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Solvent Enhancement of Reaction Selectivity: A Unique Property of Cationic Chiral Dirhodium Carboxamidates

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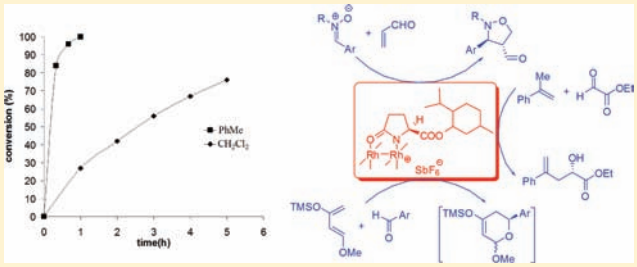
Supporting Information

ABSTRACT: 1,3-Dipolar cycloaddition reactions of nitrones with α,β-unsaturated aldehydes catalyzed by a cationic chiral dirhodium(II,III) carboxamidate with (*R*)-menthyl (S)-2-oxopyrrolidine-5-carboxylate ligands in toluene increase reaction rates, give optimum regioselectivities, and enhance stereoselectivities compared to the same reactions performed in traditionally used halocarbon solvents. Rate and enantioselectivity enhancements were also obtained in hetero-Diels−Alder and carbonylene reactions performed in toluene over those obtained in dichloromethane using the diastereomeric chiral cationic dirhodium(II,III) carboxamidate with (*S*)-menthyl (S)-2-oxopyrrolidine-5-carboxylate ligands. These enhancements are attributed to diminished or absent association of toluene with the catalyst which lessens the relative importance of the uncatalyzed background reaction, and they may also be a consequence of different coordination angles for aldehyde association with rhodium in the different solvent environments. Overall, the enhancement of reaction rates and selectivities with cationic chiral dirhodium(II,III) carboxamidates in toluene suggests broad applications for them in Lewis acid catalyzed reactions.



INTRODUCTION

Chiral dirhodium(II) carboxamidates are powerful catalysts for highly enantioselective metal-carbene transformations of diazoacetates.[1−3] When applied as Lewis acids, high enantiocontrol with high turnover numbers have been achieved with chiral dirhodium(II) carboxamidates in hetero-Diels−Alder reactions.[4] However, dirhodium(II) carboxamidates are weak Lewis acids, and attempts to effectively catalyze other Lewis acid catalyzed transformations have not been successful. Subsequent research has shown that cationic dirhodium(II,III) compounds, conveniently prepared by oxidation of dirhodium(II) carboxamidates with nitrosonium salts, possess enhanced Lewis acidity and improve catalyst selectivities for both hetero-Diels−Alder and nitrone dipolar cycloaddition reactions to methacrolein.[5] Still, regioselectivities in nitrone dipolar cycloaddition reactions with these catalysts have limited their broader applications.

The regio- and stereoselective synthesis of isoxazolines by 1,3-dipolar cycloaddition of nitrones with electron-deficient alkenes has been a challenge for asymmetric catalysis.[6] Their selective formation by cycloaddition is particularly attractive because isoxazolines are conveniently converted to β-amino acids and β-lactams, and they are precursors to γ-amino alcohols.[7] Enantioselective approaches involving transition metal catalysts have been successful with bidentate dipolarophiles (**1**) such as those derived from oxazolidinones that provide two-point binding to the chiral Lewis acid (Scheme 1),[6,8] but the structural requirements for bidentate dipolarophiles are limiting; and their applications are synthetically inefficient. Although, use of unsaturated aldehydes would be ideal, there have been few examples of highly selective nitrone 1,3-dipolar cycloaddition with α,β-unsaturated aldehydes that are monodentate dipolarophiles (**2**),[9] and only those using methacrolein have shown consistently high selectivities.

Dirhodium(II) carboxamidates are ineffective promoters of dipolar addition reactions of nitrones. They exhibit weak coordination with reacting carbonyl substrates,[4e] and catalytic reaction rates do not compete with the background reaction. However, we have recently discovered that the chiral dirhodium(II,III) carboxamidate catalyst $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**), which exhibits preferential binding to the aldehyde rather than nitrones, provides high enantioselectivities and modest regiocontrol in reactions with methacrolein.[5] Yet application of this same catalyst to acrolein in nitrone cycloaddition reactions exhibited limitations in both reaction rate and selectivity.[10] We now report that the low enantioselectivity that we initially observed in reactions with acrolein can be overcome and regioselectivity can be substantially improved by performing the cycloaddition reaction in toluene rather than in chlorocarbon solvents and that the resulting high regioselectivity and stereocontrol is broadly applicable to cycloaddition reactions between nitrones and α,β-unsaturated aldehydes but is unique to the chiral dirhodium carboxamidate catalysts. Furthermore, solvent enhanced reactivity and selectivity of $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**) and its diastereomeric form $[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ (**4**) makes possible effective applications to other Lewis acid

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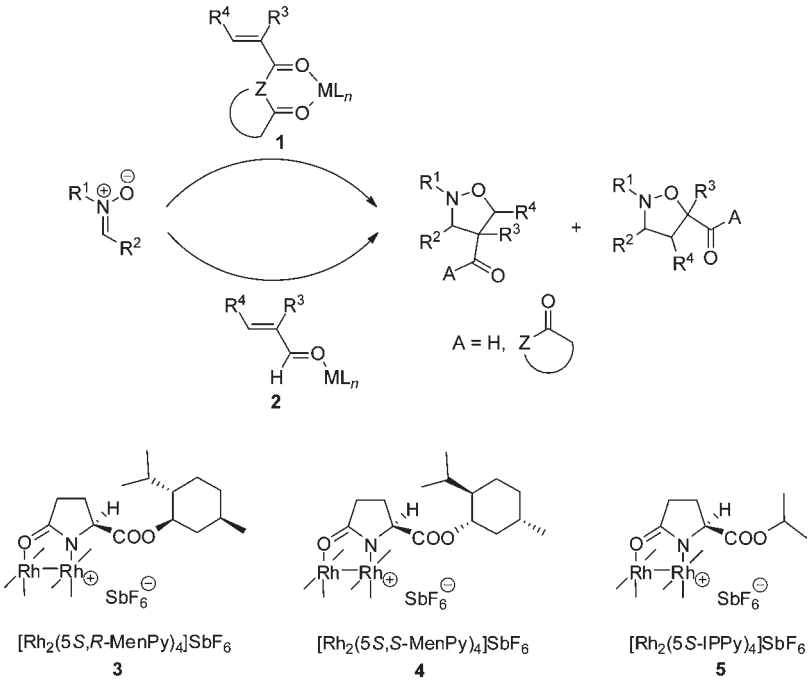
Scheme 1



catalyzed carbon−carbon bond forming reactions also with enhanced selectivities.

RESULTS AND DISCUSSION

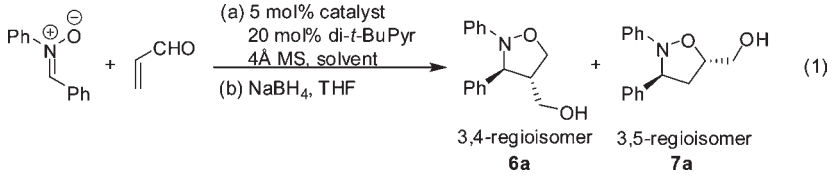
Nitrone cycloaddition reactions were performed by first preparing the $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**) catalyst from its dirhodium(II,II) precursor, $Rh_2(5S,R\text{-MenPy})_4$, by treatment with nitrosonium hexafluoroantimonate in the presence of 2,6-di-*tert*-butylpyridine and 4 Å molecular sieves in the reaction solvent and then sequentially adding the α,*β*-unsaturated aldehyde and nitrone. With 5 mol % of **3** in dichloromethane at 0 °C the cycloadducts of acrolein and *N*,α-diphenylnitrone were obtained after 5 h that, following borohydride reduction, were analyzed as a 70:30 ratio of 3,4-(**6a**):3,5-(**7a**) regioisomers in 73% isolated yield (eq 1). The diastereomeric ratio of 3,4-*endo* (**6a**-*endo*) to 3,4-*exo* product was 92:8, and **6a**-*endo* was obtained with 78% enantiomeric excess (ee). In an effort to improve selectivity by variation of the solvent, we discovered an exceptionally large influence of reaction solvent on reactivity and selectivity (Table 1). Changing the reaction solvent from dichloromethane to chloroform resulted in a slight increase in regio- and enantiocontrol, but percent conversion over the same reaction time decreased dramatically. Percent conversion increased in cyclohexane, and there was also a substantial increase in regio- and enantiocontrol. Suggestive of heteroatom influence on reactivity and selectivity, reactions performed in monohalobenzene solvents also exhibited enhanced percent conversion and regioselectivity in fluorobenzene compared to iodobenzene, with chlorobenzene in between. However, reactivity and selectivities were optimal in toluene. Similar rate and selectivity enhancements in toluene occurred with the diastereomeric $[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ (**4**), although enantioselectivity and regiocontrol for the production of **6a** were somewhat lower than those with $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**).

For comparison, published results from four catalytic systems (**8**,[9g] **9**,[9d] **10a**,[9b] and **10b**[9b]) that have been effectively employed for the same transformation are also reported in Table 1. The Kanemasa catalyst **8** provides good enantiocontrol, but cycloaddition occurs with poor regioselectivity.[9g] Maruoka has reported reactions of *N*-benzyl-α-phenylnitrone instead of *N*,α-diphenylnitrone for catalytic reactions with his *μ*-oxo bis-Ti(IV) oxide catalyst **9**, but yield, stereocontrol, and regioselectivity are high with the benzyl-substituted nitrone.[9d] Extensive studies by Carmona and co-workers with cationic Cp*Rh(III)L* (**10a**) and Cp*Ir(III)L* (**10b**) catalysts that possess a chiral bisphosphine ligand (L*) also show high regioselectivity in this dipolar cycloaddition reaction, but enantiocontrol is metal ion dependent with the Ir(III) catalyst exhibiting higher enantiocontrol than that with Rh(III).[9b,e,f] The reported reactions catalyzed by **8**−**10** were performed in dichloromethane at various reaction temperatures, and solvent effects with these systems were not available for comparison with results from the use of **3** or **4**.

Reported cycloaddition reactions catalyzed by **8**-**10** were performed at temperatures ranging from −10 to −40 °C, and we presume that they were optimized at the reported temperatures. However, with $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**) the influence of temperature on selectivity is negligible, although the rate of reaction is lower at −20 °C than at 0 °C. One can conclude from these comparative data that catalysis of nitrone cycloaddition to acrolein by **3** in toluene provides selectivities that are at least as good as the best of the alternatives and that reactions catalyzed by **3** occur at a faster rate under milder conditions.

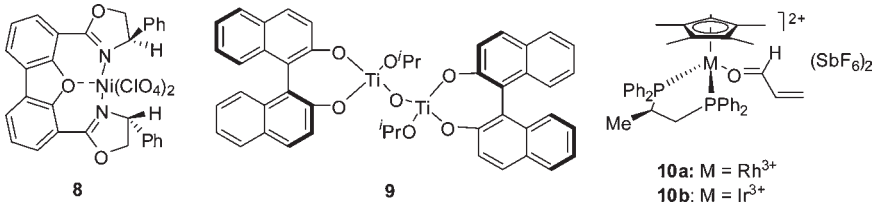
To better understand the effect of solvent in catalytic reactions of *N*,α-diphenylnitrone with acrolein catalyzed by **3**, we followed percent conversion of nitrone as a function of time. The rates of reaction in the various solvents decrease from toluene to iodobenzene (Figure 1), and they are significantly less in dichloromethane. Even two equivalents of iodobenzene, based on acrolein, in toluene produce a 1−2% decrease in regioselectivity

Table 1. Influence of Solvent on Regioselectivity and Stereocontrol in Chiral Dirhodium(II,III) Carboxamidate Catalyzed Reactions of *N*,α-Diphenylnitrone with Acrolein and Comparison of Selectivities with Reported Results Using Alternative Catalysts



catalyst/mol %	solvent	*T* (°C)	*t* (h)	yield (%)[a]	**6a**:**7a**[b]	dr of **6a**[b]	ee of **6a**-*endo* (%)[c]
3/5	CH_2Cl_2	0	5	73	70:30	92:8	78
3/5	$CHCl_3$	0	5	40	75:25	91:9	83
3/5	*c*-C_6H_{12}	0	2	93	88:12	93:7	91
3/5	PhI	0	2	73	83:17	94:6	90
3/5	PhCl	0	2	91	83:17	93:7	90
3/5	PhF	0	2	92	91:9	94:6	92
3/5	PhMe	0	1	94	96:4	94:6	94
3/5	PhMe	−20	4	93	96:4	94:6	93
4/5	CH_2Cl_2	0	5	55	74:26	91:9	71
4/5	PhMe	0	1	94	94:6	94:6	90
5/5	CH_2Cl_2	0	5	67	67:33	92:8	27
5/5	PhMe	0	2	92	88:12	93:7	76
8[d]/10	CH_2Cl_2	−10	72	75	26:74	95:5	91
9[e]/10	CH_2Cl_2	−40	24	94	>99:1	>97:3	93
10a[f]/5	CH_2Cl_2	−25	16	(100)[g]	>99:1[h]	>99:1[h]	78
10b[f]/5	CH_2Cl_2	−25	16	(100)[g]	>99:1[h]	>99:1[h]	90

[a] Isolated product yield following chromatography. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis (OD-H column). [d] Reference 9g. [e] Reference 9d, *N*-benzyl-α-phenylnitrone was used instead of *N*,α-diphenylnitrone in this case. [f] Reference 9b, a 7-fold molar excess of acrolein was used. [g] Percent conversion based on ^{1}H NMR analysis; isolated product yield not given. [h] Only the **6a**-*endo* cycloaddition product was reported.



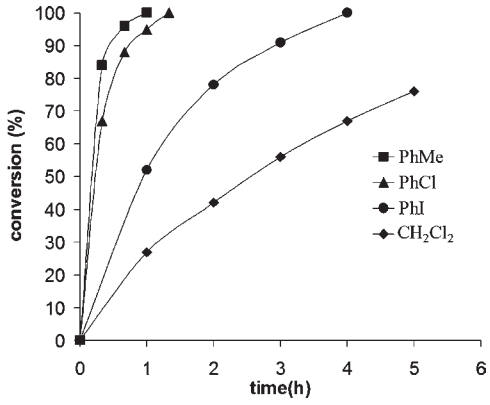


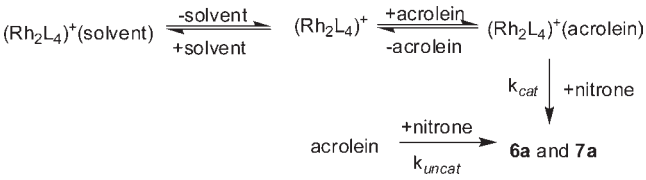
Figure 1. Plot of conversion (%) as a function of time for the standard reaction of *N*,α-diphenylnitrone with acrolein catalyzed by [Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6 in PhMe, PhCl, PhI, and CH_2Cl_2 at 0 °C.

and enantioselectivity. Use of acetonitrile as the solvent completely terminates the catalytic cycloaddition reaction, presumably because of strong axial coordination on **3** by acetonitrile.[11]

Solvent influences on reaction rates and selectivities in 1,3-dipolar cycloaddition reactions have been reviewed,[12] and in at least one case solvents of low polarity have been predicted to enhance regioselectivity based on computational analyses of activation energies.[13] However, solvent effects in catalytic reactions with transition metal compounds have been attributed to many causes, including solvent coordination to transition metals[14] and stabilization or destabilization of transition state by solvent medium.[15] The evidence presented in Figure 1 strongly suggests that the rate inhibition that is found in this dipolar addition reaction catalyzed by **3** is due to competitive association of the halocarbon solvent with the dirhodium(II,III) catalyst at an axial coordinating site thereby inhibiting association with acrolein.

There is no difference in the rates of the background reactions of *N*,α-diphenylnitrone with acrolein in dichloromethane and toluene. After 24 h of reaction at room temperature, the background reaction in both solvents resulted in 78% conversions to cycloaddition products with a 16:84 ratio of regioisomers **6a**:**7a** and a diastereomeric ratio of 3,4-*endo*:3,4-*exo* of 74:26, showing no dependence on solvent selection. Since the solvent does not influence either rate or selectivity in the background reaction, the

Scheme 2



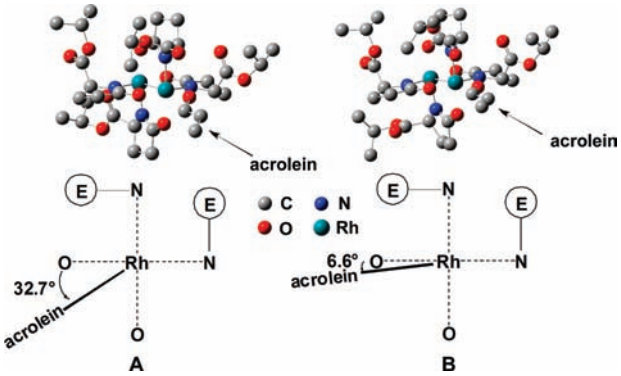
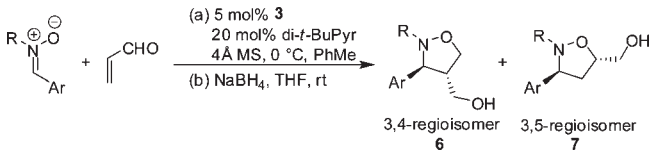


Figure 2. Energy minimized geometries of acrolein-Rh_2(5*S*-IPPy)$_4^+$ complex in dichloromethane (A) and toluene (B) obtained from DFT calculation (B3LYP). Hydrogens are omitted for clarity.

solvent effect in the Rh(II)/Rh(III) catalyzed reaction must come from the association between α,β-unsaturated aldehyde and the Rh(II)/Rh(III) catalyst. The influence on reaction rate arises from solvent association at the axial positions of the dirhodium catalyst (Scheme 2). Competition between solvent and acrolein for the catalytically active site inhibits the rate of catalytic conversion of acrolein to its dipolar cycloaddition products and increases the importance of the uncatalyzed pathway to these same products. Since the uncatalyzed reaction produces racemic **6a** and favors regioisomer **7a** over **6a**, the influence of solvent on selectivity can also be appreciated from the competition depicted in Scheme 2.

Although Scheme 2 explains reactivity and selectivity qualitatively and may be responsible for most of the selectivity enhancement, the effects of solvent on reactivity, regioselectivity, and enantioselectivity are variable (for example, the use of chloroform produces a significant decrease in reactivity, but a slight increase in selectivity, compared to dichloromethane). In a search for other contributing factors to selectivity in this dipolar cycloaddition reaction, DFT calculations were performed on the complex of acrolein with the isopropyl analog of **3** and **4**, Rh_2(5*S*-IPPy)$_4^+$(**5**) whose solvent-dependent selectivities are recorded in Table 1. The B3LYP functional with the LANL2DZ basis set and the CPCM solvation model was applied in this calculation. In the energy minimized geometries, which were calculated in the solvent environment of dichloromethane and toluene separately, acrolein coordination to Rh adopted different dihedral angles relative to catalyst ligands. In dichloromethane (**A** in Figure 2), the dihedral angle involving the atoms O—Rh(catalyst)—O═C(acrolein) was 32.7°, whereas in toluene (**B** in Figure 2) the same angle decreased to 6.6°. Considering that enantiocontrol occurs by selective shielding of the top and bottom sides of acrolein by two esters of the chiral pyrrolidinone ligands on each rhodium face (represented as E in Figure 2), the greater shielding of one side of acrolein in toluene suggests greater facial differentiation of acrolein. Regiocontrol for **6a** in this 1,3-dipolar cycloaddition reaction is dependent on the extent of the uncatalyzed reaction (Scheme 2), on the Lewis acidity of the catalyst,[9a,g,16] and, potentially, on stereoelectronic factors emanating from the catalyst ligands (note the conformational differences in ligands in **A** and **B** of Figure 2).

Table 2. Effect of Nitrone Substituents on Regioselectivity and Enantiocontrol in Cycloaddition Reactions with Acrolein Catalyzed by [Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6 (3)



entry	R	Ar	*t* (h)	yield (%)[a]	**6**:**7**[b]	dr of **6**[b]	ee of **6**-*endo* (%)[c]
1	Ph	Ph	1	94	96:4	94:6	94
2	Ph	4-$MeOC_6H_4$	1	92	>99:1	95:5	98
3	Ph	4-MeC_6H_4	1	94	99:1	94:6	96
4	Ph	4-ClC_6H_4	3	86	95:5	92:8	96
5	Ph	4-$CF_3C_6H_4$	3	90	87:13	94:6	96
6	Ph	2-furyl	4	89	>99:1	88:12	90
7	Ph	2-naphthyl	2	90	99:1	94:6	97
8	Bn	Ph	3	91	>99:1	98:2	95 (*S*,*S*)[d]

[a] Isolated product yield. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis (OD-H column). [d] The absolute configuration was determined by comparison with literature.[9d]

The generality of the high selectivity observed for nitrone cycloaddition to acrolein catalyzed by **3** is suggested by the data in Table 2 for reactions with various substituted nitrones. High yields, excellent regiocontrol, and enantioselectivities equal to or greater than 90% characterize the cycloaddition reactions catalyzed by [Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6 (**3**). As was previously established by us with methacrolein,[5] and confirmed by Kündig,[9a] electron withdrawing groups in Ar decrease regioselectivity without changing stereoselectivity; but for reactions performed in toluene, even nitrones having electron-withdrawing groups in Ar such as trifluoromethyl (entry 5) provide high regiocontrol for the 3,4-cycloaddition product (**6**). And in comparing results from the use of the *N*-benzyl nitrone in Table 2 (entry 8) at 0 °C with the previously reported outcome of this same reaction with Maruoka's *μ*-oxo bis-Ti(IV) oxide catalyst at −40 °C (**9** in Table 1),[9d] the efficiency and effectiveness of [Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6 as the catalyst is pronounced.

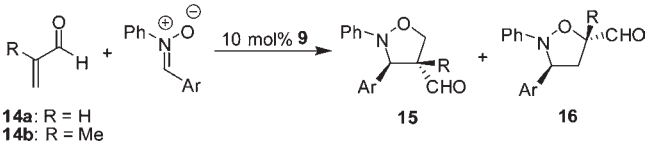
The comparative advantages of the use of **3** for dipolar cycloadditions to methacrolein (**11a**) and *trans*-crotonaldehyde (**11b**) are reported in Table 3. Solvent enhancement of regioselectivity is evident in these results. With *N*-phenyl-α-anisylnitrone, for example, regioselectivity for **12**:**13** increases from a modest 70:30 to 97:3 upon changing the solvent from dichloromethane to toluene. In addition, enantioselectivities for **12** that were already high from reactions catalyzed by **3** performed in dichloromethane are further enhanced with reactions performed in toluene. Enantiocontrol in catalytic formation of the 3,4-*endo* cycloadduct obtained from these substrates using **3** is at the highest level reported compared to the previously reported

examples.[9] The advantages of the cationic catalyst $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**) are evident.

As noted earlier, results from the use of catalysts **8**−**10** have been reported in dichloromethane but not toluene. Is the solvent enhancement observed with **3** general for other Lewis acids used for nitrone cycloaddition reactions or is it confined to this chiral dirhodium(II,III) carboxamidate? To answer this question we have investigated the effect of solvent with Maruoka's μ-oxo bis-Ti(IV) oxide (**9**). Reactions in dichloromethane and toluene result in a similar degree of selectivity, and no rate enhancement was observed (Table 4). In his earlier communication, Maruoka investigated the reactions of *N*-benzyl-α-phenylnitrones, but not *N*,α-diphenylnitrones, and he reported formation of only the 3,4-*endo* isomer in high yield and enantioselectivity.[9d] However, enantioselectivity and diastereoselectivity in reactions with acrolein are lower with *N*-phenyl substituted nitrones, and with methacrolein regioselectivity is very low. Maruoka also pointed out that a sterically encumbered *N*-substituent on the nitrone was essential for high stereocontrol with his μ-oxo bis-Ti(IV) oxide catalyst, and *N*-diphenylmethyl-substituted nitrones were used in place of the *N*-benzyl analogues when these cycloaddition reactions were carried out with methacrolein.[9c] Interestingly, in reactions with methacrolein catalyzed by Maruoka's μ-oxo bis-Ti(IV) oxide catalyst a higher % ee was obtained for the 3,5-*endo* product than for its 3,4-*endo* regioisomer, which is the reverse of what is observed with $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**). However, no similar solvent effect was observed.

Solvent enhancement of reaction selectivities was further investigated in two other Lewis acid catalyzed reactions: the hetero-Diels−Alder reaction[17] and the carbonyl-ene reaction.[18] Hetero-Diels−Alder reactions between *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (the Danishefsky diene, **17**) and aldehydes have been successfully carried out with Rh(II)Rh(III) catalysts.[4a,5] *p*-Nitrobenzaldehyde is chosen as the substrate for the investigation of the solvent influence (Table 5). With 5 mol % $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**), reactions of *p*-nitrobenzaldehyde with **17** in both solvents at room temperature are relatively slow, they do not exhibit rate enhancement by changing the solvent from dichloromethane to toluene, but enhancement in enantioselectivity is evident. However, the diastereomeric $[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ (**4**) noticeably improved reaction rates and exhibited substantial rate enhancement by changing the reaction solvent to toluene. In this latter case there was not a significant solvent-induced change in enantioselectivity.

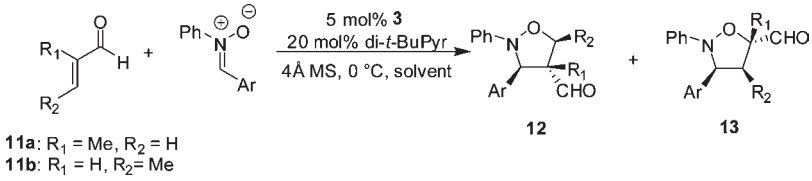
Table 4. μ-Oxo-bis-Ti(IV) Oxide (9) Catalyzed 1,3-dipolar Cycloaddition reactions[a]



enal	Ar	solvent	t (h)	yield (%)[b]	15:16[c]	dr[c]	ee% (15-*endo*/16-*endo*)[d]
14a	Ph	CH_2Cl_2	1	95	99:1	86:14	87/-
14a	Ph	PhMe	1	95	99:1	86:14	82/-
14b	Ph	CH_2Cl_2	2	88	56:44	>99:1	81/98
14b	Ph	PhMe	2	89	52:48	>99:1	80/98
14b	4-MeOPh	CH_2Cl_2	2	70	82:18	>99:1	77/95
14b	4-CF_3Ph	CH_2Cl_2	3	92	40:60	>99:1	67/95

[a] The reactions were carried out with 0.5 mmol nitrone, 0.8 mmol enal, and 0.05 mmol μ-oxo bis-Ti(IV) oxide; reactions with **14a** were carried out at −20 °C; reactions with **14b** were carried out at 0 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy; complete diastereoselectivity for *endo* product was observed for cycloadditions with **14b**. [d] Determined by ^{1}H NMR after formation of diastereomeric imines with (*R*)-(+)-α-methylbenzylamine or by HPLC (OD-H column) after borohydride reduction.

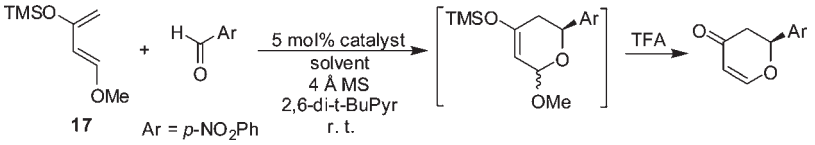
Table 3. $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (3)-Catalyzed Asymmetric Nitrone Cycloaddition Reactions with Methacrolein (11a) and *trans*-Crotonaldehyde (11b)



entry	enal	Ar	solvent	time (h)	yield[a] (%)	12:13[b]	ee% (12-*endo*/13-*endo*)[c]
1	**11a**	4-MeOPh	CH_2Cl_2	5	40	70:30	96/63
2	**11a**	4-MeOPh	PhMe	5	91	97:3	99/−
3	**11a**	Ph	CH_2Cl_2	5	42	34:66	94/66
4	**11a**	Ph	PhMe	5	95	79:21	98/56
5	**11a**	4-MePh	PhMe	4	96	89:11	97/60
6	**11a**	4-ClPh	PhMe	20	82	53:47	99/72
7	**11a**	4-CF_3Ph	PhMe	20	96	30:70	96/62
8	**11a**	2-furyl	PhMe	20	91	79:21	98/54
9	**11a**	2-naphthyl	PhMe	20	96	70:30	95/52
10	**11b**	Ph	PhMe	24	78[d]	>99:1	95[e]/−

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy; complete diastereoselectivities for *endo* products were observed for these cycloaddition reactions. [c] Determined by ^{1}H NMR after formation of diastereomeric imines with (*R*)-(+)-α-methylbenzylamine. [d] Borohydride reduction was carried out in this case; Isolated yield of the product after reduction. [e] Determined by high-performance liquid chromatography (HPLC) analysis (OD-H column).

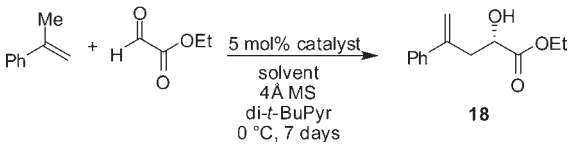
Table 5. Solvent Influence on the Asymmetric Hetero-Diels−Alder Reaction of *p*-Nitrobenzaldehyde with the Danishefsky Diene Catalyzed by Rh(II)Rh(III) Catalysts[a]



catalyst	solvent	*t* (h)	yield (%)[b]	ee%[c]
$[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**)	CH_2Cl_2	24	68	83
$[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**)	PhMe	24	52	91
$[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ (**4**)	CH_2Cl_2	24	86	91
$[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ (**4**)	PhMe	2	97	94

[a] The reactions were performed with 0.5 mmol *p*-nitrobenzaldehyde, 0.6 mmol Danishefsky diene, 0.025 mmol catalyst, 0.1 mmol 2,6-di-*t*-BuPyr, and 300 mg of 4 Å MS in 1.5 mL solvent at room temperature. [b] Isolated yield. [c] Determined by HPLC (OD-H column); The absolute configuration of the product was determined to be *S* by comparison with literature.[4d,f]

Table 6. Solvent Influence on the Asymmetric Carbonyl-ene Reaction of Ethyl Glyoxylate with α-Methylstyrene Catalyzed by Rh(II)Rh(III) Catalysts[a]



catalyst	solvent	yield (%)[b]	ee%[c]
$[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**)	CH_2Cl_2	60	38
$[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**)	PhMe	37	70
$[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ (**4**)	CH_2Cl_2	52	63
$[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ (**4**)	PhMe	90	94

[a] The reactions were performed with 2.5 mmol α-methylstyrene, 0.5 mmol ethyl glyoxylate, 0.025 mmol catalyst, 0.1 mmol 2,6-di-*t*-BuPyr, and 300 mg of 4 Å MS in 1.0 mL solvent at 0 °C. [b] Isolated yield. [c] Determined by HPLC (AD-H column). The absolute configuration of the product was determined to be *S* by comparison with literature.[19d]

The carbonyl-ene reaction is one of the most convenient methods for carbon−carbon bond formations, and the resulting homoallylic alcohols can be further transformed into more functionalized products by taking advantage of the carbon−carbon double bond.[18] Substantial effort has been directed toward developing catalytic enantioselective variants with Lewis acid catalysis.[18,19] In our survey of Lewis acid catalyzed reactions with Rh(II)/Rh(III) carboxamidates the carbonyl-ene reaction of ethyl glyoxylate with α-methylstyrene using 5 mol % $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**) in dichloromethane at 0 °C was found to produce the homoallylic alcohol **18** in 60% yield and with 38% ee (Table 6). Similar to the results from the hetero-Diels−Alder reactions (Table 5), changing the solvent to toluene resulted into a lower yield but higher ee. However, with $[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ (**4**) under the same conditions, the reaction in dichloromethane produced **18** in 52% yield and 63% ee, and using toluene as the reaction solvent improved the yield to 90% and the enantiomeric excess to 94%. From this limited study, $[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ (**4**) exhibits higher rates and selectivities for reactions occurring directly with a carbonyl group, whereas $[Rh_2(5S,R\text{-MenPy})_4]SbF_6$ (**3**) gives higher selectivities for reactions that take place at the more remote α,β-carbons of unsaturated aldehydes.

CONCLUSIONS

We have discovered solvent-dependent rate and selectivity enhancements with chiral cationic dirhodium(II,III) carboxamidates in nitrone dipolar cycloaddition reactions, hetero-Diels−Alder reactions, and carbonyl-ene reactions. With 1,3-dipolar cycloaddition reactions of nitrones with α,β-unsaturated aldehydes use of $Rh_2(5S,R\text{-MenPy})_4SbF_6$ (**3**) in toluene provided rate enhancements as well as significant improvements in regioselectivities and enantioselectivities over those obtained in dichloromethane. Rate and enantioselectivity enhancements were obtained with $[Rh_2(5S,S\text{-MenPy})_4]SbF_6$ (**4**) in hetero-Diels−Alder and carbonyl-ene reactions over those obtained in dichloromethane. These enhancements are attributed to diminished or absent association of toluene with the catalyst which lessens the relative importance of the uncatalyzed background reaction. Different coordination angles for aldehyde association with rhodium in the different solvent environments may also contribute to enhanced enantiocontrol in toluene. Further research is underway to uncover the generality of these rate and selectivity improvements.

EXPERIMENTAL SECTION

Materials. $Rh_2(5S,R\text{-MenPy})_4$,[5] $Rh_2(5S\text{-IPPy})_4$,[20] *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene,[21] and nitrones[22] were prepared according to the literature procedures. Acrolein, *trans*-crotonaldehyde, methacrolein, ethyl glyoxylate, and α-methylstyrene were obtained from commercial sources and freshly distilled before use. Solvents were used after distillation. All the other chemicals were obtained from commercial sources and used without further purification.

Synthesis of (*S*)-[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl] 2-Oxopyrrolidine-5-carboxylate. A flask was charged with L-pyroglutamic acid (1.29 g, 10 mmol), (+)-menthol (1.56 g, 10 mmol), and 4-dimethylaminopyridine (0.24 g, 2 mmol) and purged with nitrogen. Dry CH_2Cl_2 (20 mL) was added, and the mixture was cooled to 0 °C. A solution of *N*,*N*′-dicyclohexylcarbodiimide (2.27 g, 11 mmol) in CH_2Cl_2 (20 mL) was added to the reaction mixture over a period of 30 min, and then the reaction mixture was stirred at room temperature for 20 h. The white solid was removed by filtration. The solution was evaporated to dryness under reduced pressure, and the residue was dissolved in ethyl

acetate (100 mL) and washed with 1 M HCl (20 mL), 5% $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The resulting solid was purified by column chromatography (ethyl acetate:hexane = 5:2) to yield a white solid product (2.30 g, 86% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.44 (s, 1H, NH), 4.74 (dt, 1H, J = 4.4, 10.9 Hz), 4.23 (dd, 1H, J = 5.4, 8.6 Hz), 2.55−2.45 (m, 1H), 2.40−2.32 (comp, 2H), 2.22−2.16 (m, 1H), 2.02−1.96 (m, 1H), 1.85−1.80 (m, 1H), 1.72−1.66 (comp, 2H), 1.55−1.39 (comp, 2H), 1.10−0.85 (comp, 9H), 0.76 (d, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.68, 171.47, 75.73, 55.61, 46.87, 40.66, 34.05, 31.33, 29.28, 26.26, 24.97, 23.21, 21.89, 20.71, 16.08. $[\alpha]^{20}_D$ = +59.3 (c 0.96, CH_2Cl_2). HRMS (ESI) calculated for $C_{15}H_{26}NO_3$, m/z 268.1907 ($[M + H]^+$); found, m/z 268.1912.

Synthesis of Dirhodium(II) Tetrakis{(*S*)-[(1*S*,2*R*,5*S*)-2-isopropyl-5-methyl-cyclohexyl] 2-Oxopyrrolidine-5-carboxylate}, Rh_2(5*S*,*S*-MenPy)$_4$. The previously reported standard procedure was followed.[20] Dirhodium(II) acetate (330 mg, 0.747 mmol), (*S*)-[(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl] 2-oxopyrrolidine-5-carboxylate (2.1 g, 7.85 mmol) and chlorobenzene (20 mL) were mixed in a flask fitted with Soxhlet extraction apparatus into which was placed a cellulose thimble containing 2:1 Na_2CO_3/sand. The resulting mixture was heated at vigorous reflux for 20 h, at which time HPLC analysis (Microsorb-MV 100−5 CN column, 2% MeCN in MeOH, flow 1.0 mL/min) showed the reaction to be complete. After cooling to room temperature, the solvent was removed under reduced pressure, and the resulting blue oil was chromatographed on BAKERBOND-CN silica (40 μm Prep LC packing) eluting with MeOH. The first brown band was the excess ligand, and then using 1% MeCN in MeOH to wash off the desired catalyst band which had a red color. The solvent of the collected catalyst band was removed under reduced pressure and the resulting blue solid material was heated at 120 °C under high vacuum for 2 h. The catalyst was finally obtained as a green powder (696 mg, 73% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.67−4.59 (comp, 4H), 4.28−4.24 (comp, 2H), 3.94−3.89 (comp, 2H), 2.85−0.71 (comp, 88H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 188.58, 187.44, 174.40, 173.89, 74.44, 74.13, 66.41, 47.29, 47.24, 41.56, 40.88, 34.55, 34.26, 31.49, 31.39, 31.32, 26.68, 26.60, 26.22, 23.54, 23.36, 22.18, 20.77, 20.72, 16.29. 16.13 (missing 4 carbons due to overlapping signals). $[\alpha]^{20}_D$ = −113.85 (c 0.130, i-PrOH). HRMS (ESI) calculated for $C_{60}H_{97}N_4O_{12}Rh_2$, m/z 1271.5208 ($[M + H]^+$); found, m/z 1271.5207.

General Procedure for the Asymmetric 1,3-Dipolar Cycloaddition Reactions of Nitrones with α,β-Unsaturated Aldehydes Catalyzed by [Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6. A 10-mL Schlenk flask charged with a magnetic stir bar and 4-Å Molecular Sieves (300 mg) was placed under high vacuum and heated by Bunsen burner to dryness. After cooling to room temperature, Rh_2(5*S*,*R*-MenPy)$_4$ (33.8 mg, 0.026 mmol), 2,6-di-*tert*-butylpyridine (22 μL, 0.10 mmol), and toluene (1.0 mL) were added under the flow of N_2. The resulting green solution was stirred for 10 min before $NOSbF_6$ (6.6 mg, 0.025 mmol) was added. The solution was allowed to stir for additional 30 min, during which time the color gradually turned from green to deep red. Freshly distilled acrolein (54 μL, 0.80 mmol) was added via a microsyringe to the flask that was then placed in an ice bath, and the mixture was stirred for 10 min. The nitrone (0.50 mmol) in toluene (1.5 mL) was added dropwise (gentle heating aids dissolution of nitrones in toluene; *N*-phenyl-α-(4-chlorophenyl)nitrone and *N*-phenyl-α-(4-trifluoromethylphenyl)nitrone were added as solids because of their relatively poor solubility, followed by the addition of 1.5 mL toluene). The solution was stirred at 0 °C until the completion of the reaction. The entire reaction mixture was then loaded on a short silica column and eluted with CH_2Cl_2 to remove the catalyst and 4-Å molecular sieves. The collected solution was concentrated, and regioselectivity and diastereoselectivity were determined by ^{1}H NMR analyses. The aldehyde product mixture was then dissolved in THF (5.0 mL) and treated with $NaBH_4$ (56.7 mg, 1.50 mmol) at room temperature for 30 min. The mixture was then poured into a saturated solution of NH_4Cl (aq) (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated. The resulting oil was purified by flash chromatography (hexane:ethyl acetate = 2:1) to obtain the final product that was then analyzed for enantiomeric excess by HPLC analysis.

General Procedure for the Asymmetric 1,3-Dipolar Cycloaddition Reactions of Nitrones with α,β-Unsaturated Aldehydes Catalyzed by the μ-Oxo Bis-Ti(IV) Oxide Catalyst.[9c,d] To a stirred mixture of Ag_2O (12 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added 1.0 M hexane solution of ClTi(O*i*-Pr)$_3$ (100 μL, 0.10 mmol) at room temperature. After stirring for 5 h at room temperature, a solution of (*S*)-BINOL (28.6 mg, 0.10 mmol) in CH_2Cl_2 (0.7 mL) was added to the mixture, which was then stirred for 2 h at room temperature to afford the dark orange solution of chiral μ-oxo bis-Ti(IV) oxide. The solution was cooled to −20 °C (or to 0 °C for methacrolein). To the catalyst solution was added acrolein (54 μL, 0.80 mmol) and was followed by the nitrone in CH_2Cl_2 (1.3 mL). The resulting mixture was stirred at −20 °C until the completion of the reaction. The workup was identical to the procedure described for [Rh_2(5*S*,*R*-MenPy)$_4$]SbF_6.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, characterization of all new compounds, and computational details. This material is free of charge via the Internet at http://pubs.acs.org.

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(10) Compared with methacrolein which gave enantioselectivities of >90% with the use of **3**,[5] enantioselectivities that were <80% were obtained with acrolein using the same catalyst.

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