Chiral Dirhodium(II) Carboxamidate-Catalyzed [2+2]-Cycloaddition of TMS-Ketene and Ethyl Glyoxylate

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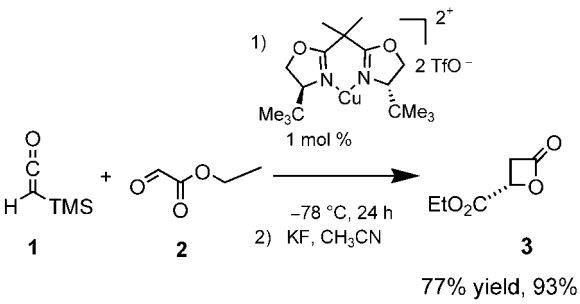
Abstract: The [2+2]-cycloaddition reaction between ethyl glyoxylate and trimethylsilylketene is reported. Enantiomeric excesses up to 83% have been achieved with the use of only 1.0 mol % of a previously unreported chiral imidazolidinone-ligated dirhodium(II) carboxamidate catalyst. An extensive survey of chiral catalysts has shown that enantiocontrol for cycloaddition increases as the steric bulk of the ligand is increased. However, enantioselectivity is increased to 99% ee by the addition of 10 mol % of quinine as a co-catalyst with a chiral dirhodium(II) azetidinone-ligated catalyst, and there is a significant decrease in reaction time.

Keywords: [2+2]-cycloaddition; dirhodium(II) carboxamidates; ethyl glyoxylate; Lewis acid catalysis; trimethylsilylketene

Introduction

Studies from this laboratory have shown that chiral dirhodium(II) carboxamidates are weak Lewis acids that can be used as asymmetric catalysts for the hetero-Diels–Alder reaction,[1] and recent results from Hashimoto have complimented this development.[2] High enantioselectivities (>90%) have been obtained in reactions of aromatic aldehydes with Danishefsky's diene, and these reactions occur with turnover numbers (TON) that exceed 10,000. The mechanism is reported to occur through a concerted [4+2]-cycloaddition, rather than by a Mukiyama aldol pathway.[3] In our efforts to broaden the applicability of these catalysts in Lewis acid-catalyzed reactions we have investigated the [2+2]-cycloaddition reaction between ethyl glyoxylate (**2**) and trimethylsilylketene (**1**) [Eq. (1)] that was recently shown by Evans to be effectively promoted with high selectivity through catalysis by copper(II) triflate ligated to chiral bis-oxazoline.[4]

Unlike the copper(II) catalysts that are capable of bidentate coordination with substrate,[5] however, dirhodium(II) catalysts possess only one available coordination site per rhodium.[6] This was thought to be a controlling factor in reactions with glyoxylates and that, with chiral dirhodium(II) catalysis, use of these substrates could yield product with low enantiocontrol. We report, however, that dirhodium(II) carboxamidates are effective catalysts for this cycloaddition reaction, operating with TON greater than 100 and selectivities up to 83% ee in reactions that occur at room temperature.



(1)

Results and Discussion

Our study began with the investigation of the Lewis acid-catalyzed [2+2]-cycloaddition between trimethylsilylketene and ethyl glyoxylate utilizing a broad selection of chiral dirhodium(II) carboxamidate catalysts (**5–8**) as the Lewis acid. These catalysts were selected to be representative of the four classes of carboxamidate ligated dirhodium(II) compounds that we have developed – those with 2-oxapyrrolidine-5-carboxylate (**4**),[7] 2-oxaoxazolidine-4-carboxylate (**5**),[8] 2-oxaazetidine-4-carboxylate[9] (**6**), and 2-oxaimidazolidine-4-car-

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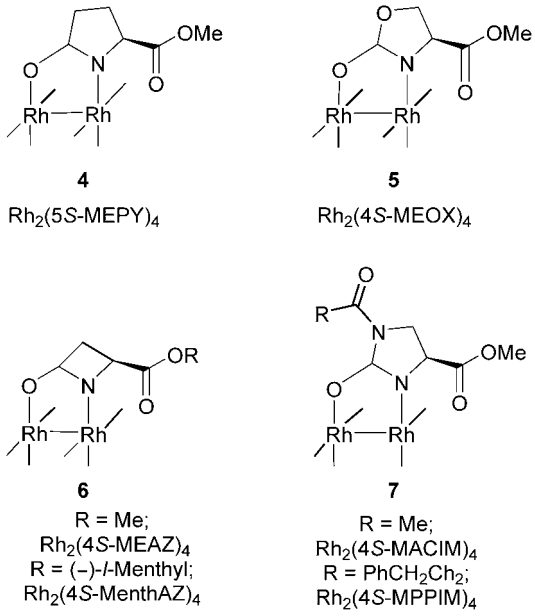


boxylate[10] (**7**) ligands – but, as seen in Table 1, very low selectivity was achieved.

All reactions were slow at room temperature, taking up to 3 days to reach completion; but in most cases good to excellent product yields were achieved. The *cis*:*trans* ratio of the cycloaddition product **9** was determined by integration of the ^{1}H NMR resonance of H-4 prior to desilylation [*cis* (4.95 ppm, d, $J=7.2$ Hz); *trans* (4.57 ppm, d, $J=4.5$ Hz)].

Since electronic differences in these dirhodium(II) catalysts[11] do not have a significant influence on enantiocontrol (entries 2–4 and 6 and7), we looked to steric influences from ligand attachments to increase selectivity. Thus, when the pendant methyl ester of the 2-oxaazetidine-4-carboxylate ligand was replaced by the much bulkier *l*-menthyl ester, 4→5, a nearly five-fold increase in enantioselectivity was observed. However, when the *d*-menthyl ester derivative was used, no enantiocontrol was observed, likely the result of a mismatch between chiral centers in the ligand that frustrates asymmetric induction in the cycloaddition process. In the case of the imidizolidinone catalyst system (entry 7→8), however, only a modest increase (13→18% ee) was observed by use of the *N*-(3-phenylpropanoyl) group in place of the much smaller acetyl group. Based on these observations we have incorporated a (−)-*l*-menthyl group into the ester side chain of an imidizolidinone catalyst in hope of increasing enantiocontrol of the [2+2]-cycloaddition reaction.

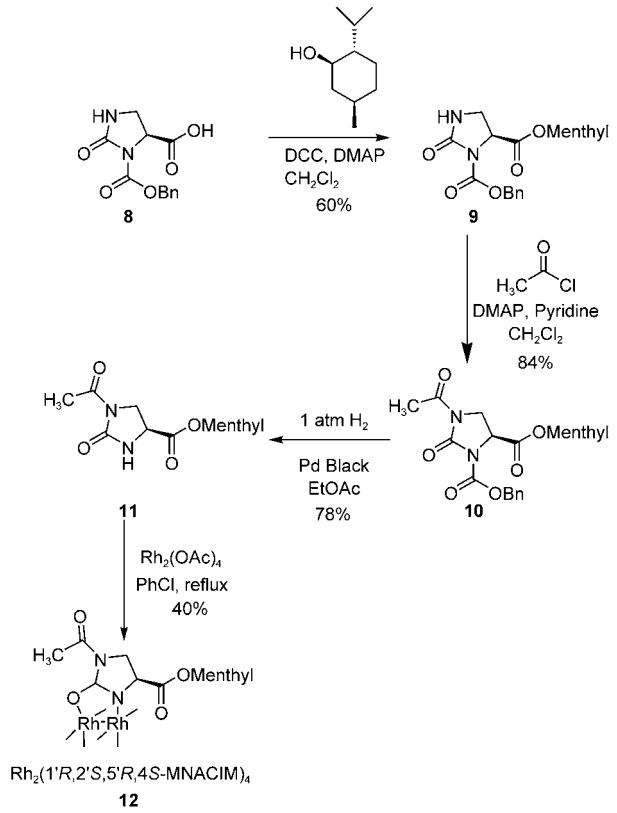
The synthesis of compound **12** began with the previously reported 4(*S*)-imidazolidinonecarboxylic acid **8**, which was esterified with (−)-*l*-menthol through a DCC coupling to generate **9** as a white powder in 60% yield (Scheme 1).[8] The *N*-acyl chain was then attached using acetyl chloride in the presence of DMAP and pyridine to afford **10** in an 84% yield. The carbobenzyloxy-protected ligand was subjected to hydrogenolysis with palladium black in ethyl acetate to afford ligand **11** in 78% yield after recrystallization. Catalyst **12** was successfully generated through standard ligand exchange reaction with rhodium acetate in refluxing chlorobenzene[10] to yield a dark red powder that was subsequently recrystallized from boiling acetonitrile to afford compound **12** as red crystals in 40% yield. The crystals were of sufficient quality for an X-ray crystallographic structural determination. Table 2 reports selected bond lengths and bond angles of **12**.

With ethyl glyoxylate and TMS-ketene under the same conditions as reported for the reactions in Table 1, use of this catalyst formed β-lactone **3** in 90% yield after three days at room temperature. While Rh_2(*S,R*-MANICM)$_4$ (**12**) possesses a rhodium-rhodium bond length (2.46 Å) and bond angles similar to catalyst **7** [Rh_2(4*S*-MPPIM)$_4$], it displayed much improved enantiocontrol (83% ee). We believe that the steric crowding of the menthyl esters around the active rhodium site plays an important role in enhancing enantiocontrol.[12]

Table 1. Dirhodium(II) catalyst screening for [2+2]-cycloaddition in Eq. (1).[a]

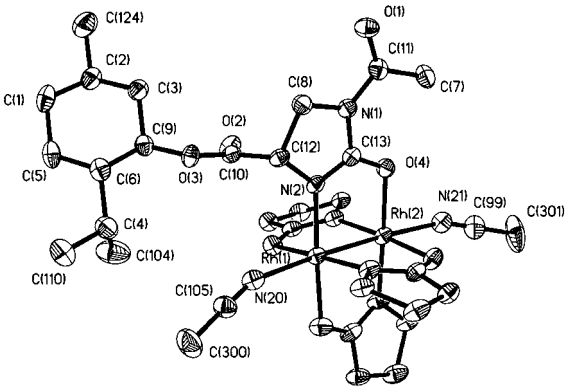
Entry	Catalyst	*cis*:*trans*[b]	Yield [%][c]	ee [%][d]
1	Rh_2(OAc)$_4$[e]	13:1	90	NA
2	Rh_2(5*S*-MEPY)$_4$ (**4**)	10:1	16	4 (*R*)
3	Rh_2(4*S*-MEOX)$_4$ (**5**)	62:1	90	24 (*R*)
4	Rh_2(4*S*-MEAZ)$_4$ (**6a**)	24:1	79	5 (*S*)
5	Rh_2(*S,R*-MenthAz)$_4$ (**6b**)	22:1	74	28 (*S*)
6	Rh_2(*S,S*-MenthAz)$_4$ (**6b**)	19:1	65	0
7	Rh_2(4*S*-MACIM)$_4$ (**7a**)	99:1	99	13 (*R*)
8	Rh_2(4*S*-MPPIM)$_4$ (**7b**)	22:1	40	18 (*R*)

[a] All reactions were performed with 0.498 mmol of ethyl glyoxylate.
[b] The diastereomer ratio was determined by ^{1}H NMR spectroscopy.
[c] Yield [%]was determined by integration of H-4 and comparison of naphthalene internal standard.
[d] Enantiomeric excess was determined by capillary GLC using a Cyclodex β column.
[e] Reaction was complete in 20 h.



Scheme 1.

Table 2. Selected bond lengths [Å] and angles [°] for dirhodium(II) carboxamidate **12**.



Rh1–Rh2	2.459(4)	O4–Rh2–Rh1	89.29(8)
Rh1–N2	2.005(3)	N20–Rh1–Rh2	176.54(9
Rh2–O4	2.073(3	N2–Rh1–O14	91.66(13)
Rh1–N20	2.214(4)	N2–Rh1–N4	91.36(13)
N2–C13	1.305(5)	N2–Rh1–O11	175.57(12)
N2–C12	1.444(5)	O100–Rh2–O4	89.46(12)
O4–C13	1.262(5)	N2–Rh1–N20	97.97(13)
N1–C13	1.411(5)	O4–Rh2–N2	92.42(12)
N1–C8	1.463(5)	C13–N2–Rh1	121.3(3)
C12–C8	1.545(6)	C12–N2–Rh1	126.4(3)
N1–C11	1.362(5)	C13–O4–Rh2	115.1(3))
O1–C11	1.233(5)	N2–C13–N1	111.2(3)
N2–Rh1–Rh2	85.45(9)	C13–N1–C8	109.2(3)

Table 3. Effect of catalyst loading and temperature on yield and selectivity.[a]

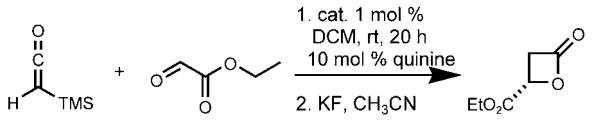
Entry	Catalyst [mol %]	Temperature [°C]	Yield [%][b]	ee [%]
1	1.0	24	90	83 (*R*)
2	0.5	24	77	73 (*R*)
3	0.1	24	39	50 (*R*)
4	1.0	4	57	82 (*R*)
5	1.0	35[d]	99	59 (*R*)

[a] Reactions were performed as previously described using Rh_2(*S,R*-MANICM)$_4$.
[b] Yield determined by integration of H-4 and comparison of naphthalene internal standard.
[c] Enantiomeric excess was determined by capillary GLC using a Cyclodex B-DM column.
[d] Reaction was complete in 26 h.

With this application we investigated the effect of catalyst loading of Rh_2(*S,R*-MANICM)$_4$ and of reaction temperature on the outcome of the reaction (Table 3). Lowering the amount of catalyst from 1.0 mol % to 0.5 mol % lowered product yield and reaction selectivity (entry 2), and a further decrease in yield and selectivity was observed when only 0.1 mol % of catalyst was used (entry 3). Similar effects on selectivity and/or yield were observed when the reaction temperature was varied. Product yield diminished (57%) upon lowering the temperature to 4 °C (entry 4) due to incomplete conversion of starting material. On the other hand, increasing the temperature to 35 °C reduced the reaction time to 26 h, while increasing product yield, but decreased enantioselectivity to 59% ee (entry 5). Efforts to extend this methodology beyond the use of ethyl glyoxylate, to aromatic aldehydes and cinnamaldehyde, were unsuccessful; cycloaddition was not observed.

The specificity of this cycloaddition reaction for glyoxylate, and the low response from the catalysts reported in Table 1, suggested a more complex process than had been anticipated. In an effort to further optimize the reaction conditions, we investigated the use of co-catalysts. Confident that the chiral dirhodium(II) carboxamidate was activating the aldehyde based on previous work on the hetero-Diels–Alder reaction,[1b] we believed that if activation of the ketene could be achieved a decrease in reaction time would be observed. We chose the Lewis base quinine as a co-catalyst due to its known activation of ketenes[13] in an effort to shorten the reaction time and possibly increase enantiocontrol. We hypothesized that added steric bulk associated with the putative ammonium ketene enolate would be beneficial in increasing the selectivity of the reaction. One major concern was whether or not the *Cinchona* alkaloid would inhibit the activity of the dirhodium(II) catalyst through coordination of either the hindered tertiary amine or the quinoline nitrogen. To test the compatibility of the

Table 4. Screening of dirhodium(II) catalysts with quinine for selectivity.



Entry	Catalyst	*cis:trans*[a]	Yield [%][b]	ee [%][c]
1	$Rh_2(OAc)_4$	1:99	68	90 (*R*)
2	none		NR	
3	Rh_2(5*S*-MEPY)$_4$ (**4**)	1:99	34	12 (*R*)
4	Rh_2(4*S*-MEOX)$_4$ (**5**)	1:99	84	52 (*R*)
5	Rh_2(4*S*-MEAZ)$_4$ (**6a**)	1:99	87	99 (*R*)
6	Rh_2(4*S*-MACIM)$_4$ (**7a**)	1:99	85	60 (*R*)
7	Rh_2(4*S*-MPPIM)$_4$ (**7b**)	1:99	88	30 (*R*)
8	Rh_2(4*S*-MANICM)$_4$ (**12**)	1:99	85	59 (*R*)
9	Rh_2(5*R*-MEPY)$_4$ (**ent-4**)	1:99	33	11 (*R*)
10	Rh_2(5*S*-MEPY)$_4$[d] (**4**)	1:99	36	12 (*S*)

[a] Diastereomeric ratio determined by ^{1}H NMR spectroscopy.
[b] Yield determined by integration of H-4 and comparison of naphthalene internal standard.
[c] Enantiomeric excess was determined by capillary GC using a Chiraldex β column.
[d] Quinidine (10 mol %) used in place of quinine.

two catalysts, the reaction was performed under standard conditions utilizing 1 mol % of $Rh_2(OAc)_4$ as the Lewis acid and 10 mol % of quinine. The desired β-lactone was obtained in 68% yield and 90% ee in 20 h at room temperature (Table 4, entry 1). To rule out the possibility that the reactivity and selectivity of this reaction were completely controlled by quinine, we performed the reaction under identical conditions in the absence of $Rh_2(OAc)_4$ and observed no background reaction (entry 2). Confident that there was a synergistic effect between the two catalysts, we screened chiral dirhodium(II) carboxamidate catalysts for the best possible match. The results from this investigation are summarized in Table 4.

In all cases an increase in enantioselectivity and a significant decrease in reaction time were observed with the most dramatic outcome being that with Rh_2(4*S*-MEAZ)$_4$ which gave a single enantiomer in high yield (entry 5). Interestingly, no change in enantioselectivity was observed in quinine-catalyzed reactions when the 5*R*-MEPY was used in place of 5*S*-MEPY (entries 3 and 9); however, when quinidine was used in place of quinine with 5*S*-MEPY (entry 10), a reversal of enantioselectivity was observed. Since quinine and the dirhodium(II) catalysts both influence enantiocontrol of the reaction, even though the influence of quinine is dominant, the change in % ee from the chiral catalyst suggests that bifunctional catalysis is operative. The low yield of product with rhodium acetate and $Rh_2(MEPY)_4$ (entries 1, 3, 9 and 10) may be a consequence of rhodium catalyst inhibition due to association of quinine at the axial coordination site of dirhodium(II). This rationale is substantiated by the observation of a red color upon addition of quinine to the green $Rh_2(OAc)_4$ reaction solution, indicating nitrogen coordination to the axial coordination site.[14] Preliminary results in our laboratory lead us to believe that coordination with $Rh_2(OAc)_4$ is to the quinoline nitrogen, and further investigation is currently underway to evaluate the validity of this claim.

Since addition of *Cinchona* alkaloids proved fruitful in increasing the enantiocontrol of the [2+2] reaction, other tertiary chiral nitrogen sources were also investigated, including *N*-methyl-L-proline, 2,2′-isopropylidenebis[4(*S*)-4-*tert*-butyl-2-oxazoline] and 2,2′-isopropylidinebis[4(*S*)-4-isopropyl-2-oxazoline].[15] In all cases moderate yields of β-lactone were obtained (55–78%) in reactions of TMS-ketene and ethyl glyoxylate performed with rhodium acetate, but only with 4(*S*)-isopropyl-2-oxazoline was any enantioselectivity (14% ee) observed. This result suggests that in Evans' bis-oxazoline-catalyzed [2+2]-cycloaddition reaction an excess of ligand is not a contributor to reaction selectivity through independent activation of the ketene for cycloaddition.

Conclusion

We report the first example of the intermolecular [2+2]-cycloaddition reaction between ethyl glyoxylate and trimethylsilylketene catalyzed by dirhodium(II). The successful development and application of Rh_2(*S,R*-MNACIM)$_4$ and other dirhodium(II) carboxamidate catalysts[2] specifically for use as a Lewis acids opens the door for further catalyst development in this arena. The use of quinine as a co-catalyst with Rh_2(4*S*-MEAZ)$_4$ suggests a novel bifunctional catalysis capable of exceptional enantiocontrol and enhanced reactivity.

Experimental Section

Preparation of Trimethylsilylketene

To a stirred solution of 5.00 g (40% by wt. in hexanes, 28.0 mmol) of ethyl ethynyl ether in THF (100 mL) at 0 °C was added 16.0 mL (2 M in THF, 32 mmol) of ethylmagnesium chloride. The solution was stirred for 3 h with warming to room temperature. After cooling to 0 °C, 4.0 mL (32.0 mmol) of chlorotrimethylsilane were added, and the reaction was stirred overnight (15 h) at room temperature. After concentration to one-third of the original volume on a rotary evaporator, 100 mL of pentanes were added, and the resulting slurry was decanted and filtered through Celite. Concentration under vacuum was followed by distillation (40 °C/8 mm Hg) of trimethylsilylethoxyacetylene as a colorless oil. ^{1}H NMR (500 MHz): $\delta = 0.01$ (s, 9H), 1.26 (t, $J = 7.0$ Hz, 3H), 4.00 (q, $J = 7$ Hz, 2H).

Thermolysis and distillation at 120 °C and atmospheric pressure gave trimethylsilylketene; yield: 1.14 g (35% overall); ^{1}H NMR: $\delta = 0.18$ (s, 9H), 1.79 (s, 1H).

Distillation of Ethyl Glyoxylate

Commercial ethyl glyoxylate/toluene solution (12–13 mL) was added to an oven-dried 25-mL round-bottom flask, to which a short path distillation apparatus was subsequently attached. Heating at 140–150 °C removed the majority of the toluene, and raising the temperature of the oil bath to 160–170 °C allowed collection of the remaining ethyl glyoxylate/toluene solution. The ratio of these components was determined by ^{1}H NMR, and a 4:1 solution of ethyl glyoxylate to toluene was typical.

Typical Procedure for Ketene/Aldehyde Cycloadditions

To a 0.5-dram vial containing 5 μmol of catalyst in 300 μL of anhydrous CH_2Cl_2 was added 50.9 mg (0.50 mmol) of ethyl glyoxylate solution in 400 μL of CH_2Cl_2. Next a solution of 70 μL (0.50 mmol) of trimethylsilylketene in 400 μL of CH_2Cl_2 was added. Finally, a solution of 50.0 mg of naphthalene in 200 μL of CH_2Cl_2 was introduced, and the vial was sealed. The reaction was allowed to proceed for three days before filtering the resulting solution through a plug of silica. After solvent evaporation, the crude reaction mixture was analyzed by ^{1}H NMR to determine the yield and the *cis*/*trans* ratio. Product yield was found by comparing the integrated areas of the product and naphthalene. The diastereomeric ratio was assessed using the integrations of H-4 in the *cis* (4.95 ppm, d, $J = 7.2$ Hz) and *trans* (4.57 ppm, d, $J = 4.5$ Hz) configured products.

The silylated intermediate was dissolved in 2.0 mL of acetonitrile, followed by addition of 60.0 mg (1.0 mmol) of KF with stirring at room temperature for 20 min. Purification was achieved by column chromatography on silica gel, eluting with 30% diethyl ether in hexanes. ^{1}H NMR (600 MHz): $\delta = 1.34$ (t, $J = 7.2$ Hz, 3H), 3.61 (dd, $J = 4.8$ Hz, 16.8 Hz, 1H), 3.79 (dd, $J = 6.6$ Hz, 16.8 Hz, 1H), 4.31 (m, 2H), 4.85 (dd, $J =$ 4.2 Hz, 6.6 Hz, 1H); ^{13}C NMR (150 MHz): $\delta = 14.0$, 43.4, 62.4, 65.2, 165.7, 168.0. Enantiomeric excess was determined by gas chromatography using a 30-m Chiraldex B-DM chiral column operated isothermally at 100 °C. Typical values for the retention times of the *S* and *R* enantiomers were 20.3 min and 22.1 min, respectively.

Typical Procedure for Ketene/Aldehyde Cycloadditions with Quinine

To a 0.5-dram vial containing 5 μmol of catalyst in 300 μL of anhydrous CH_2Cl_2 was added 16.0 mg (0.05 mmol) of quinine and 50.9 mg (0.50 mmol) of ethyl glyoxylate solution in 400 μL of CH_2Cl_2. Next a solution of 70 μL (0.50 mmol) of trimethylsilylketene in 400 μL of CH_2Cl_2 was added. Finally, a solution of 50 mg of naphthalene in 200 μL of CH_2Cl_2 was introduced, and the vial was sealed. The reaction was allowed to proceed for three days before filtering the resulting reaction solution through a plug of silica. After solvent evaporation, the crude reaction mixture was analyzed by ^{1}H NMR to obtain the yield and the *cis*/*trans* ratio. The yield was determined by comparison of the integrated areas of the product and naphthalene. The diastereomeric ratio was assessed using the integrations of H-4 in the *cis* (4.95 ppm, d, $J = 7.2$ Hz) and *trans* (4.57 ppm, d, $J = 4.5$ Hz) configured products.

The silylated intermediate was dissolved in 2 mL of acetonitrile, followed by addition of 60 mg (1.0 mmol) of KF, and this solution was stirred at room temperature for 20 min. Purification was achieved by column chromatography on silica gel, eluting with 30% diethyl ether in hexanes. Analyses were performed as previously described.

Supporting Information

For the synthesis of imidazolidinones **9–11** and catalyst **12**, and for the crystallographic study of **12**, see Supporting Information.

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