diene (1-methoxy-3-[(trimethylsilyl)oxy]butadiene). We found that performing the reaction with 10 mol % [Cp*$_2$Ln][BPh$_4$] (Ln = La, Ce) in toluene gave comparable results to Eu(fod)$_3$ (Table 1, compare entries 1−3).[15] We then screened several different cationic complexes for reactivity. Our results using 1 mol % catalyst show that a change in the size of the lanthanide metal from Sm to La does not detrimentally affect the outcome of the reaction (entries 4−6). Interestingly, the THF-bound cerium complex also catalyzes the reaction (entry 7). However, when tetrakis(pentafluorophenyl)borate was used as the counterion, the dihydropyranone was provided in only 15% yield (entry 8). We also observed catalysis with the cerium complex **1** using 0.1 mol % catalyst, although reaction times were considerably lengthened (entry 10).

To exclude the possibility of adventitious H$^+$ acting as a catalyst, the reaction between benzaldehyde and Danishefsky's diene was carried out in the presence of Proton-Sponge[16] and 2 mol % catalyst (Table 2). Our results confirm that the cerium complex acts as catalyst even in the presence of a proton scavenger. During the course of the study we examined the functional group compatibility of the catalyst by reacting several substituted benzaldehydes with Danishefsky's diene in the presence of 2 mol % catalyst at room temperature. The results depicted in Table 2 reveal that catalyst activity was not impeded and the reaction provided the desired dihydropyran-4-ones in good yields even in the presence of nitro and pyridyl groups.

There are two possible mechanisms for the hetero Diels−Alder reaction. Examples utilizing boron[13e] and titanium[13d] catalysts indicates a stepwise mechanism involving an initial Mukaiyama aldol addition. On the other hand, Danishefsky[17] and Jacobsen[13a] have reported evidence implying a concerted [4 + 2] mechanism. To test the possibility of a Mukaiyama aldol mechanism, we performed the reaction between 1-phenyl-1-(trimethylsilyloxy)ethene with benzaldehyde in the presence of 2 mol % of our cerium catalyst (eq 1). After 14 h, no detectable amount of aldol product was observed. Failure to initiate the Mukaiyama aldol reaction suggests our cerium catalyst operates via a concerted pathway.



(1)

Conclusions

In conclusion, we have demonstrated the synthetic utility of the cationic lanthanide complex, [(C$_5$Me$_5$)$_2$Ce][BPh$_4$], as an effective Lewis acid catalyst for the hetero Diels−Alder reaction between Danishefsky's diene and substituted benzaldehydes. The reactions can be performed with as little as 0.1 mol % catalyst, although 2 mol % catalyst loading provides for more reasonable reaction times. Various functionalities are tolerated in the reaction. We have also provided evidence suggesting this reaction follows a concerted pathway. These results suggest that cationic organolanthanides may be useful catalysts in other important organic reactions.

Experimental Section

Representative Procedure for the Hetero Diels−Alder Reaction of Danishefsky's Diene with Aldehydes. 2-Phenyl-2,3-dihydro-4*H*-pyran-4-one (2a). To a solution of catalyst **1**[6h] (10 mg, 0.014 mmol) and Proton-Sponge (8 mg, 0.037 mmol) dissolved in 1.4 mL of toluene, in a glovebox, was added benzaldehyde (78 mg, 0.74 mmol), and 1-methoxy-3-[(trimethylsilyl)oxy]butadiene (200 μL, 1.03 mmol) was added via syringe at 25 °C. The progress of the reaction was monitored by TLC or ^{1}H NMR spectroscopy. After 20 h, the reaction was removed from the glovebox, diluted with 3 mL of CH$_2$Cl$_2$, and treated with four drops of trifluoroacetic acid. After 1 h, the reaction was concentrated in vacuo, and the crude residue was purified by flash chromatography on SiO$_2$ eluting with hexanes/EtOAc (19:1 to 4: 1) to give 117 mg (91%) of 2-phenyl-2,3-dihydro-4*H*-pyran-4-one[18] as a clear oil.

2-(4-Methoxyphenyl)-2,3-dihydro-4*H*-pyran-4-one (2b): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.46 (d, $J = 6.0$ Hz, 1H), 7.34 (d, $J = 8.8$ Hz, 2H), 6.94 (d, $J = 8.8$ Hz, 2H), 5.52 (d, $J = 6.0$ Hz, 1H), 5.38 (dd, $J = 3.5$, 14.5 Hz, 1H), 3.83 (s, 3H), 2.93 (dd, $J = 14.5$, 17.0 Hz, 1H), 2.63 (dd, $J = 3.5$, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 192.5, 163.3, 160.0, 129.8, 127.7, 114.1, 107.2, 80.9, 55.3, 43.1; IR (neat) 2962, 1681 cm^{-1}. Anal. Calcd for C$_{12}$H$_{12}$O$_3$: C, 70.58; H, 5.92. Found: C, 70.30; H, 5.94.

2-*p*-Tolyl-2,3-dihydro-4*H*-pyran-4-one (2c): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.47 (d, $J = 6.0$ Hz, 1H), 7.29 (d, $J = 8.3$ Hz, 2H), 7.23 (d, $J = 8.3$ Hz, 2H), 5.52 (d, $J = 6.0$ Hz, 1H), 5.39 (dd, $J = 3.5$, 14.5 Hz, 1H), 2.92 (dd, $J = 14.5$, 17.0 Hz, 1H), 2.64 (dd,

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[15] For a literature reference using CDCl$_3$ as solvent see: Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.

[16] Bosnich, B. *Aldrichim. Acta* **1998**, *31*, 76.

[17] Larson, E. R.; Danishefsky, S. *Tetrahedron Lett.* **1982**, *23*, 1975.

[18] Sher, F.; Isidor, J. L.; Taneja, H. R.; Arlson, R. M. *Tetrahedron Lett.* **1973**, *8*, 577.

$J = 3.5$, 17.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 163.4, 138.9, 134.8, 129.5, 126.2, 107.2, 81.0, 43.2, 21.2; IR (neat) 3031, 1682 cm^{-1}. Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.34; H, 6.18.

2-(4-Fluorophenyl)-2,3-dihydro-4*H*-pyran-4-one (2d): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, $J = 6.0$ Hz, 1H), 7.38−7.43 (m, 2H), 7.13 (t, $J = 8.8$ Hz, 2H), 5.55 (dd, $J = 1.5$, 6.0 Hz, 1H), 5.43 (dd, $J = 3.5$, 14.5 Hz, 1H), 2.91 (dd, $J = 14.5$, 17.0 Hz, 1H), 2.67 (ddd, $J = 1.5$, 3.5, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 163.0, 162.8 ($J_{C-F} = 247$ Hz), 133.7, 128.0 ($J_{C-F} = 9$ Hz), 115.8 ($J_{C-F} = 22$ Hz), 107.4, 80.4, 43.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ 64.1; IR (neat) 3015, 1674 cm^{-1}. Anal. Calcd for $C_{11}H_9FO_2$: C, 68.75; H, 4.72. Found: C, 68.20; H, 5.05.

2-(4-Nitrophenyl)-2,3-dihydro-4*H*-pyran-4-one (2e): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, $J = 8.5$ Hz, 2H), 7.61 (d, $J = 8.5$ Hz, 2H), 7.52 (d, $J = 6.0$ Hz, 1H), 5.59 (d, $J = 6.0$ Hz, 1H), 5.56 (dd, $J = 3.5$, 14.0 Hz, 1H), 2.85 (dd, $J = 14.0$, 16.5 Hz, 1H), 2.73 (dd, $J = 3.5$, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 162.6, 148.0, 144.8, 126.7, 124.1, 107.9, 79.7, 43.4; IR ($CHCl_3$) 1678 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_4$: C, 60.28; H, 4.14; N, 6.39. Found: C, 59.90; H, 4.13; N, 6.38.

2-(2-Pyridyl)-2,3-dihydro-4*H*-pyran-4-one (2f): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, $J = 4.0$ Hz, 1H), 7.90 (t, $J = 7.5$ Hz, 1H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.49 (d, $J = 6.0$ Hz, 1H), 7.41 (dd, $J = 5.0$, 7.0 Hz, 1H), 5.63 (dd, $J = 4.0$, 13.5 Hz, 1H), 5.57 (d, $J = 6.0$ Hz, 1H), 2.98 (dd, $J = 13.5$, 17.0 Hz, 1H), 2.88 (dd, $J = 4.0$, 17.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4, 162.3, 156.3, 148.7, 138.1, 123.9, 121.1, 107.8, 80.4, 41.6; IR (neat) 3062, 1681 cm^{-1}. Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.24; H, 5.14; N, 7.70.

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