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Addition of Diethylzinc to Dicobalt Hexacarbonyl Complexes of α,β-Acetylenic Aldehydes with Virtually Complete Enantioselectivity. A Formal Synthesis of (+)-Incrustoporin

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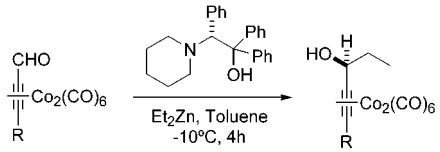
ABSTRACT



The addition of diethylzinc to dicobalt hexacarbonyl complexes of acetylenes mediated by (*R*)-2-piperidino-1,1,2-triphenylethanol takes place with very high enantioselectivity (96–99% ee) to afford the *S* enantiomers of dicobalt hexacarbonyl complexes of 1-alkynyl-1-propanols. The utility of this process is exemplified by the development of a short, highly enantioselective (99% ee) synthesis of unnatural incrustoporin.

The secondary carbynol moiety is present in the structures of many natural products. Accordingly, a great deal of synthetic effort has been devoted to its enantiocontrolled formation. Additions to carbonyl groups (either reduction of prochiral ketones or nucleophilic alkylation of aldehydes) are key to this purpose, the current emphasis being on catalytic enantioselective processes.[1]

Achievement of enantioselectivity in these reactions normally relies on the successful preferential recognition of one of the enantiotopic faces of the carbonyl substrate by a chiral ligand/metal assembly. Accordingly, the existence of a significant difference in steric bulk between the carbonyl substituents is key for success in this endeavor.

When we center our attention on the enantioselective addition of dialkylzincs to aldehydes, many different ligands ensure nearly complete enantiocontrol over the addition of diethylzinc to benzaldehydes, while the corresponding additions to substrates unsubstituted at the α and β carbons constitute a less well-solved problem.[2]

Dialkylzinc addition to α,β-acetylenic aldehydes (**1**) could provide a convenient entry to the synthetically useful enantiopure propargyl alcohols (**2**).[3] However, despite considerable effort dedicated to the study of this problem, enantioselectivities reported so far are generally not satisfactory,[4] and just one report describes a highly enantioselective (ee > 95%) addition of diethylzinc to 3-phenylpropanal (**1a**) by a process involving a titanium-based catalyst.[5]

(1) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999.

(2) (a) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159−2231. (b) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. II, pp 911−961. (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757, 824.

(3) Other approaches have been devised for the enantiocontrolled preparation of this structural motif; see: (a) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017−3020. (b) Anand, N. K.; Carreira, E. K. *J. Am. Chem. Soc.* **2001**, *123*. (c) Lütjens, H.; Nowotny, S.; Knochel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 2675−2678.

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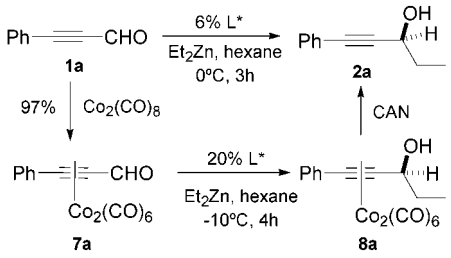
We disclose in the present paper a convenient solution to this problem that allows the ethylation of diversely substituted α,β-acetylenic aldehydes with virtually complete enantioselectivity.

Over the last few years, we have been involved in a research program devoted to the synthesis of modular ligands for a variety of catalytic enantioselective processes from purely synthetic yet enantiopure epoxides. As a result of lead identification and structural refining processes, we have developed the new ligands **3**−**6** that, besides a great structural simplicity, depict very high catalytic activity and enantiocontrol in the addition of diethylzinc to aldehydes of many different structural types.[6]

As a first step in our research and with the purpose of determining the optimal ligand for these reactions, we studied the use of **3**−**6** in the addition of diethylzinc to 3-phenylpropynal (**1a**). The reactions were performed at 0 °C for 3 h with 6 mol % ligand, and the results are summarized in Table 1. As it can be seen, all four studied ligands exhibited poor behavior in the reaction. This result was particularly surprising, since **3**−**6** have been previously shown to induce the addition of diethylzinc to α-unsubstituted saturated and α,β-unsaturated aldehydes with enantioselectivities in the 85−95% range. We interpreted these results to indicate that the amino alcohol ligands encountered difficulties in efficiently differentiating between the rather similar substituents of the aldehyde in the space near the reaction center.

Table 1. Ligand Evaluation for the Enantioselective Et_2Zn Addition to Phenylpropynal (**1a**) and Its Dicobalt Hexacarbonyl Complex (**7a**)



ligand	**2a** from **1a** ee [%][a]	**8a** from **7a** ee [%][b]
3	38	88
4	43	99
5	31	79
6	51	98

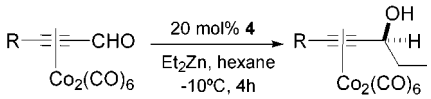
[a] Enantiomeric excesses were determined by GC analysis. [b] Enantiomeric excesses were determined by HPLC analysis.

In view of these results, we decided to submit the substrate aldehyde to a reversible modification that could increase the difference in steric bulk between the carbonyl branches and, hence, favor stereodifferentiation in the attack. The formation of the dicobalt hexacarbonyl complex of **1a** was designed for this purpose: this robust class of alkyne complexes, widely used for protection of the triple bond,[7] has also found application for enhanced stereodifferentiation in the oxazaborolidine-mediated borane reduction of ketones.[8]

Complex **7a** was prepared in essentially quantitative yield, and the addition of Et_2Zn in the presence of ligands **3**−**6** was next studied. While the increase in enantioselectivity was spectacular from the first moment, the reaction conditions required optimization. At room temperature, reaction yields were not satisfactory. Carbonyl groups within the dicobalt complex may compete with the aldehyde for coordination with the active catalyst, thus diminishing total conversion.

A thorough examination of reaction conditions led to the following set of optimal parameters: 20% mol ligand, 2.0 equiv Et_2Zn, toluene as the solvent, 4 h reaction at −10 °C. Use of **3**−**6** under these conditions led to the results shown in Table 1. Simultaneous consideration of yields and enantioselectivities led us to select ligand **4** for the continuation of our study.[9] Thus, **4** was used for the ethylation of an array of dicobalt hexacarbonyl complexes of alkynals that covers a range of substitutions (primary, secondary, or tertiary) and natures (alkyl, vinyl, or aryl) at the carbon directly bonded to the triple bond, as shown in Table 2. Starting complexes (**7a**,**b**) were readily available from complexation of commercial aldehydes or by formylation and complexation of the corresponding alkynes (**7c**,**d**).[10]

Table 2. Enantioselective Ethylation of Dicobalt Hexacarbonyl Complexes of α,β-Acetylenic Aldehydes Mediated by (*R*)-2-Piperidino-1,1,2-triphenylethanol (**4**)



		alcohol **8**	
entry	R	yield [%]	ee [%]
a	Ph	63	99
b	*n*-C_5H_{11}	82	99
c	*t*-C_4H_9	51	96
d	1-cyclohexen-1-yl	83	98

Under the optimized conditions, the ethylation reactions took place, as a general trend, at elevated conversions

(4) (a) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937−943. (b) Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207−217. (c) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364−1365.

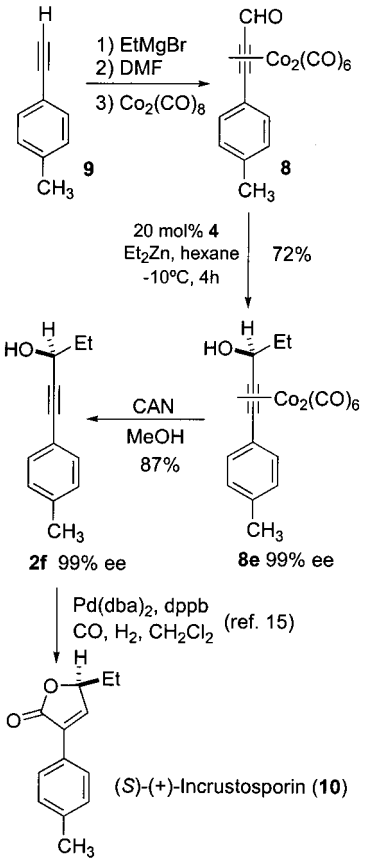
(5) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363−4384.

(6) (a) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773−8776. (b) Solà, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1998**, *63*, 7078−7082. (c) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970−4982. (d) Reddy, K. S.; Sola, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synthesis* **2000**, 165−176. (e) Reddy, K. S.; Sola, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 3969−3974.

(7) Nicholas, K. M.; Pettit, R. *Tetrahedron Lett.* **1971**, *37*, 3475−3478.

(8) (a) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153−9156. (b) Bach, J.; Berenguer, R.; Garcia, J.; Loscertales, T.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021−9025.

Scheme 1. Formal Enantioselective Synthesis of (*S*)-(−)-Incrustoporin (**10**)



(>90%), and the target propargyl alcohol complexes could be isolated in good purity after acidic workup. It is worth noting that enantioselectivities are outstanding in all cases (>96% ee) and virtually complete for **8a** and **8b** (>99% ee).

The enantiomeric purities of the resulting complexes were determined by HPLC.[11] Comparison of optical rotation and retention times of **2a** obtained by decomplexation of **8a** with literature values allowed the configurational assignment of the formed alcohol complex as *S*.[12] This is in agreement with Noyori's empirical rule and with previous experience with the same ligand.[13] On this basis and taking into account the regularity of the elution behavior in HPLC, the configurations of **8b**−**d** were also assigned as *S*.

To show the potential of the present method, we have developed a highly efficient enantioselective synthesis of (*S*)-incrustoporin (**10**), the enantiomer of the antifungal antibiotic isolated from the basidiomycete *Incrustoporia carneola* (Scheme 1).[14]

p-Tolylacetylene (**9**) was formulated with DMF via its bromomagnesium derivative, and the crude aldehyde was treated with octacarbonyl dicobalt in toluene to afford the aldehyde complex **7e** in 68% overall yield. Ethylation of this aldehyde under the optimized conditions previously used for **7a**−**d** afforded the propargyl alcohol complex **8e** in >99% ee and 72% yield. A subsequent oxidative decomplexation with cerium ammonium nitrate (CAN) in methanol led to propargyl alcohol (*S*)-(−)-**2f** in 87% yield with no loss of optical purity as ascertained by chiral HPLC. Since this alcohol had been previously converted to incrustoporin by a Pd-catalyzed cyclocarbonylation taking place with retention of configuration,[15] the formation of enantiopure **2f** completes a formal enantioselective synthesis of unnatural incrustoporin that takes place with a very high level of enantiocontrol.

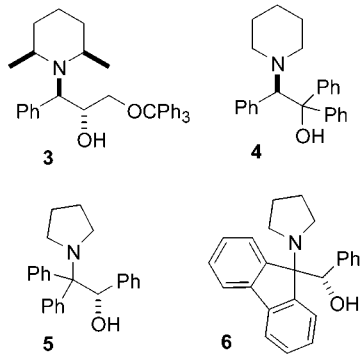


Figure 1. Modular ligands for the highly enantioselective addition of diethylzinc to aldehydes.

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Supporting Information Available: Full characterization and experimental details for the synthesis of dicobalthexacarbonyl−alkynal complexes and their corresponding diethylzinc addition products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Ligand **4** is commercially available in both enantiomeric forms.

(10) Jones, E. R. H.; Skattebol, L.; Whiting, M. C. *J. Chem. Soc.* **1958**, 1054−1059.

(11) Ethylation product mixtures were compared with racemic samples prepared by addition of ethylmagenesium bromide to the starting aldehydes in ether.

(12) Soai, K.; Niwa, S. *Chem. Lett.* **1989**, 481−484.

(13) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley & Sons: New York, 1994.

(14) Zapf, S.; Anke, T.; Sterner, O. *Acta Chem. Scand.* **1995**, *49*, 233−234.

(15) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1163−1172.