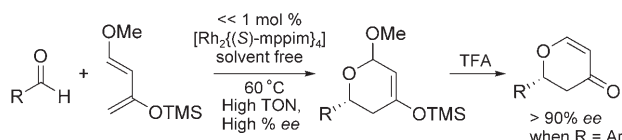


Cationic Chiral Dirhodium Carboxamides Are Activated for Lewis Acid Catalysis**

Yuanhua Wang, Joffrey Wolf, Peter Zavalij, and Michael P. Doyle*

Dedicated to Professor Henri Brunner on the occasion of his 72nd birthday

Chiral dirhodium(II) carboxamides have high potential for enantioselective Lewis acid catalyzed reactions because they hold the Lewis base, which is activated for reaction, at the axial coordination site in close proximity to the ligand attachments for chiral differentiation. As has already been demonstrated for the hetero-Diels–Alder reaction (Scheme 1)^[1,2] and for trimethylsilylketene/glyoxal cycloaddition,^[3] the chiral environment around the axial coordination



Scheme 1. Hetero-Diels–Alder reaction catalyzed by chiral dirhodium(II) carboxamides. TMS = trimethylsilyl, TFA = trifluoroacetic acid.

site strongly influences enantiocontrol and also pushes the product off the rhodium axial coordination site to provide turnover numbers (TON) as high as 10000.

However, the Lewis acidity of dirhodium(II) carboxamides is low compared to that of many other catalysts for these reactions.^[4] Suitable Diels–Alder, ene, and dipolar cycloaddition reactions, for example, show no catalytic activity with chiral dirhodium(II) carboxamides, even with α,α -difluoro analogues of the mepy and meaz catalysts that were developed to enhance Lewis acid association with Lewis bases.^[5] We have prepared cationic $\text{Rh}^{\text{II}}/\text{Rh}^{\text{III}}$ counterparts to the moderately active chiral dirhodium(II) carboxamides to enhance the Lewis acidity of these chiral dirhodium catalysts. Cationic metal complexes are now commonly used to achieve rate and selectivity enhancements for those transformations

suitable to catalysis by the cationic metal complex.^[6] We anticipated that cationic chiral $\text{Rh}^{\text{II}}/\text{Rh}^{\text{III}}$ compounds could increase the closeness of association of the catalyst with Lewis bases, increase the rate of reaction with selected substrates, and enhance enantiocontrol.

Oxidation of dirhodium(II) (Rh_2^{4+}) compounds is well known,^[6] but their Rh_2^{5+} counterparts have been produced in the presence of either a less labile ligand such as halide^[7] or by using another transition metal such as Ag^{I} , Ce^{IV} , or Cu^{II} for the oxidation,^[6,8] none of which are amenable to the use of Rh_2^{5+} complexes as catalysts without laborious separation or further catalyst manipulation. However, we have recently discovered that nitrosonium salts effect facile oxidation of dirhodium(II) carboxamides at room temperature to form the corresponding $\text{Rh}^{\text{II}}/\text{Rh}^{\text{III}}$ salts quantitatively, evolving nitric oxide in the process. These complexes exhibit a characteristic electronic absorption near 1000 cm^{-1} . A crystal structure for the bis(acetonitrile) complex of $[\text{Rh}_2\{((4S)\text{-meox})_4\}]\text{BF}_4$ is shown in Figure 1.

To test the ability of chiral Rh_2^{5+} carboxamides to enhance selectivity in Lewis acid catalyzed transformations we turned our attention to the hetero-Diels–Alder reaction and to $[\text{Rh}_2(\text{mepy})_4]$ as the catalyst. As has been reported,^[1a] the use of 1.0 mol % $[\text{Rh}_2(\text{mepy})_4]$ with *p*-nitrobenzaldehyde and the Danishefsky diene (see Scheme 1) resulted in the corresponding hetero-Diels–Alder product (53 % yield) in 73 % ee; use of the corresponding Rh_2^{5+} complex, $[\text{Rh}_2\{((5S)\text{-mepy})_4\}]\text{BF}_4$, produced the same product in 93 % ee (Table 1). With the slow-reacting benzaldehyde,^[1b] $[\text{Rh}_2\{((5S)\text{-$

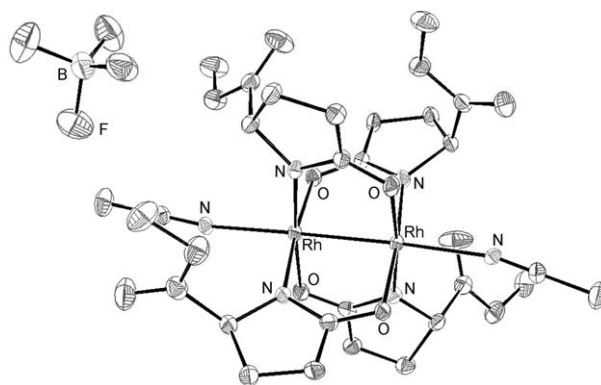


Figure 1. ORTEP view of $[\text{Rh}_2\{((4S)\text{-meox})_4\}]\text{BF}_4$ as its bis(acetonitrile) complex. Ellipsoids are shown at 30 % probability; hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: Rh–Rh 2.4600(3); Rh–N_{meox} 1.958, 1.960, 1.983, 2.010(5); Rh–O 2.031, 2.031, 2.045, 2.046(4); Rh–NCMe 2.214, 2.265(6).

[*] Dr. Y. Wang, P. Zavalij, Prof. M. P. Doyle
Department of Chemistry and Biochemistry
University of Maryland
College Park, MD 20742 (USA)
Fax: (+1) 301-405-7058
E-mail: mdoyle3@umd.edu
Dr. J. Wolf
Laboratoire de Chimie de Coordination
205 route de Narbonne
31077 Toulouse Cedex 4 (France)

[**] We are grateful to the National Institutes of Health (GM 46503) and the National Science Foundation for their generous support. J.W. thanks the “Fonds Social Européen” for a fellowship.

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mepy₄]BF₄ provides a substantial rate enhancement. With ethyl glyoxylate, enantioselectivity rose from 20 to 74% *ee* with the enantiomer of the same catalyst under the same conditions, and the rate of reaction with [Rh₂{(5*S*)-mepy₄}]BF₄ is significantly faster than that with [Rh₂{(5*S*)-

Table 1: Influence of the cationic dirhodium (5*S*)-mepy catalysts on reactivity and selectivity in hetero-Diels–Alder reactions of the Danishefsky diene with representative aldehydes.^[a]

Aldehyde	Catalyst	Conv. [%] ^[b]	<i>ee</i> [%] ^[c]
<i>p</i> -NO ₂ C ₆ H ₄ CHO	[Rh ₂ {(5 <i>S</i>)-mepy ₄ }]	53	73
<i>p</i> -NO ₂ C ₆ H ₄ CHO	[Rh ₂ {(5 <i>S</i>)-mepy ₄ }]BF ₄	70	93
C ₆ H ₅ CHO	[Rh ₂ {(5 <i>S</i>)-mepy ₄ }]	< 5	–
C ₆ H ₅ CHO	[Rh ₂ {(5 <i>S</i>)-mepy ₄ }]BF ₄	40	88
EtOOCCHO	[Rh ₂ {(5 <i>S</i>)-mepy ₄ }]	< 10	20
EtOOCCHO	[Rh ₂ {(5 <i>S</i>)-mepy ₄ }]BF ₄	100	74
EtOOCCHO	[Rh ₂ {(5 <i>S</i>)-mepy ₄ }]PF ₆	100	76
EtOOCCHO	[Rh ₂ {(5 <i>S</i>)-mepy ₄ }]SbF ₆	100	76

[a] Reactions were performed with 1.0 mol% catalyst at room temperature in anhydrous dichloromethane with a reaction time of 24 h using 1.1 equiv diene. [b] Determined by ¹H NMR analysis. [c] Determined by HPLC on an OD-H or AD-H column.

mepy₄]. The estimated increase in rate by [Rh₂{(5*S*)-mepy₄}]BF₄ is at least a factor of ten. As can be seen from this data, the anion of the Rh₂⁵⁺ complex has no measurable effect on the enantioselectivity. In its use as a Lewis acid catalyst, coordination of the Rh₂⁵⁺ complex with water was expected to produce a protonic acid; to circumvent this problem these reactions were performed in the presence of a noncoordinating base.

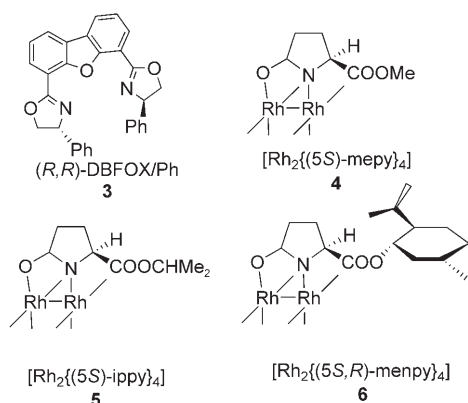
The oxidation of organic compounds by dirhodium(II/III) carboxamides was anticipated. Indeed, we have known for many years that Rh₂⁵⁺ complexes are reduced to Rh₂⁴⁺ by diazoacetates, and this is one of the factors that allows dirhodium(II) catalysts to be used with high TON.^[9] However, we anticipated that there are other oxidizable substrates in whose presence Rh₂⁵⁺ will be reduced to Rh₂⁴⁺; thus, one procedural requirement of our investigation has been to test the redox stability of the reacting partners with the Rh₂⁵⁺ catalyst. We have found, for example, that [Rh₂{(4*S*)-meox₄}]BF₄ is reduced by the Danishefsky diene, and the rate of this oxidation is competitive with catalysis at temperatures above 40 °C. In contrast, [Rh₂{(5*S*)-mepy₄}]BF₄, which has a much lower oxidation potential (358 mV vs. 742 mV),^[5] is stable to reduction by the Danishefsky diene over long reaction times.

One of the significant challenges in asymmetric Lewis acid catalysis is a 1,3-dipolar cycloaddition between nitrones and enals^[10–13] to form isoxazolidines. A variety of chiral catalysts have been used for the transformation with methacrolein, which occurs in variable yields, usually below room temperature, with the use of 5–10 mol% of catalyst and excess methacrolein (Table 2). Ruthenium and iron catalysts (Table 2, entries 1–2) appear to favor the formation of **2**,^[10,11] and the only example of a nickel catalyst (Table 2, entry 5, with chiral ligand **3**, which is shown in Scheme 2) shows complete selectivity for the formation of **2**.^[12] Chiral dirhodium(II) carboxamides have been unsuitable because they lack catalytic activity (e.g., Table 2, entry 6). In contrast, chiral Rh⁵⁺ carboxamides show high catalytic activity (Table 2, entry 7). [Rh₂{(5*S*)-mepy₄}]BF₄ exhibited high regioselectivity for **2** with modest enantioselectivity. Increasing the steric bulk of the ligand ester group from methyl (**4**⁺) to isopropyl (**5**⁺)^[9] and, reported for the first time, to (*R*)-menthyl (**6**⁺) enhanced the enantioselectivity for **1**, but not for **2**, for which the *ee* value remained at nearly the same level throughout the selection of dirhodium catalysts. Other chiral cationic dirhodium carboxamide catalysts, [Rh₂{(4*S*)-meox₄}]BF₄ and [Rh₂{(4*S*)-meaz₄}]BF₄, gave regio- and enantioselectivities that were lower than those from [Rh₂{(5*S*)-mepy₄}]BF₄. Results do not vary when the molar ratio of methacrolein over the nitrone is varied from 1.4 to 10, and the enantioselectivity is the same when the catalyst loading is increased from 5 to 10 mol%. Furthermore, there is no detectable variation of regioselectivity or enantioselectivity with the anion of the cationic catalyst (BF₄[–] vs. PF₆[–] or SbF₆[–]). Use of 2,6-di-*tert*-butylpyridine (DTBP) to remove

Table 2: Comparative influence of cationic dirhodium carboxamide catalysts on reactivity and selectivity in 1,3-dipolar cycloaddition reactions between *C,N*-diphenylnitrone and methacrolein.^[a]

Entry	Catalyst	Mol%	<i>T</i> [°C]	Yield [%]	1/2 ^[b]	1/2 <i>ee</i> [%] ^[c]
1	[CpRu{Ar ₂ POCH*(Ph)C*(H)(Ph)OPAr ₂ }] ^[d]	5	–20	92	40:60	94:76
2	[CpFe{Ar ₂ POCH*(Ph)C*(H)(Ph)OPAr ₂ }] ^[d]	5	–20	85	20:80	91:87
3	[Cp*Rh{Ph ₂ PC*(H)(Me)CH ₂ PPh ₂ }] ^[e]	5	–25	100	63:37	90:75
4	[Cp*Rh{Ph ₂ PC*(H)(Me)CH ₂ PPh ₂ }] ^[e]	5	0	100	53:47	85:68
5	Ni(ClO ₄) ₂ ·6H ₂ O + (<i>R,R</i>)-DBFOX/Ph (3) ^[f]	10	RT	73	0:100	–:96
6	[Rh ₂ {(5 <i>S</i>)-mepy ₄ }] (4)	5	–20	< 5	3:97	22:20
7	[Rh ₂ {(5 <i>S</i>)-mepy ₄ }]BF ₄ (4 -BF ₄)	5	–20	80	13:87	30:64
8	[Rh ₂ {(5 <i>S</i>)-ippy ₄ }]BF ₄ (5 -BF ₄)	5	RT	64	12:88	63:71
9	[Rh ₂ {(5 <i>S,R</i>)-menpy ₄ }]SbF ₆ (6 -SbF ₆)	5	RT	88	33:67	88:67
10	[Rh ₂ {(5 <i>S,R</i>)-menpy ₄ }]SbF ₆ (6 -SbF ₆) ^[g]	5	RT	90	37:63	94:71
11	[Rh ₂ {(5 <i>S,R</i>)-menpy ₄ }]SbF ₆ (6 -SbF ₆) ^[h]	1	RT	95	24:76	95:53

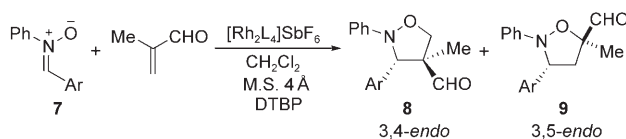
[a] Reactions were performed in anhydrous dichloromethane with a reaction time of 24 h using a slight excess of methacrolein (1.4 equiv), 10 mol% 2,6-di-*tert*-butylpyridine, and 4-Å molecular sieves (0.5 g per mmol of nitrone). [b] Yield determined by product mass and 1/2 ratio determined by ¹H NMR analysis of reaction mixture using easily distinguished aldehydic protons. [c] Determined by ¹H NMR of the diastereomeric imine protons formed from reaction of **1** and **2** with (*S*)-(–)-α-methylbenzylamine (reference [11a]); racemic product was obtained by reaction with dirhodium caprolactamate. [d] Reference [10a]. [e] Reference [11a]. [f] Reference [12]. [g] In situ generated catalyst. [h] Catalyst generated in situ with a reaction time of 48 h.



Scheme 2. Structures of catalysts/ligands in Table 2.

protonic acid does not affect the catalytic activity of the Rh^{5+} salt. In situ preparation of 6^+ gave higher product yields and selectivities and allowed this reaction to be performed with only 1.0 mol % of catalyst (Table 2, entries 10 and 11), but the background reaction forming **2** was more pronounced. The (*S*)-menthyl diastereoisomer of 6^+ gave the same product outcome as 6^+ .

Early results from Kündig and co-workers^[10a] in which an electron-withdrawing substituent on the *C*-phenyl ring of *C,N*-diphenylnitrone was reported to increase the regioselectivity of 3,4-*endo*/3,5-*endo* products (**8/9**; Scheme 3) from



Scheme 3.

40:60 to 0:100 prompted us to examine the influence on selectivity by *C*-aryl substituents of *C*-aryl-*N*-phenylnitrone in reactions with methacrolein. Since catalyst 6^+ provides high enantiocontrol for **8** but not for **9**, our goal was to use substituent effects on nitrone **7** to direct reaction regioselectivity toward **8**, which was anticipated to be formed with high enantioselectivity. Indeed, with 5.0 mol % $[\text{Rh}_2\{(\text{5S},\text{R})\text{-mepy}\}_4]$ at room temperature, use of **7a** ($\text{Ar} = p\text{-NO}_2\text{C}_6\text{H}_4$) produced an increase in regioselectivity favoring **9**, but nitrone **7c** with the *p*-methoxy substituent reversed the selectivity, and the *p*-dimethylamino substituent (**7e**) gave **8** almost exclusively with similarly high enantioselectivity (Table 3). The background reaction which forms **9**, exclusively, is obviously competitive with the use of 1 mol % catalyst (Table 3, entry 4) in the reaction of **7c**.

In summary, we have developed a new class of chiral catalysts for reactions that are promoted by Lewis acids. These catalysts are cationic chiral dirhodium carboxamidates that can be formed in situ and used with low catalyst loadings. Further studies to develop cationic chiral dirhodium carboxamidate salts for Lewis acid catalyzed reactions are underway.

Table 3: Nitrone substituent effects in $[\text{Rh}_2\{(\text{5S},\text{R})\text{-mepy}\}_4]\text{SbF}_6$ -catalyzed 1,3-dipolar cycloaddition reactions between *C*-aryl-*N*-phenylnitrones **7** and methacrolein.^[a]

Entry	Ar in 7	Mol %	Yield [%]	8/9	8/9 ee [%]
1	<i>p</i> -NO ₂ C ₆ H ₄ (7a)	5	82	16:84	21:46
2	C ₆ H ₅ (7b)	5	90	37:63	94:71
3	<i>p</i> -MeOC ₆ H ₄ (7c)	5	83	67:33	91:60
4 ^[b]	<i>p</i> -MeOC ₆ H ₄ (7c)	1	86	47:53	93:28
5	3,4-(MeO) ₂ C ₆ H ₃ (7d)	5	60	65:35	90:55
6	<i>p</i> -Me ₂ NC ₆ H ₄ (7e)	5	50	90:10	90:45

[a] Reactions were performed in anhydrous dichloromethane with a reaction time of 24 h using $[\text{Rh}_2\{(\text{5S},\text{R})\text{-mepy}\}_4]\text{SbF}_6$ as the catalyst, a slight excess of methacrolein, 10 mol % 2,6-*tert*-butylpyridine, and 4-Å molecular sieves (0.5 g per mmol of nitrone). Products were analyzed as reported in Table 2. [b] Catalyst generated in situ with a reaction time of 48 h.

Experimental Section

A flask containing $[\text{Rh}_2\{(\text{5S},\text{R})\text{-mepy}\}_4]\text{SbF}_6$ (11.95 mg, 7.61 μmol) and 4-Å molecular sieves (75 mg) was evacuated and purged with nitrogen. Anhydrous dichloromethane (0.5 mL) was added, and the mixture was stirred for 10 min at room temperature before 2,6-*tert*-butylpyridine (3.52 μL, 0.015 mmol) was added by microsyringe. After stirring for another 10 min at room temperature, freshly distilled methacrolein (0.013 mL, 0.152 mmol) was added, and the resulting solution was stirred for 30 min. A solution of the *C,N*-diphenylnitrone (30 mg, 0.152 mmol) in dichloromethane (1 mL) was then added dropwise to the flask, and the solution was stirred at room temperature for 24 h and monitored by TLC for complete consumption of the nitrone. The mixture was loaded directly onto a short silica gel column to remove the catalyst and was washed with CH₂Cl₂ (20 mL). The combined organic layer was evaporated to dryness. The regioisomer ratio was determined on the reaction mixture by ¹H NMR analysis. The reaction mixture was purified by flash chromatography on silica gel (CH₂Cl₂) to afford an inseparable mixture of the desired products (35.8 mg, 88 %).

CCDC 661689 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: October 6, 2007

Published online: January 10, 2008

Keywords: asymmetric catalysis · cycloaddition · hetero-Diels–Alder reactions · nitrones · rhodium

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