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Highly Enantioselective Carbonyl-ene Reactions Catalyzed by a Hindered Silyl–Salen–Cobalt Complex

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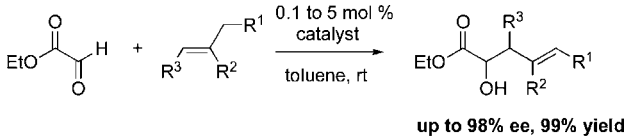
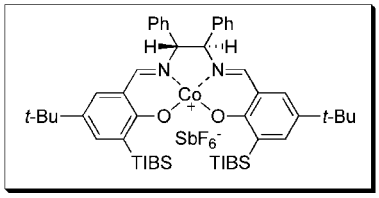
ABSTRACT





We report here the enantioselective carbonyl-ene reactions of various 1,1-disubstituted and trisubstituted alkenes with ethyl glyoxylate. The reactions are catalyzed by a new Co–salen complex, in which bulky triisobutylsilyl (TIBS) substituents occupy the positions ortho to the phenolic oxygens. This complex catalyzes the reactions under nearly ideal conditions—at room temperature and using catalyst loadings as low as 0.1 mol %—and provides the chiral, homoallylic alcohol products in excellent yields, enantioselectivities, and diastereoselectivities.

The enantioselective carbonyl-ene reaction, an atom-economic analogue of the asymmetric metal-allylation reaction, provides direct access to chiral homoallylic alcohols under mild conditions.[1] Since the first report on the topic by Yamamoto and co-workers,[2] the catalytic enantioselective carbonyl-ene reaction has been the subject of investigation in several laboratories. The electronic requirements of the reaction generally necessitate that the carbonyl component be strongly electron-deficient, most often a glyoxylate. Among the notable contributions to the development of enantioselective carbonyl-ene reactions is the use of Ti−BINOL complexes by Nakai/Mikami,[3] Cu−Box catalysts by Evans[4a,b] and Vederas,[5] Sc−PyBox catalysts by Evans,[4c] and tridentate−Cr(III)−Schiff base complexes by Jacobsen.[6,7] Our recent work on the use of C_2-symmetric metal−salen

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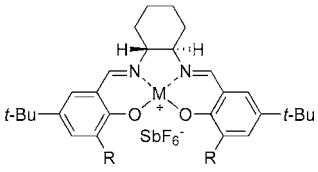
complexes as effective Lewis acid catalysts for Diels−Alder reactions motivated us to examine such complexes for the carbonyl-ene reaction.[8]

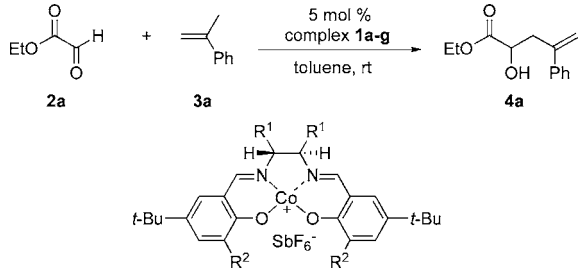


1a: R = *t*-Bu, M = Co
1b: R = $SiMe_3$, M = Co

Over the years, C_2-symmetric metal−salen complexes have proven to be useful in a wide range of reaction types.[9] First developed in the context of epoxidation and epoxide opening chemistry, these complexes have also been utilized more recently as chiral Lewis acid catalysts for many other reactions, including Diels−Alder,[8,10] hetero-Diels−Alder,[11] hydrocyanation,[12] silylcyanation,[13] aldol,[14] alkylation,[15] and conjugate addition[16] reactions. These complexes are easy to prepare and have good benchtop stability. Importantly, the steric and electronic environment of the salens can be varied with ease. In connection with our enantioselective Diels−Alder work, we sought to accentuate the subtle asymmetric topology of the commonly used C_2-symmetric salen framework (**1a**) and found the corresponding silyl-substituted salen cobalt complexes (e.g., **1b**) to be superb catalysts for Diels−Alder reactions, functioning at loadings as low as 0.05 mol %.[8c] The enhanced effectiveness of the silyl salens was rationalized to be a result of sterics-based distortion of the otherwise flat salen framework. Through similar reasoning, we have developed a triisobutylsilyl(TIBS)-substituted C_2-symmetric Co−salen complex for promoting the carbonyl-ene reaction of various 1,1-disubstituted and trisubstituted alkenes with ethyl glyoxylate. These reactions proceed at room temperature using catalyst loadings as low as 0.1 mol % and produce γ,δ-unsaturated-α-hydroxy carboxylic esters in excellent yields, enantioselectivities, and diastereoselectivities.[17]

For the initial studies, we examined the carbonyl-ene reaction of ethyl glyoxylate (**2a**) and α-methyl styrene (**3a**), promoted by the cobalt complex of the commercially available *t*-butylsalen ligand (Table 1).[18] The reaction was carried out in methylene chloride at room temperature in the presence of 5 mol % of catalyst **1a** and produced chiral alcohol **4a** in >95% conversion and 28% ee, with the (*R*)-enantiomer predominating. Solvent optimization studies revealed that in toluene the product was formed in comparable conversion and with higher selectivity (34% ee, entry 1). On the other hand, the product was formed in only trace amounts in coordinating solvents such as diethyl ether and

Table 1. Variation of the Cobalt(III) Salen Scaffold at the R^1 and R^2 Position



entry	catalyst	R^1	R^2	time (h)	yield[a] (%)	ee[b] (%)
1	**1a**	$-(CH_2)_4-$	*t*-Bu	24	84	34
2	**1b**	$-(CH_2)_4-$	TMS	2	77	51
3	**1c**	Ph	*t*-Bu	15	93	46
4	**1d**	Ph	TMS	2	97	54
5	**1e**	Ph	TES	2	98	62
6	**1f**	Ph	TIPS	2	95	90
7	**1g**	Ph	TIBS[c]	2	97	98

[a] Isolated yield. [b] Determined by chiral HPLC analysis using a Daicel Chiralcel AD column (98.5% hexanes, 1.5% *i*PrOH). [c] TIBS = triisobutyl silyl.

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(9) (a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691−1693. For salen reviews, see: (b) Cozzi, P. G. *Chem. Soc. Rev.* **2004**, *33*, 410−421. (c) Katsuki, T. *Adv. Synth. Catal.* **2002**, *344*, 131−147. (d) McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*, 1563−1602. (e) Katsuki, T. *Synlett* **2003**, 281−297. (f) Canali, L.; Sherrington, D. C. *Chem. Soc. Rev.* **1999**, *28*, 85−93. (g) Achard, T. R. J.; Clutterbuck, L. A.; North, M. *Synlett* **2005**, 1828−1847. (h) Atwood, D. A.; Harvey, M. J. *Chem. Rev.* **2001**, *101*, 37−52. (i) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Chem. Commun.* **2002**, 919−927.

(10) Yamashita, Y.; Katsuki, T. *Synlett* **1995**, 829−830.

(11) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403−405.

(12) For example, see: Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315−5316.

(13) Chen, F.; Feng, X.; Qin, B.; Zhang, G.; Jiang, Y. *Org. Lett.* **2003**, *5*, 949−952.

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(15) (a) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62−63. (b) Kwiatkowski, P.; Chaladaj, W.; Jurczak, J. *Tetrahedron Lett.* **2004**, *45*, 5343−5346.

(16) (a) Bandini, M.; Fagioli, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5843−5846. (b) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313−1317.

(17) Hutson, G.; Rawal, V. H. *Abstracts of Papers*, 233rd ACS National Meeting, Chicago, IL, United States, March 25−29, 2007; American Chemical Society: Washington DC, 2007; ORGN-557 (Chemical Abstracts: 2007:296584). While this manuscript was being readied for publication, a report appeared on the use of C_2-symmetric salen complexes for carbonyl-ene reactions (4−92% ee). See: Chaladaj, W.; Kwiatkowski, P.; Maker, J.; Jurczak, J. *Tetrahedron Lett.* **2007**, *48*, 2405−2408.

(18) Other metal−salen complexes of the general structure **1a** were examined for this carbonyl-ene reaction, but none gave satisfactory results. Under similar conditions (5 mol % of catalyst, toluene, 24 h), the following results were obtained: Cr−salen, 28% ee, >95% conversion; Mn−salen, 7% ee, 33% conversion; Al−salen, 16% ee, 85% conversion.

ethyl acetate. As anticipated, the corresponding silyl−salen complex was more effective at promoting the reaction, albeit only marginally.

To improve the enantioselectivities to useful levels, we next examined salen complexes derived from the acyclic diamine, 1,2-diphenylethane-1,2-diamine. The parent, *t*-butyl-substituted salen complex (**1c**) gave the product in higher ee and promoted the reaction at a good rate (entry 2). As before, the corresponding TMS-substituted salen complex (**1d**) was even more effective. The reaction was complete in less than 2 h, giving the product in 97% yield and 54% ee. A steady increase in enantioselectivity was observed as the steric bulk of the silyl substituent was increased from TMS to TES to TIPS. When the TIBS-substituted salen complex was employed, the product was obtained in 98% ee (Table 1, entry 6).[19]

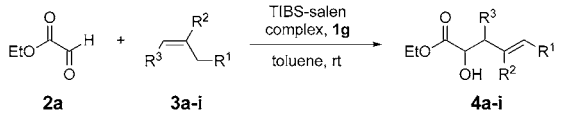
The TIBS−salen-catalyzed carbonyl-ene reaction protocol proved to be broadly effective. A variety of 1,1-disubstituted and trisubstituted alkenes were reacted with ethyl glyoxylate and gave the expected homoallylic alcohol products in good to excellent yields and uniformly excellent enantioselectivities (Table 2). For the reaction with α-methyl styrene, the reaction proceeded nearly as well when the catalyst loading was lowered from 5 mol % to 1 mol %. The lower loading decreased the rate of the reaction slightly, with no change in ee (Table 2, entry 1). The catalyst loading could be decreased to 0.1 mol % and still provide a synthetically useful reaction. As in the case of α-methyl styrene (**3a**), methylene cyclopentane (**3b**) also underwent the asymmetric carbonyl-ene reaction with **2a** in excellent yields and enantioselectivities with catalyst loadings as low as 0.1 mol % (entry 2). It is noteworthy that at 1 mol % loading this reaction went to completion in just 10 min.

Symmetric alkenes **3c**−**f** were effective partners in the carbonyl-ene reaction and provided the expected alcohol products in high enantioselectivities (entries 3−6). The reaction of alkene **3f** was both highly enantioselective and diastereoselective, producing the *E*-alkene isomers in 33:1 ratio (entry 6). Bulky alkenes such as 2,3,3-trimethylbutene (**3g**) and 2,4,4-trimethylpent-1-ene (**3h**) also reacted well but required longer time to complete the reaction (entries 7 and 8). Hydrogen abstraction in the latter took place exclusively from the less-substituted carbon. Trisubstituted alkene 3-ethyl-2-pentene (**3i**) gave the ene product in good diastereoselectivity, with the major diastereomer having been formed in 96% ee (entry 9).

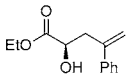
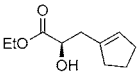
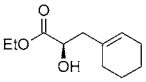
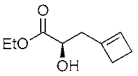
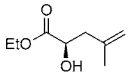
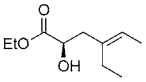
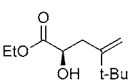
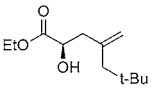
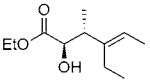
The use of silyl enol ethers in the carbonyl-ene reaction presents the possibility of forming either fuctionalized silyl enol ethers or, upon hydrolysis, the attainment of useful aldol products of ketones and glyoxylate.[3c,6] To assess the capability of TIBS−salen complex **1g** to promote such reactions, we carried out the reaction of enol-TBS ether of cyclohexanone (**3j**) and ethyl glyoxylate in the presence of complex **1g** (eq 1). The reaction went to completion in under 30 min

(19) The different silyl salen ligands were readily prepared using the procedure described in the accompanying publication: Thadani, A. N.; Huang, Y.; Rawal, V. H. *Org. Lett.* **2007**, *9*, 3873−3876. See also the Supporting Information.

Table 2. Salen Complex Catalyzed Enantioselective Carbonyl-ene Reactions

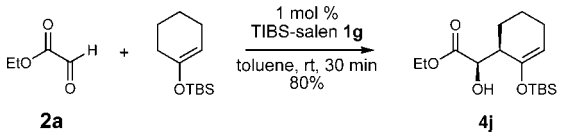


2a **3a-i** **4a-i**

entry	ene (**3a-i**)	product (**4a-i**)	cat. mol (%)	time (h)	yield[a] (%)	%ee[b] (dr)
1[c]	 **3a**		1 0.1	3 24	91 99	98 92
2	 **3b**		1 0.1	0.16 1	95 98	98 96
3	 **3c**		1	5	86	96
4	 **3d**		5	24	64	94
5[d]	 **3e**		5	24	61	98
6	 **3f**		1	10	89	98 33:1[h]
7	 **3g**		1	24	84	98
8[e]	 **3h**		2	48	98	97[g]
9[f]	 **3i**		5	40	84	96 (9:1) 22:1[h]

[a] Isolated yields. [b] Determined by chiral HPLC or chiral GC. Please see the Supporting Information for details on the assignment of absolute and relative stereochemistry of the reaction products. [c] With 5 mol % of catalyst loading, reaction reached 80% conversion within 10 min. [d] Isobutylene was added at −80 °C, then a −20 °C bath was used. [e] Reaction performed at 0 °C. [f] (*S*,*S*)-catalyst used for ee determination. [g] Regioselectivity was >99:1. [h] *E*/*Z* ratios determined by ^{1}H NMR spectroscopic analysis; (*E*)-configuration established by NOESY.

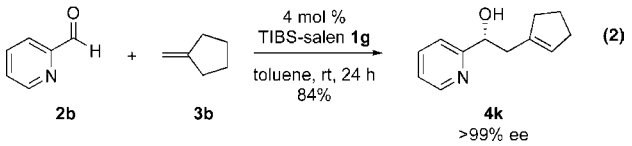
and gave enol ether product **4j** in good yield, high diastereoselectivity, and excellent enantioselectivity (80% yield, 18:1 dr, 98% ee). The relative stereochemistry of the major diastereomer was assigned by converting it to the benzoyl-protected *β*-hydroxy ketone and comparing its NMR spectrum with that reported in the literature.[20]



2a **4j** dr 18:1 major - 98% ee (1)

Examination of other aldehydes resulted in the discovery of Co(III)TIBS−SbF_6 salen promotion of unactivated olefin

additions to pyridine-2-carboxaldehyde (eq 2). This interesting result represents, to our knowledge, the first example of a catalyzed, asymmetric carbonyl-ene reaction between a monocarbonyl and an unactivated alkene.[21,22] The reaction is very efficient, producing product **4k** in 84% yield and >99% enantioselectivity. It is noteworthy that neither pyridine-3-carboxaldehyde nor pyridine-4-carboxaldehyde are reactive under the same conditions. Similarly, other electron-deficient aromatic aldehydes (2-nitrobenzaldehyde, 4-nitrobenzaldehyde, pentafluorobenzaldehyde) were also unreactive under identical conditions. On the basis of the observation that only glyoxylate and pyridine-2-carboxaldehyde are effective partners in the present carbonyl-ene reaction, we postulate that the reaction involves activation of the aldehyde via bidentate coordination to the cobalt(III) metal center.[23]



To develop an understanding of the chiral environment in the hindered TIBS−salen complex, we sought to obtain a crystal structure of this compound. A crystalline solid suitable for X-ray diffraction was obtained from an ether−hexane solution of **1g**.[24] The X-ray structure (Figure 1)[20] appears to be that of either the Co(IV) oxo complex or the Co(III) hydroxide. On the basis of the large Co−O(3) bond length (2.109 Å) as well as the presence of residual electron density near the oxygen, corresponding to a hydrogen atom, the structure is determined to be that of the cobalt hydroxide. The edge view of the square pyramidal complex shows that the bulky TIBS groups induce a significant twist to the plane of the salen ligand. Furthermore, coordination of the hydroxyl group to the salen backbone is highly asymmetrical, such

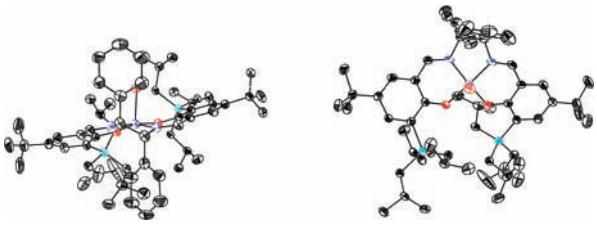


Figure 1. ORTEP representations (edge and top views) of TIBS−salen complex **1g**.

that one of the quadrants on the hydroxyl-coordinated face is much larger than the other (O1−Co−O3 angle = 108.5°). Naturally, because the structure is not that of the catalyst complexed to a reactive carbonyl compound,[8c] it does not provide direct information on the factors responsible for the observed high enantioselectivities. What is clear is that the large TIBS groups accentuate the otherwise subtle asymmetric environment of the salen scaffold.

The results above demonstrate the high effectiveness of Co(III)TIBS−SbF_6 salen complex **1g** to function as a catalyst for the carbonyl-ene reaction of ethyl glyoxylate with a wide range of alkenes. The catalyst is easily prepared and does not require a drybox for its preparation or handling. This methodology provides chiral β-hydroxy esters in high yields and excellent enantioselectivities (up to 98% ee) and diastereoselectivities. The reactions are carried out under nearly ideal conditions—at room temperature and using catalyst loadings as low as 0.1 mol %. The catalyst has also been found to promote the carbonyl-ene reaction of a silyl enol ether and ethyl glyoxylate as well as that of an alkene and 2-pyridinecarboxaldehyde.

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Supporting Information Available: Experimental details and characterizations for all new compounds and crystal structure data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) See Supporting Information for further details.

(21) Asymmetric carbonyl-ene reactions of simple unactivated aldehydes and electron-rich alkenes, such as silyl enol ethers, have been reported. See, inter alia, refs 6, 7b, and 3c.

(22) For recent examples of racemic carbonyl-ene reactions of unactivated alkenes and aromatic/aliphatic aldehydes, see: Ho, C.; Ng, S.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 11513−11528.

(23) For examples of bidentate-coordinated cobalt−salen complexes, see: (a) Kushi, Y.; Tada, T.; Fujii, Y.; Yoneda, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1834−1839. (b) Bailey, N. A.; Higson, B. M.; McKenzie, E. D. *J. Chem. Soc., Dalton Trans.* **1972**, 503−508.

(24) To date, our attempts to obtain a crystalline complex of **1g** and glyoxylate have proven unsuccessful.