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Enantioselective Rare-Earth Catalyzed Quinone Diels−Alder Reactions

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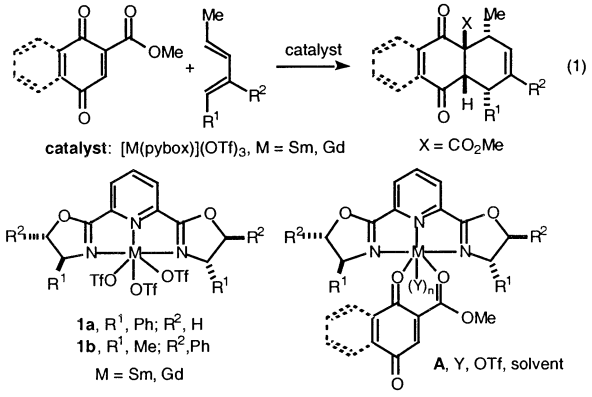
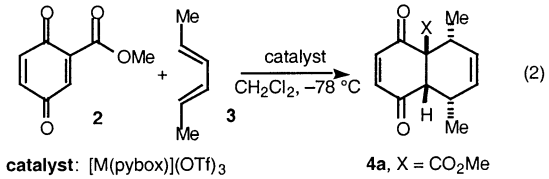
Remarkable progress in the development of enantioselective Diels−Alder reactions has been achieved through the use of both chiral auxiliaries[1] and chiral Lewis acids.[2] However, only a handful of chiral catalysts effectively mediate selected quinone Diels−Alder reactions in moderate to good enantioselectivities.[3,4] It has even been suggested that quinone ketals might well be more useful quinone surrogates in these reactions.[5] The purpose of this communication is to describe a new family of chiral Lewis acid complexes **1** derived from pyridyl-bis(oxazoline) (pybox) ligands and samarium and gadolinium triflates that are effective catalysts in quinone Diels−Alder reactions (eq 1).



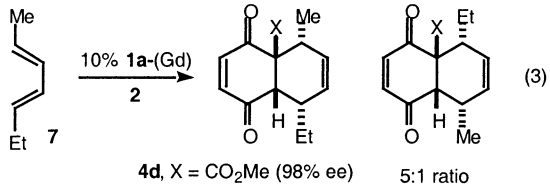
We have recently documented the utility of chiral [Sc(Ph-pybox)](OTf)$_3$ and [Sc(Ph-pybox)](Cl$_2$)SbF$_6$ complexes as Lewis acids in carbonyl addition reactions to glyoxylate esters.[6] These results suggested that trivalent scandium as well as other lanthanide(pybox) complexes might likewise prove to be effective catalysts for the illustrated family of quinone Diels−Alder reactions. Accordingly, the evaluation of a series of metal triflates M(OTf)$_3$: Sc, La, Sm, Gd, and Yb, as their derived pybox complexes, was carried out in dichloromethane (DCM, −78 °C) in the catalyzed reaction between benzoquinone **2**[7] and *trans*-2,4-hexadiene (**3**) (eq 2).

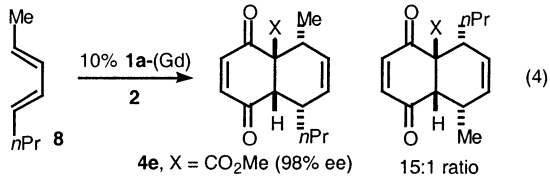


During the ligand/metal triflate survey, the reaction was generally completed in less than 10 min, affording the illustrated cycloadduct as a single diastereomer. Four complexes emerged from this screen as promising catalysts: (*S*,*S*)-Ph-pybox complexes **1a**-(Sc) and **1a**-(Sm) and (2*S*,3*S*)-norephedrine-derived gadolinium pybox complex **1b**-(Gd). Due to the exceptional yields and absence of byproducts of the Sm- and Gd-catalyzed reactions, these complexes were chosen for further study.

A systematic survey of solvents using 10 mol% of **1a**-(Sm) revealed that product enantioselectivity is highly dependent on the choice of solvent system. Of the solvents that were evaluated (DCM, THF, and mixtures of ether, THF, and DCM with toluene), the best results were obtained when the reaction was conducted in a 1:1 mixture of THF and toluene at −78 °C.[8] Using the samarium complex **1a**-(Sm), cycloadduct **4a** was produced in 97% ee and 87% isolated yield (Table 1, entry 1). The analogous reaction carried out with **1a**-(Gd) afforded comparable results (98% ee, 99% yield).[9] From this study, we infer that THF is playing an integral role as a metal ligand in these reactions.

A number of dienes were then evaluated to determine reaction scope and catalyst generality (Table 1). A selection of *trans*-1-substituted dienes, including 2,4-hexadiene, piperylene, and 2-methyl-1,3-pentadiene (entries 1−6), were effective in the quinone Diels−Alder reaction with **2**. In all cases, only the endo product was observed, and complete consumption of the quinone occurred in less than 1 h. We anticipated that *trans*-1,3-hexadiene (**13**) would also undergo facile [4 + 2] cycloaddition; however, its reaction with **2** was extremely sluggish and displayed only moderate product enantiomeric excess (63%). Although an ethyl substituent is only marginally more sterically demanding than its methyl counterpart, it appears that the additional methylene unit reduces the reaction rate as a consequence of the increased nonbonding interactions between the diene and the chelated catalyst−quinone complex **A**. From rate data obtained in competition experiments between piperylene and **13**[10] catalyzed by both **1a**-(Sm) and **1a**-(Gd), we anticipated that the reaction between quinone **2** and dienes possessing differing alkyl substituents in the 1- and 4-positions might also be regioselective. Indeed, the reaction of **2** with *trans*-2,4-heptadiene (**7**) and *trans*-2,4-octadiene (**8**) afforded a 5:1 and 15:1 mixture of regioisomers in 98% ee for both reactions with the **1a**-(Gd) catalyst (eq 3, 4, entries 7, 8).





Naphthoquinones may also be employed as dienophiles. While the reaction of naphthoquinone **11** with diene **3** catalyzed by **1a**-(Sm) was slow, affording cycloadduct **12a** in low ee (43%), the more Lewis acidic Gd-complex **1b**-(Gd) delivered exceptional results (91% ee, 99% yield, entry 13).

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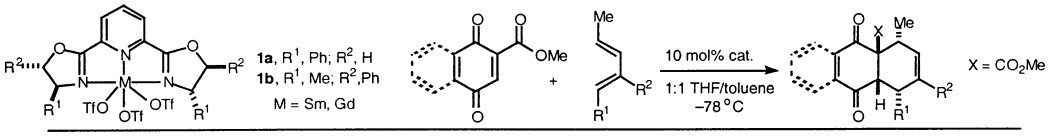
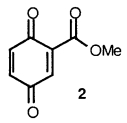
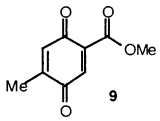
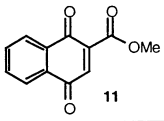
Table 1. Quinone Diels−Alder Reaction Scope



entry	quinone	catalyst	R^1	R^2	diene	product	ee %	yield %
1		**1a**-(Sm)	Me	H	**3**	**4a**	97	87
2		**1a**-(Gd)	Me	H	**3**	**4a**	98	99
3		**1a**-(Sm)	H	H	**5**	**4b**	96[a]	96
4		**1a**-(Gd)	H	H	**5**	**4b**	98	99
5	**2**	**1a**-(Sm)	H	Me	**6**	**4c**	91	97
6		**1a**-(Gd)	H	Me	**6**	**4c**	97	99
7		**1a**-(Gd)	Et	H	**7**	**4d**	98[c]	99[b]
8		**1a**-(Gd)	*n*-Pr	H	**8**	**4e**	98[c]	96[b]
9		**1a**-(Sm)	Me	H	**3**	**10a**	>99	91
10		**1a**-(Sm)	H	H	**5**	**10b**	95	88
11	**9**	**1a**-(Gd)	H	H	**5**	**10b**	>99	88
12		**1a**-(Sm)	H	Me	**6**	**10c**	98	84
13		**1b**-(Gd)	Me	H	**3**	**12a**	91	>99
14	**11**	**1b**-(Gd)	H	H	**5**	**12b**	91[a]	91

[a] Absolute stereochemistry was determined by selective Luche reduction of the less sterically hindered ketone, followed by Mosher ester analysis. The remaining product configurations were assigned by analogy. [b] Isolated yields of a mixture of regioisomers 5:1 and 15:1 for entries 7 and 8, respectively.[c] Ee of major diastereomer was determined after selective Luche reduction of the less sterically hindered ketone.

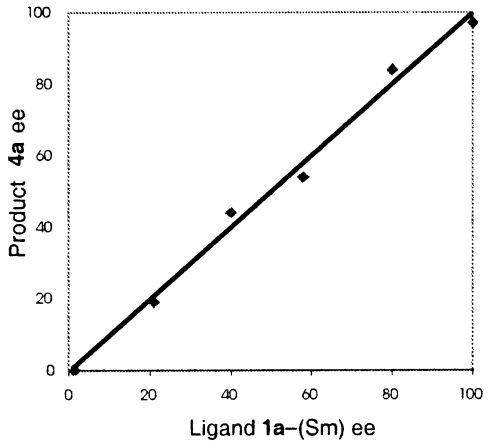


Figure 1. Plot of percent ee of **4a** vs ee of complex **1a**-(Sm).

Preliminary mechanistic studies with the **1a**-(Sm) catalyst indicate the absence of a nonlinear effect (Figure 1).[11] The enantioselectivities of cycloadduct **4a** were monitored as a function of catalyst enantiomeric composition. The illustrated linear relationship between ee (ligand) and ee (product) suggests that neither catalyst aggregation nor dimer formation is occurring.

This investigation has highlighted three new lanthanide pybox complexes, **1a**-(Sm), **1a**-(Gd), and **1b**-(Gd) that might have broader applications in enantioselective Lewis acid-catalyzed reactions.

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Supporting Information Available: Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org

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(8) See the Supporting Information for a list of reaction solvent effects.

(9) On the basis of chiral HPLC analysis, it was determined that (*S*,*S*)-**1a**-(Sm) and (*S*,*S*)-**1a**-(Gd) complexes furnished products possessing the same (illustrated) absolute stereochemistry.

(10) The rate of reaction using piperylene was at least 7.4 and 10.0 times greater than with **13** when catalyzed by complexes **1a**-(Sm) and **1a**-(Gd), respectively, as determined by chiral HPLC analysis.

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