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A New Class of Chiral Lewis Acid Catalysts for Highly Enantioselective Hetero-Diels-Alder Reactions: Exceptionally High Turnover Numbers from Dirhodium(II) Carboxamidates

Michael P. Doyle,* Iain M. Phillips, and Wenhao Hu

Department of Chemistry, The University of Arizona
Tucson, Arizona 85721

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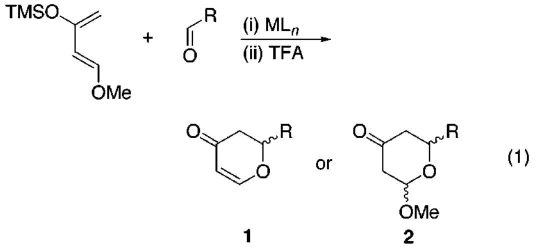
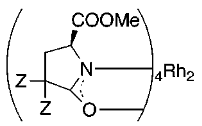
The hetero-Diels−Alder reactions of carbonyl compounds with conjugated dienes is an important methodology for the synthesis of dihydropyrans.[1] Accelerated by Lewis acids, these reactions have been a veritable training ground for evaluation of the effectiveness of chiral catalysts as Lewis acids for enantioselective transformations.[2−8] Although selectivities of 99% ee have been achieved in select cases, a major drawback of this methodology has been its high catalyst loading [substrate/catalyst (S/C) usually ≤ 50]. We have previously developed chiral dirhodium(II) carboxamidate catalysts for effective and efficient metal carbene transformations,[3−11] and we now report a major extension of their applications to hetero-Diels−Alder reactions where their operations allow substrate-to-catalyst loadings of up to 10,000.

To ascertain the viability of the approach with dirhodium(II) catalysts, we first employed rhodium acetate at 1.0 mol % for the cycloaddition of Danishefsky's diene with an equivalent amount of *p*-nitrobenzaldehyde (eq 1), and this reaction was complete within 6 h at room temperature in CH_2Cl_2. Treatment of the reaction solution with trifluoroacetic acid resulted in the formation of dihydropyran **1**, whereas treatment with 5% Et_3N/MeOH gave acetal **2** that we used to monitor the syn/anti diasteromer ratio which, by reason of oxonium ion formation, is an indicator of the Lewis acidity of the catalyst (high activity → isomerization).

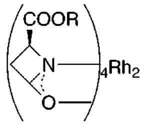


(1)

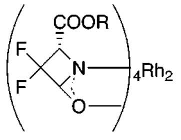
A comparison of results from the use of a broad selection of chiral dirhodium(II) catalysts is presented in Table 1. Both chiral carboxamidate-ligated (**3**−**6**) and carboxylate-ligated (**7**) dirhodium complexes were employed. Dirhodium(II) complexes with the new fluorinated MEPY (**3b**) and IBAZ (**5a**) or CHAZ (**5b**) ligands[12] were expected to provide enhanced Lewis acid activity to dirhodium(II) even beyond that from representative azetidinone ligands[13] or from chiral carboxylates.[14] However, the highest level of enantiocontrol was achieved with the less Lewis acidic Rh_2(4*S*-MPPIM)$_4$, which in metal carbene reactions was considered



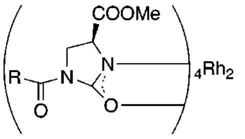
3a: Rh_2(5*S*-MEPY)$_4$, Z = H
3b: Rh_2(5*S*-dFMEPY)$_4$, Z = F



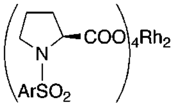
4a: Rh_2(4*S*-MEAZ)$_4$, R = Me
4b: Rh_2(4*S*-IBAZ)$_4$, R = ^{i}Bu
4c: Rh_2(4*S*-CHAZ)$_4$, R = $^c C_6H_{11}$



5a: Rh_2 (4*R*-dFIBAZ)$_4$, R = ^{i}Bu
5b: Rh_2 (4*R*-dFCHAZ)$_4$, R = $^c C_6H_{11}$



6a: Rh_2 (4*S*-MACIM)$_4$, R = Me
6b: Rh_2 (4*S*-MPPIM)$_4$, R = CH_2CH_2Ph



7a: Rh_2(*S*-DOSP)$_4$, Ar = *p*-C_6H_4-$C_{12}H_{25}$
7b: Rh_2(*S*-TBSP)$_4$, Ar = *p*-C_6H_4-^{t}Bu

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Table 1. Enantioselectivity in Catalytic Cycloaddition of *p*-Nitrobenzaldehyde to Danishefsky's Diene[a]

catalyst	yield, %[b] **1** (syn:*anti* **2**)	ee, %[c] **1** (config.)
$Rh_2(OAc)_4$	67 (100:0)	–
Rh_2(5*R*-MEPY)$_4$	53 (100:0)	73 (*R*)
Rh_2(5*S*-dFMEPY)$_4$	53 (50:50)	78 (*S*)
Rh_2(4*S*-MEAZ)$_4$	63 (95:5)	56 (*S*)
Rh_2(4*S*-IBAZ)$_4$	62 (100:0)	66 (*S*)
Rh_2(4*R*-dFIBAZ)$_4$	68 (60:40)	70 (*R*)
Rh_2(4*R*-dFIBAZ)$_4$	93[d]	72 (*R*)
Rh_2(4*S*-CHAZ)$_4$	54 (100:0)	61 (*S*)
Rh_2(4*R*-dFCHAZ)$_4$	98[d]	76 (*R*)
Rh_2(4*S*-MACIM)$_4$	76[d]	74 (*S*)
Rh_2(4*S*-MPPIM)$_4$	82[d]	95 (*S*)
Rh_2(*S*-DOSP)$_4$	68	20 (*S*)
Rh_2(*S*-TBSP)$_4$	61	16 (*S*)

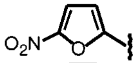
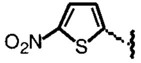
[a] Unless indicated otherwise, reactions were performed at room temperature in anhydrous CH_2Cl_2 using equivalent amounts of reactants and 1.0 mol % of catalyst with a reaction time of 24 h. [b] Isolated yield after column chromatography. The *syn*:*anti* ratio was determined by ^1H NMR after quenching with 5% Et_3N in MeOH: syn at δ 4.82, anti at δ 5.32 and 5.18; *syn* $\rightarrow$ *anti*. [c] Determined by HPLC using a Chiralpak OD column (hexane:*i*PrOH = 85:15). [d] Reactions were performed with a 5-fold molar excess of aldehyde.

to be the least reactive of dirhodium(II) carboxamidate catalysts for diazo decomposition.[15] By comparison, the normally more reactive chiral dirhodium(II) carboxylates (**7**) provided low enantiocontrol for this reaction.

A survey of aldehyde substrates considered to be representative was undertaken, and the results obtained with two catalysts (**5b** and **6b**) are reported in Table 2. As can be seen from data for reactions of substituted benzaldehydes, there is a significant electronic influence on enantiocontrol so that % ee values increase with increasing electron withdrawal from a para-substituent. Also, the effect of catalyst ligands on enantioselectivity (compare **3**−**6** for selectivity) is substantial but not apparently uniform (steric or electronic effects).[10−12] Still, enantiomeric excess beyond 90% can be achieved with several substrates (Tables 1 and 2), but additional efforts will be required for full optimization.

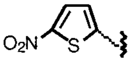
We are aware of only one example of a hetero-Diels−Alder reaction in which less than 1.0 mol % of catalyst was effectively employed, and that one used 0.5 mol % of a copper(II)−bis-oxazoline complex in nitromethane.[16,17] Consequently, we were surprised to find that the substrate-to-catalyst ratio could be reduced by more than 2 orders of magnitude below commonly used S/C ratios of 10−50. Representative data are given in Table 3 with two catalysts.

Table 2. Hetero-Diels−Alder Reactions of Representative Aldehydes with the Danishefsky Diene[a]

R	catalyst	yield, % **1**[b]	ee, % **1**[c]
(a) *p*-$NO_2C_6H_4$	Rh_2(4*R*-dFIBAZ)$_4$	68	70
(b) *p*-ClC_6H_4	Rh_2(4*R*-dFIBAZ)$_4$	86[d]	65
(c) C_6H_5	Rh_2(4*R*-dFIBAZ)$_4$	50[d,e]	65
(d) *p*-$MeOC_6H_4$	Rh_2(4*R*-dFIBAZ)$_4$	27[d,e]	18
(e) *trans*-*p*-$NO_2C_6H_4CH{=}CH$	Rh_2(4*R*-dFIBAZ)$_4$	33	68
	Rh_2(4*S*-MPPIM)$_4$	41[d]	89
(f) EtOOC	Rh_2(4*R*-dFIBAZ)$_4$	43	54
	Rh_2(4*S*-MPPIM)$_4$	83[d]	10
(g) 	Rh_2(4*R*-dFIBAZ)$_4$	78[d]	80
	Rh_2(4*S*-MPPIM)$_4$	48[d]	93
(h) 	Rh_2(4*R*-dFIBAZ)$_4$	98[d]	85
	Rh_2(4*S*-MPPIM)$_4$	81[d]	94

[a] Reactions were performed as described in Table 1. [b] Isolated yield after chromatography. [c] Determined by HPLC using a Chiralpak OD column. [d] A 5-fold molar excess of aldehyde was used. [e] Reaction in refluxing CH_2Cl_2.

Table 3. Substrate-to-Catalyst Ratios in Hetero-Diels−Alder Reactions of Aldehydes with the Danishefsky Diene[a]

R	catalyst	S/C	reaction time, d	yield, % **1**[b]	ee, % **1**[c]
p-$NO_2C_6H_4$	Rh_2(4*R*-dFIBAZ)$_4$	500	4	95	64
		2,000	4	82	64
		5,000	4	78	63
		10,000	4	71	61
	Rh_2(4*S*-MPPIM)$_4$	1,000	3	79	81
		10,000	10	62	80
	Rh_2(4*S*-MPPIM)$_4$	10,000	10	81	73

[a] Reactions were performed as described in Table 1 using a five-fold molar excess of aldehyde.

The slight decrease in % ee values as the S/C ratio is increased may be due to a background reaction, but this is unclear at this time. What is evident is that dirhodium(II) catalysts do not have the same restrictions for catalyst turnover that are common with previously reported Lewis acid catalysts. The implications of this for other Lewis acid catalyzed reactions are currently under investigation.

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(17) In this case aldehyde was the limiting reagent. With dirhodium(II) catalyst the hetero-Diels−Alder reaction occurs with the same % ee value whether aldehyde or Danishevsky's diene is in excess, but the rate of reaction increases with increasing concentration of aldehyde.