Carbon-Substituted Co(III) Salens as Effective Catalysts for Enantioselective Diels–Alder Reactions

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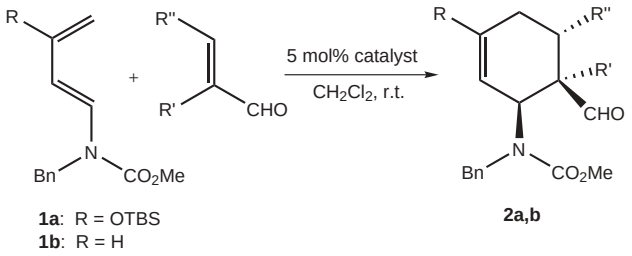
Abstract: Seven newly synthesized Co(III) salen hexafluoroantimonate complexes having aryl or alkyl-aryl substituents in place of the bay region *t*-Bu or silyl substituents were synthesized and examined as catalysts for the enantioselective Diels–Alder reaction of 1-benzylaminocarbamate-1,3-butadiene and methacrolein. The results were consistent with a working model for rationalizing enantioselectivity in these cycloaddition reactions: an increase in the steric bulk of the internal substituents gives, in most instances, a predictable increase in the ee of adducts. The best results were obtained with a homobenzyl-substituted salen, which yielded cycloadducts in >97% ee, and with an increased reaction rate compared to the previously studied TMS-Co(III) salen. Insights from this study suggest that helical asymmetry, induced by increasing the steric size of the internal substituents, alone does not account for increased ee of the products. The present study also shows that fully carbon-based substituents can be as effective enantiodiscriminating elements as trialkylsilanes, and, unlike silanes, are not succeptible to protodesilylation.

Key words: asymmetric catalysis, Lewis acids, enantioselective Diels–Alder, substituent effects, aminodienes



Equation 1

The Diels–Alder (DA) reaction serves as a valuable synthetic tool for the stereocontrolled construction of complex six-membered ring systems.[1] With potential for setting up to four embedded chiral centers in a single synthetic operation, the development of highly regio- and enantioselective catalysts with a broad reagent scope remains an attractive objective for total synthesis applications.[2,3] Recent reports from this laboratory have detailed the use of Jacobsen's Cr(III) salen catalyst[4] to effectively promote the enantioselective DA reaction of substituted acroleins and substituted aminodienes including 1-amino-3-siloxy-1,3-butadiene[5] (**1a**) and simple carbamate-substituted diene **1b** (Equation 1).[6,7] Studies of salen complexes of additional metals revealed that the Co(III) complex of Jacobsen's ligand was remarkably effective in catalyzing the reaction of **1b** with methacrolein, giving **2b** in 95% ee after two hours at room temperature using 5 mol% catalyst.

Critical insight into the activation of the carbonyl compound was obtained from an X-ray structure of the benzaldehyde–catalyst complex of **3a**.[8] This structure showed a remarkably flat topography of the salen scaffold, save for a small step at the metal center deriving from the chiral diamine, with two aldehyde molecules coordinated axially in a non-perpendicular manner with respect to the scaffold, giving an octahedral arrangement about the metal center. The current model of enantioselection for the DA reaction using these catalysts can be explained via this non-perpendicular coordination, with preferential approach of the diene from the 'open' quadrants of the complex. A space-filling model of this complex suggests that the two bay region *t*-Bu groups (R in Figure 1) reside in close proximity. It was hypothesized that steric congestion from bulkier groups at this position might force the two aromatic rings out of near-parallel arrangement, engendering greater helical asymmetry in the scaffold and higher enantioselectivity in the cycloadducts. Silyl-substituted salens were developed using this rationalization and provided catalysts having superior enantioselection and turnover for DA reactions with several dienophiles.[8]

Based on the above model, it was expected that increasing either the steric bulk of the carbon substituent, compared to the *t*-Bu group, or its projection into the bay region could give rise to a more effective catalyst. The objective of the present study was to determine if the superior results observed for the silyl-substituted salens arose from some 'special' property of the silyl group or if appropriately sized all-carbon substituents would have the same beneficial effect on asymmetric catalysis. Additional impetus for further developing a non-silyl salen catalyst came from a concern regarding the long-term stability of the silyl–salen complexes. Protodesilation, even if it occurred to a small extent, would potentially produce a catalyst that would be less encumbered, hence less enantioselective and, in all likelihood, more active. Utilizing an appropriate carbon-substituted aryl group in place of the trialkylsilane would alleviate this concern of protodesilylation.

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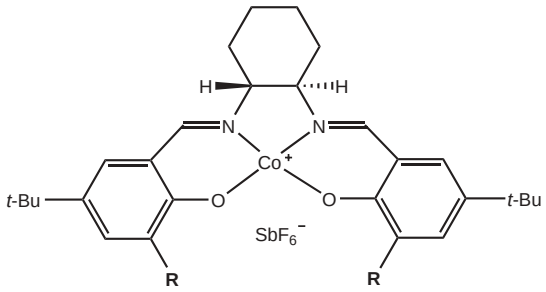
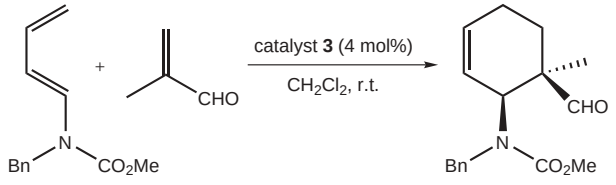


3a: R = *t*-Bu
3b: R = TMS
3c: R = Ph
3d: R = *o*-tolyl
3e: R = *p*-tolyl
3f: R = 4-biphenyl
3g: R = *p*-*t*-BuPh
3h: R = benzyl
3i: R= -$(CH_2)_2$Ph

Figure 1 Catalyst test group for enantioselective DA reaction

Seven ligands containing aryl- or alkyl-aryl groups in the bay region were prepared via Suzuki coupling of aryl boronic acids or alkyl-BBNs with a properly functionalized salicaldehyde, followed by imine condensation. Metal complexation and oxidation, following previously reported methods,[8] afforded the various Co salen complexes (Figure 1). The ability of the newly prepared complexes to catalyze the enantioselective Diels–Alder reaction between aminodiene **1b** and methacrolein was evaluated and the results are summarized in Table 1. The reactions proceeded under convenient conditions, at room temperature using 4 mol% of the catalysts.

Table 1 Enantioselective Diels–Alder Reaction of Synthetic Salen Catalysts[a]



1b **4**

Entry	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]	er[c]
1	**3a**	3.0	97	95	42:1
2	**3b**	1.2	98	>97	71:1
3	**3c**	1.5	85	95	38:1
4	**3d**	1.1	85	90	19:1
5	**3e**	1.5	87	94	35:1
6	**3f**	12	82	97	64:1
7	**3g**	13	97	94	35:1
8	**3h**	1.3	82	96	46:1
9	**3i**	0.8	86	>97	73:1

[a] Reactions carried out at r.t. in CH_2Cl_2 (0.9 M) with 2 equiv of methacrolein and 4 mol% of catalyst **3** with respect to **1b**.
[b] Yield based on **1b** after isolation by column chromatography.
[c] Determined by ^{1}H NMR analysis of a Mosher ester derivative.

A range of substituents was selected based on an evaluation of the molecular models of the corresponding salen complexes. All of the synthetic complexes were found to be viable catalysts for the enantioselective DA reaction. Catalysts **3a** and **3b** were reevaluated and gave ee values of 95% and slightly greater than 97%, respectively, and yields exceeding 97%.[9]

Substituted aryl groups were deemed a reasonable starting point for this study, as the aryl–aryl bond places the carbon group into the desired region without the flexibility of a corresponding saturated carbon chain. Though the aryl group itself is flat, the use of substituted aryls allows for the inclusion of steric bulk at various available sites on the aryl ring. Catalyst **3c**, in which a phenyl group occupies the desired region, was found to be effective, with a higher rate of reaction than **3a** and only a moderate decrease in selectivity, with an er of 38:1 (vs. 42:1, R = *t*-Bu).

Catalysts **3d** and **3e** were prepared to test the effect of increasing sterics via mono-methyl substitution on the aryl ring. Catalyst **3e** was slightly less selective than the corresponding phenyl catalyst **3c**, suggesting that accentuated helical asymmetry alone may not tell the entire story when it comes to facial discrimination of the DA reaction as tested. The results utilizing catalyst **3d** are less clear as it is uncertain where the methyl group will reside in the catalytically active species, though mono-*o*-methyl substitution has an overall negative effect on selectivity.

Initial results for DA reaction using catalysts **3d** and **3e** gave ee values that varied from the low to upper 80's depending on the batch of ligand utilized. ^{1}H NMR analysis of the arylaldehyde precursors used to form the imine ligands showed contamination of the desired aryl with ca. 2–3% of the corresponding compound where R = H (i.e., reduction product from prior Suzuki coupling reaction). Kugelrohr distillation followed by ligand formation and metal complexation gave pure **3d** and **3e**, which now reliably gave adducts of 90% and 94% ee, respectively. This data gives merit to the concern that a partially desilylated catalyst will result in lower selectivity.[10] Preparation of the silyl-salen complex, **3b**, directly from a stored sample of the ligand provided an adduct in a similar yield to that reported, but ee values were consistently 1% lower than anticipated. Catalyst prepared from freshly purified ligand from this same batch provided the adduct in slightly higher ee (>97%), as previously reported, suggesting that slow partial desilylation of the ligand may take place on long-term storage.

Catalyst **3f** was prepared with the expectation that placing a larger group at the *para* position of the aryl ring would increase enantioselection over that of methyl-substituted catalyst **3e**. Gratifyingly, **3f** gave a high ee of 97%, approaching the selectivity of the TMS catalyst (er = 64:1 vs. 71:1, R = TMS), although reaction time was significantly increased. Simple model studies revealed that the outlying phenyl rings of the biphenyl groups appear to project into the same space, which could lead to significant steric congestion and, presumably, twisting of the

scaffold. Catalyst **3g** incorporates a bulky *t*-Bu group at the *para* position and affords reasonable enantioselection (94% ee) although the reaction rate was further attenuated. This reduced reactivity and overall decrease in selectivity with *p*-*t*-Bu substitution suggests that the increased strain placed on these bulky scaffolds on complexing with cobalt has a negative effect on rate and selectivity. The strain and twisting in the scaffold is, evidently, so severe that it alters the immediate environment about the complexed aldehyde.

Two catalysts were prepared in which a phenyl group was tethered to the ligand scaffold by either one (**3h**) or two (**3i**) methylene units. Conformational flexibility was expected to mitigate the rate and selectivity issues observed for the overly bulky *p*-substituents, while still projecting steric bulk into the desired bay region. Benzyl catalyst **3h** provided **4** in 96% ee, slightly greater than the *t*-Bu catalyst, with a rate of reaction closer to TMS catalyst **3b**. Extending the alkyl tether by one methylene to give **3i** provided the adduct in short reaction time in >97% ee. The selectivity and rate of reaction using this catalyst slightly exceeds that seen with TMS catalyst **3b**.[8] Crystal structures of these catalysts complexed with an appropriate dienophile are currently being pursued to better understand the observed selectivities.

In summary, we have shown that aryl-substituted Co(III) salen catalysts, developed to examine the current working model of DA enantioselectivity, serve as viable catalysts in the reaction of aminodiene **1** and methacrolein. Specifically, homobenzyl catalyst **3i** was found to give higher enantioselectivity and rate of reaction than that of previously developed TMS–salen catalyst **3b**. The present results support the working model for asymmetric induction in these reactions. The study also indicates that helical asymmetry alone does not account for increased ee of the products.

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References

(1) (a) Oppolzer, W. In *Comprehensive Organic Synthesis*, Vol. 5; Pergamon Press: New York, **1999**, 315. (b) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis I–III*, Vol. 3; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: New York, **1999**, 1177. (c) Dell, C. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3873.

(2) For selected reviews, see: (a) Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650. (b) Hayashi, Y. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S.; Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, **2002**, 5. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (d) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289. (e) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.

(3) For selected reviews see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668. (b) Tietze, L. F.; Kettschau, K. *Top. Curr. Chem.* **1997**, *189*, 1. (c) Jurczak, J.; Bauer, T.; Chapuis, C. In *Stereoselective Synthesis (Houben-Weyl)*, 4th ed., Vol. E21c; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, **1995**, 2905.

(4) (a) Tokunaga, M. J.; Larrow, F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.

(5) (a) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039. (b) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562. (c) Kozmin, S. A.; He, S.; Rawal, V. H. *Org. Synth.* **2000**, *78*, 152. (d) Kozmin, S. A.; He, S.; Rawal, V. H. *Org. Synth.* **2000**, *78*, 160.

(6) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 7843.

(7) Huang, Y.; Iwama, T.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 1163.

(8) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 5950.

(9) Values for the enantiomer ratio are included to distinguish subtle differences in selectivity for systems that would otherwise appear identical due to rounding of the ee values.

(10) These results show that even a small amount of mono-aryl substituted salen complex (~2%), similar to that which would be produced from partial protodesilation of the silyl salens, produces cycloadducts with significantly lower ee values. Presumably, the less encumbered complex catalyzes a faster, less enantioselective reaction.