Cycloadditions

A New Dirhodium(II) Carboxamidate Complex as a Chiral Lewis Acid Catalyst for Enantioselective Hetero-Diels–Alder Reactions**

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Over the last decade, the exceptional power of chiral dirhodium(II) carboxylate and carboxamidate catalysts has been demonstrated in a diverse array of enantioselective metal carbene transformations of diazocarbonyl compounds.[1] Aside from the superiority in diazo decomposition, a dirhodium(II) complex with vacant coordination sites at the

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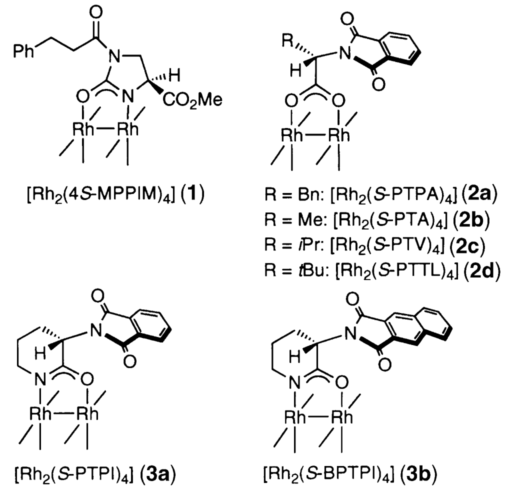
axial position of each octahedral rhodium center is Lewis acidic as the molecule has a high affinity for axial ligands.[2] Although this important feature provides a great incentive to develop dirhodium(II) complexes as a new class of chiral Lewis acid catalysts, this goal has remained elusive until a recent breakthrough by Doyle et al.[3] Doyle and co-workers reported that use of 1 mol% of dirhodium(II) tetrakis[4*S*-methoxycarbonyl-1-(3-phenylpropanoyl)-2-oxoimidazolidinate], $[Rh_2(4S\text{-MPPIM})_4]$ (**1**, Scheme 1), promoted hetero-

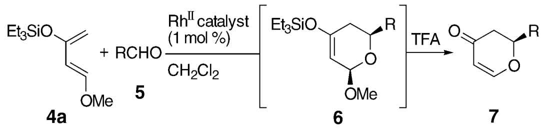


Scheme 1. Chiral dirhodium(II) complexes. MPPIM = 4-methoxycarbonyl-1-(3-phenylpropanoyl)-2-oxoimidazolidinate, PTPA = *N*-phthaloylphenylalaninate, PTA = *N*-phthaloylalaninate, PTV = *N*-phthaloylvalinate, PTTL = *N*-phthaloyl-*tert*-leucinate, PTPI = 3-phthalimido-2-piperidinonate, BPTPI = 3-(benzene-fused-phthalimido)-2-piperidinonate.

Diels–Alder (HDA) reactions[4–6] between 1-methoxy-3-(trimethysilyloxy)-1,3-butadiene (the Danishefsky diene) and nitro-substituted aromatic aldehydes to give, after treatment with trifluoroacetic acid (TFA), dihydropyranones with a maximum of 95% *ee*. Although an exceptionally high turnover number of 6200 was possible with *p*-nitrobenzaldehyde (10 days, 62% yield, 80% *ee*), a major challenge in terms of reaction rates, enantioselectivity, and the scope with regard to dienes and aldehydes still remained. Herein we report that $[Rh_2(S\text{-BPTPI})_4]$ (**3b**), a new dirhodium(II) carboxamidate complex that incorporates (*S*)-3-(benzene-fused-phthalimido)-2-piperidinonate as chiral bridging ligands, is a more general and highly efficient catalyst for *endo*- and enantioselective HDA reactions.

At the outset of this work, the HDA reaction between 1-methoxy-3-(triethylsilyloxy)-1,3-butadiene (**4a**) and *p*-nitrobenzaldehyde (**5a**) in dichloromethane was explored at room temperature in the presence of 1 mol% of our dirhodium(II) catalysts **2a–d**[7] and **3a**[8] (Table 1, entries 1–5). Whereas dirhodium(II) carboxylate catalysts **2a–d** displayed poor enantioselectivities similar to those found by Doyle et al., catalysis with dirhodium(II) tetrakis[3(*S*)-phthalimido-2-piperidinoate], $[Rh_2(S\text{-PTPI})_4]$ (**3a**), provided dihydropyranone (*S*)-**7aa**[9] in 91% yield with 94% *ee* after desilylation (Table 1, entry 5). Interestingly, the activity of **3a** is similar to that of **2a–d**, although dirhodium(II) carboxamidates are

Table 1: Rh^{II}-catalyzed enantioselective HDA reactions.[a]



Entry	Rh^{II}	5	R	*T* [°C]	*t* [h]	7	Yield [%][b]	*ee* [%][c]
1	**2a**	**5a**	$4\text{-}NO_2C_6H_4$	23	2	**7aa**	95	6
2	**2b**	**5a**	$4\text{-}NO_2C_6H_4$	23	2	**7aa**	97	22
3	**2c**	**5a**	$4\text{-}NO_2C_6H_4$	23	2	**7aa**	92	29
4	**2d**	**5a**	$4\text{-}NO_2C_6H_4$	23	2	**7aa**	90	45
5	**3a**	**5a**	$4\text{-}NO_2C_6H_4$	23	2	**7aa**	91	94
6	**3a**	**5b**	C_6H_5	23	32	**7ab**	92	95
7	**3a**	**5c**	$4\text{-}MeOC_6H_4$	23	48	**7ac**	83	96
8	**3a**	**5d**	2-furyl	23	18	**7ad**	94	93[d]
9	**3a**	**5e**	PhC≡C	23	0.5	**7ae**	97	69
10	**3a**	**5e**	PhC≡C	−20	6	**7ae**	96	87
11	**3b**	**5e**	PhC≡C	23	0.5	**7ae**	95	90
12	**3b**	**5e**	PhC≡C	−20	6	**7ae**	91	92

[a] All reactions were performed on a 0.3-mmol scale (0.5 M) with 1.5 equivalents of diene. [b] Yields of isolated products. [c] Determined by HPLC on a Daicel Chiralcel OD-H (see Supporting Information for details). [d] The absolute stereochemistry was not determined.

commonly regarded as weaker Lewis acids than dirhodium(II) carboxylates. It is also noteworthy that **3a** is even more active than **1**, which is manifested by much shorter reaction times (2 h vs. 24 h).[3] With respect to the mechanism of the Lewis acid catalyzed HDA reaction, two mechanistic pathways have been proposed: either a pericyclic or a Mukaiyama aldol–Michael pathway.[5] In the present reaction, the ^{1}H NMR spectrum of the crude reaction mixture obtained without the use of TFA revealed the exclusive formation of the 2,6-*cis*-dihydropyran **6aa**. Furthermore, no detectable cyclization of the Mukaiyama aldol adduct prepared independently was observed under the present reaction conditions. These results demonstrated that the reaction proceeds through a concerted [4+2] mechanism in an *endo* mode.[6i,m,10]

The applicability of this catalytic system to a range of aldehydes was then investigated. The use of aromatic aldehydes, including benzaldehyde, *p*-anisaldehyde, and furfural, afforded the corresponding dihydropyranones in similar high yields and asymmetric induction as those found with electron-poor *p*-nitrobenzaldehyde, although these reactions required significantly longer times to reach completion (Table 1, entries 6–8). In contrast, switching from aromatic aldehydes to phenylpropargylaldehyde dramatically accelerated the reaction, but caused a sharp drop in enantioselectivity (69% *ee*; Table 1, entry 9). This result suggests that the steric interaction between the acetylenic moiety and the phthalimido group protruding toward the rhodium–aldehyde adduct might be less severe than that with an aromatic ring (see below). Although the reaction at −20°C gave an improved enantioselectivity (87% *ee*; Table 1, entry 10), we were particularly attracted to the possibility of enhancing the enantioselectivity by extending the phthalimido group with an additional benzene ring, as was with the case with dirhodium(II) carboxylate catalysts in enantioselective carbonyl ylide cycloadditions.[11] Gratifyingly, the HDA reaction at room temperature under the influence of the newly developed

$[Rh_2(S\text{-BPTPI})_4]$ (**3b**)[12] produced **7ae** in 95% yield with 90% *ee* (Table 1, entry 11), in which a slight enhancement (up to 92% *ee*) was observed at −20 °C without lowering the yield (Table 1, entry 12).

The present $[Rh_2(S\text{-BPTPI})_4]$ catalytic system allowed considerable variations in the substitution pattern of the activated diene and the nature of the aldehyde component (Table 2). The applicable aldehydes include aromatic, α,β-acetylenic, α,β-olefinic, aliphatic, and α-alkoxy derivatives (Table 2, entries 1–9). The HDA reaction with 4-methyl-substituted Danishefsky-type dienes **4c** and **4d** produced 2,3-*cis*-dihydropyranones **7ca** and **7da** with essentially complete diastereoselectivities and enantioselectivities in excess of 96% (Table 2, entries 10 and 11), which confirmed the preference for the *endo*-mode transition state. $[Rh_2(S\text{-BPTPI})_4]$-catalyzed reactions of monooxygenated dienes **4e** and **4f** with phenylpropargylaldehyde proceeded smoothly at −20 °C to yield *all-cis* tetrahydropyranones **8ee** and **8fe** in 99% and 97% *ee*, respectively (Table 2, entries 12 and 13).[13] As expected from the robustness and high activity of **3b**, selected reactions with highly reactive aldehydes proceeded smoothly with very low catalyst loadings (0.0075–0.002 mol%) without compromising the yield or enantioselectivity (Table 2, entries 14–16). The turnover numbers (as high as 48000) are probably among the highest ever reported for Lewis acid catalyzed asymmetric reactions.[14,15]

The stereochemical outcome of the present HDA reaction can be rationalized based on the crystal structure of the bis(acetonitrile) adduct of $[Rh_2(S\text{-PTPI})_4]$ (**3a**; Figure 1)[16] coupled with the formyl C–H···O hydrogen-bond concept proposed by Corey and co-workers.[17] As in the case of **3a**, **3b** is considered to adopt a conformation with a C_2-like symmetry in which the benzene-fused-phthalimido groups are aligned in a "down-down-up-up" arrangement. Consequently, two stereochemical models of the rhodium catalyst–RCHO complexes, **A** and **B**, can be presented in which a favorable hydrogen bond between the formyl hydrogen atom and the carboxamidate oxygen atom is allowed (Figure 2). The approach of dienes (e.g. **4**) to **A** in an *endo* mode to avoid intrusion into the rhodium framework is preferred over the pathway via **B** owing to the serious repulsion between the incoming diene and the benzene-fused phthalimido wall in **B**, which leads to the observed cycloadduct. In this context, it should be noted that the benzene-fused-phthalimido group,

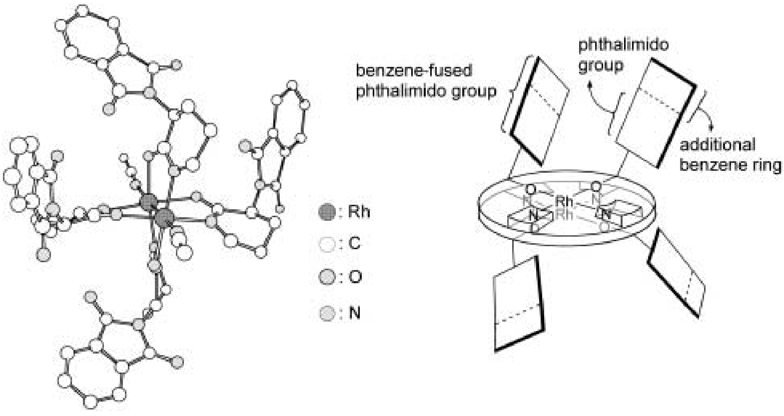
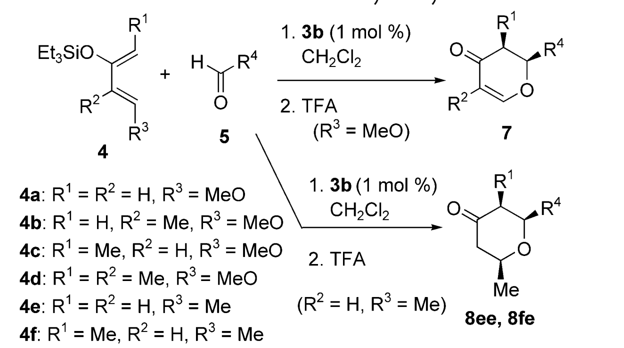


Figure 1. Ball-and-stick (left) and schematic (right) representation of the crystal structure of **3a**·$(MeCN)_2$.

Table 2: Enantioselective HDA reactions catalyzed by **3b**.



Entry	4	5	R4	T [°C]	t [h]	Prod.	Yield [%][a]	ee [%][b]
1	**4a**	**5f**	4-MeC_6H_4	23	24	**7af**	97	96[c]
2	**4a**	**5g**	4-ClC_6H_4	23	6	**7ag**	95	95[c]
3	**4a**	**5h**	4-CNC_6H_4	23	3	**7ah**	93	95[c]
4	**4a**	**5i**	4-$CF_3C_6H_4$	23	1	**7ai**	93	95[c]
5	**4a**	**5j**	$n\text{-}C_5H_{11}C{\equiv}C$	−20	2	**7aj**	71	93[c]
6	**4a**	**5k**	(*E*)-PhCH=CH	23	36	**7ak**	86	96
7	**4a**	**5l**	$PhCH_2CH_2$	23	9	**7al**	89	94
8	**4a**	**5m**	$BnOCH_2$	−20	18	**7am**	83	91
9	**4b**	**5n**	$MOMOCH_2$	−20	24	**7bn**	86	93[c,d]
10	**4c**	**5a**	4-$NO_2C_6H_4$	23	18	**7ca**	97	96[c]
11	**4d**	**5a**	4-$NO_2C_6H_4$	23	10	**7da**	92	97[c]
12	**4e**	**5e**	PhC≡C	−20	20	**8ee**	87	99[c]
13	**4f**	**5e**	PhC≡C	−20	12	**8fe**	81	97[c]
14[e]	**4a**	**5a**	4-$NO_2C_6H_4$	0	48	**7aa**	96[f]	94
15[g]	**4a**	**5h**	4-CNC_6H_4	0	72	**7ah**	88[h]	96[c]
16[i]	**4a**	**5e**	PhC≡C	0	64	**7ae**	96[j]	91

[a] Yields of isolated products. [b] Determined by HPLC on a Daicel Chiralcel OD-H unless otherwise stated. [c] The absolute stereochemistry was not determined. [d] Determined by HPLC on a Daicel Chiralpak AD. [e] Performed on a 10-mmol scale with 0.0075 mol% of **3b**. [f] Turnover number (TON) = 12800. [g] Performed on a 10-mmol scale with 0.005 mol% of **3b**. [h] TON = 17600. [i] Performed on a 10-mmol scale with 0.002 mol% of **3b**. [j] TON = 48000. MOM = methoxymethyl.

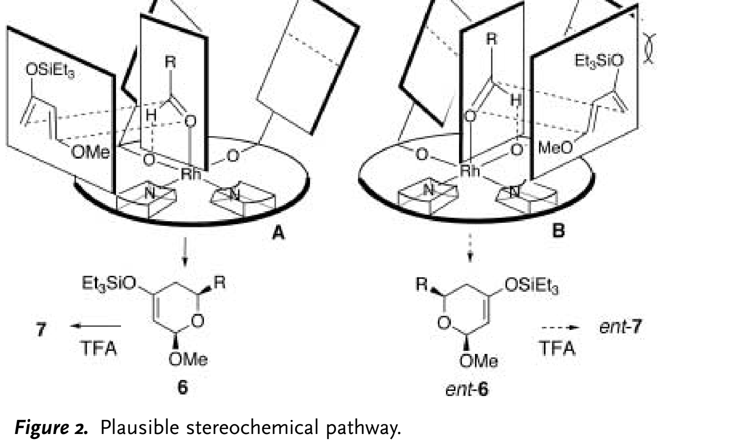


Figure 2. Plausible stereochemical pathway.

which interacts more severely with the aldehyde substituent R than the parent phthalimido group, also greatly favors the formation of a complex **A** as demonstrated by the reaction with the sterically less demanding phenylpropargylaldehyde. This model also explains the preference of dirhodium(II) carboxamidate catalysts **3a**,**b** over the carboxylate counterparts **2a–d** with similar C_2-symmetry-like conformations[18] in these reactions, in which four sets of formyl C−H···O hydrogen-bonding interactions are possible.

In conclusion, we have demonstrated that **3b** is an exceptionally effective Lewis acid catalyst for *endo* and enantioselective HDA reactions of a diverse range of aldehydes with Danishefsky-type dienes as well as with monooxygenated dienes, in which up to 99% *ee* and turnover numbers as high as 48000 have been achieved. The catalyst is readily synthesized, air-stable, and easily handled. The absolute stereochemical model proposed herein will provide a useful guide for the development of other classes of Lewis acid catalyzed enantioselective reactions.

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Keywords: aldehydes · asymmetric catalysis · cycloaddition · heterocycles · rhodium

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[16] CCDC 222738 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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