Tetrahedron Letters, Vol. 33, No. 13, pp. 1693-1696, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

Chiral Arene Chromium Tricarbonyl Complexes as Enantioselective Catalysts: Highly Selective 1,2 Alkyl Additions to Aldehydes

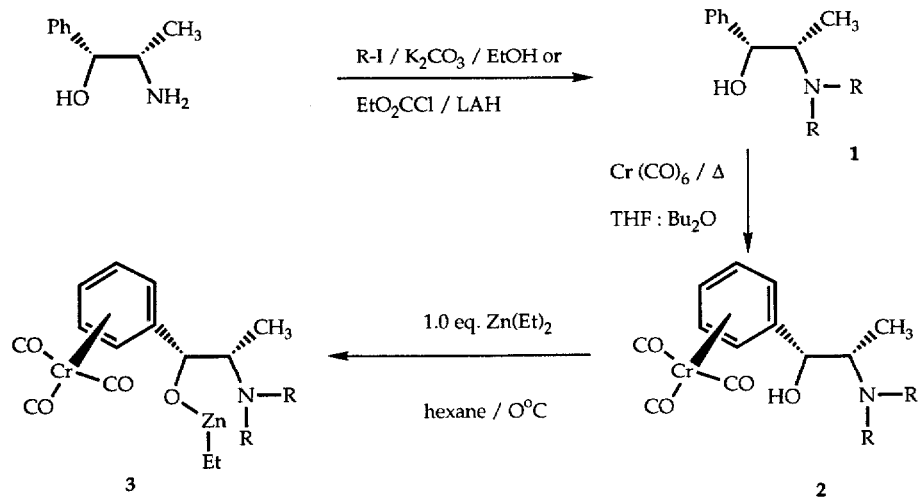
Steven B. Heaton and Graham B. Jones*

Department of Chemistry, Clemson University, Clemson SC 29634-1905, USA

Key Words: enantioselective catalyst ; norephedrine ; arene chromium tricarbonyl ; diethyl zinc ; chiral 1,2 addition.

Abstract: The preparation of a rationally designed catalyst system derived from norephedrine is reported. The key stereodirective element emanates from a chromium tricarbonyl group complexed to one face of the aryl ring. The catalysts mediate the addition of diethyl zinc to a variety of aldehydes with extremely high enantioselectivity.

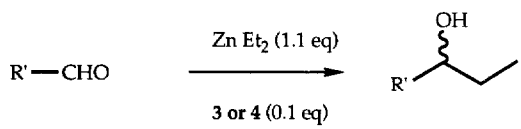
The development of efficient enantioselective catalysts, applicable to a wide range of carbon-carbon bond forming reactions represents a pivotal challenge to the synthesis community.[1] As part of an ongoing study concerned with the development of chiral metallocyclic Lewis acids sourced from readily available enantiopure precursors, we envisioned that an arene chromium carbonyl group (ACC group) linked with a rigidly defined chiral metallocyclic Lewis acid structure would serve as a highly selective catalyst system by virtue of the stereodirective capacity of the ACC group, and because of the potential *attractive* dipole based interactions between the ACC group and the reacting species.[2] In order to demonstrate this approach assembly **3** was constructed with the rationale that efficient enantioselective addition of diethyl zinc to aldehydes may be mediated by this system *via* the transition state assembly shown in Figure 1. As described below, this premise has been confirmed by experiment.



(1R, 2S) Norephedrine was bis alkylated to give N,N dialkyl precursors **1** using a variety of alkyl iodides.[3] The bis alkylated norephedrines were then subjected to ACC complexation, achieved using chromium

hexacarbonyl, to give catalyst precursors **2** in good yield.[4] Deprotonation using diethyl zinc in hexane then gave zinc alkoxides **3**, which proved to be highly selective catalysts for the addition of diethyl zinc to benzaldehyde (Scheme 1, R'=Ph), the results being summarized in Table 1. Using 10 mol% of **3**, R=Bu, the enantioselective addition of diethyl zinc to benzaldehyde proceeded (0°C/ hexanes / 12h) in quantitative yield and gave a 99% enantioexcess of (R)-(+) 1-phenyl propanol, (entry 3).[5] A control reaction using the same catalyst but devoid of the ACC group i.e **5**, R=Bu gave a similar yield, but diminished enantioexcess.[6]

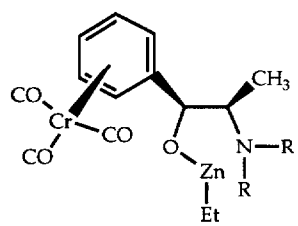
Scheme 1. Enantioselective alkylation of aldehydes.



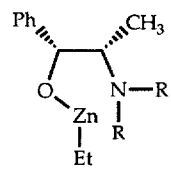
By switching to a (1S, 2R) derived ACC catalyst i.e **4**, R=Bu, the same reaction gave a 99% e.e. of the S-(-) enantiomeric carbinol (entry 4). The N,N dimethyl (entry 1) and N,N cyclopiperidyl (entry 2) catalysts also gave high enantiomeric excess, and *in all cases an appreciable enhancement in e.e. was observed using catalysts of type **3** and **4** relative to non ACC complexed catalysts **5/6**, confirming the rationale behind the catalyst design.*

Table 1 Formation of 1- phenyl propanol using norephedrine based catalysts **3** and **5**

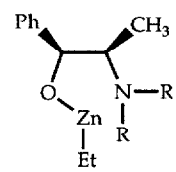
entry	cat, config.	R group.	ACC complexed	non complexed (**5/6**)	prod. config.
1	**3**,1R,2S	Me	**86%**	67%	R
2	**4**,1S,2R	-(CH2)5-	**96%**	90%	S
3	**3**,1R,2S	Bu	**99%**	94%	R
4	**4**,1S,2R	Bu	**99%**	94%	S



4



5



6

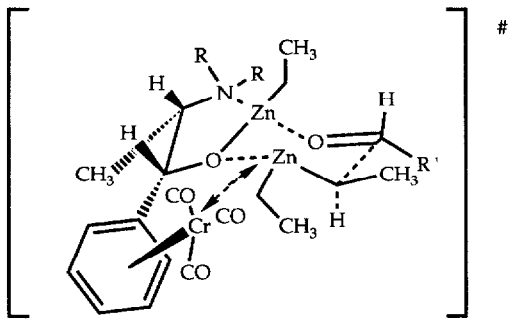
Having identified **3, 4 R=Bu** as excellent catalysts, these were tested in the enantioselective addition of diethyl zinc to a variety of aldehydes, the results are shown in Table 2. Nearly total selectivity is achieved in the addition of diethyl zinc to the napthaldehydes, with only traces of the other enantiomer detectable by chiral H.P.LC. analysis.[7] In all cases examined the chemical yields of product carbinols was excellent,[8] and the catalysts were recovered in near quantitative yield on work up, suitable for reuse.

Table 2. Addition of diethyl zinc to various aldehydes catalyzed by **3,4** R=Bu

cat, config.	aldehyde	%e.e. prod.	% yield prod.
3, (1R,2S)	benzaldehyde	99%	99%
4, (1S,2R)	1-napthaldehyde	>99%	98%
3, (1R,2S)	2-napthaldehyde	>99%	99%
4, (1S,2R)	p-anisaldehyde	94%	99%
3, (1R,2S)	phenanthrene-9-carboxaldehdye	93%	97%

In order to account for the extremely high selectivity observed in these reactions a transition state assembly is proposed as shown in Figure 1. In this orientation a cyclic chair transition state is established, with attractive dipole-dipole interactions between the ACC group and the coordinated diethyl zinc species, providing order.[2]

Figure 1.



The coordinated aldehyde alkyl group (R') lies equitorially, its orientation being a function of the size of the N,N dialkyl groups this giving rise to the expected (R) product alcohols using a (1R,2S) derived catalyst (**3**). In support of this attractive interaction ordered transition state theory, is the fact that an impure mixture (c.a. 3:1) of precursor **2, R= Bu** and **1, R=Bu** gave on treatment with 1 eq. of diethyl zinc, a catalyst which still delivered diethyl zinc to benzaldehyde (0°C/ hexanes / 12h) in 99% e.e. using 15 mol % of the catalyst. The enhanced reactivity of the ACC based catalysts can therefore be explained by increased transition state activation,[6] and as expected, in practice it is found that crude **2, R=Bu** (containing up to 20%of **1, R=Bu**) can be used with little or no loss in e.e. for the reactions reported herein.

The methodology described is noteworthy for several reasons.(1) Both the (1R,2S) and (1S,2R) norephedrine precursors are commercially available in enantiopure form. (2) Formation of the catalysts is a trivial operation, requiring no special purification procedures. (3) Extremely high enantioexcess is attainable for the 1,2 addition of diethyl zinc to a variety of aldehydes. (4) This represents the first example of an ACC containing controller ligand being used as a catalyst, based on attractive interactions in the transition state, and holds promise for future application in a variety of systems.[9] The development and scope of these and related catalyst systems is currently under study.

Preparation of **2, R=Bu**

(1R,2S) N,N Dibutyl norephedrine (0.480 g, 1.83 mmol) and chromium hexacarbonyl (0.4 g, 1.82 mmol) were placed in a flame dried round bottomed flask fitted with a reflux condenser. The contents were evacuated and purged with argon three times. A 10:1 mixture of deoxygenated di-n-butyl ether:THF (10 ml) was cannulated into the flask, and the resulting mixture was heated to reflux under argon for 12 h. The mixture was cooled to -78°C then warmed to room temperature, filtered through a fritted funnel, thence through a plug of silica. The washings were subjected to dry flash chromatography (1:1 ether:hexanes eluent), then the fractions condensed *in vacuo* to yield the product **2**, R=Bu (0.603 g, 83%) as a pale yellow oil.[10]

References:

1. For review see Narasaka, K. ; *Synthesis*, **1991**, 1.
2. This phenomenon has been suggested in a number of cases. See Roush, W. R. ; Park, J. C. ; *J. Org. Chem.*, **1990**, *55*, 1143; Mukai, C. ; Cho, W. J. ; Kim, I. J. ; Hanaoka, M. ; *Tetrahedron Lett*, **1990**, *31*, 6893; For a recent report of a catalyst system based on steric and attractive interactions see Corey, E. J. ; Loh, T. P. ; *J. Am. Chem. Soc.* , **1991**, *113*, 8966.
3. All new compounds gave satisfactory spectroscopic and analytical data.Yields of **1**; R= Me (using ethyl chloroformate then LAH),99%; **1**, R=Bu (using n-butyl iodide), 68%; **1**, R=cyclopiperidyl (using 1,5 diiodopentane), 99%.
4. X-ray crystallographic studies on derivatives of this and other complexes will be reported elsewhere.
5. Absolute configurations were determined by optical rotation.
6. Whilst this work was in progress, a report appeared detailing similar studies on non ACC containing catalysts (generally lower enantioselectivities) see Soai, K. ; Yokoyama, S. ; Hayasaka, T. ; *J. Org. Chem.* , **1991**, *55*, 4264.
7. Retention times using a Diacel OD column; 254 nm U.V. detector; flow rate 1.0 ml / min; (10% isopropanol / 90% hexanes as eluent) : 1-(1-napthyl) propanol: (R)=13.4 min, (S)=7.9 min; 1-(2-napthyl)propanol: (R)=28.8 min, (S)=26.4 min; 1-(p-anisyl)propanol: (R)=6.9 min, (S)=7.75 min; 1-(9-phenanthryl) propanol: (R)=14.8 min, (S)=17.2 min: 1-phenyl propanol:(2.5% isopropanol / 97.5% hexanes eluent) (R)= 12.2 min, (S)= 13.1 min; Racemic comparison samples were synthesized using Grignard additions (EtMgBr) on the corresponding aldehydes.
8. Isolated yields after preparative chromatography.
9. A recent report details the use of wholly synthetic chiral 1,2 disubstituted arene chromium tricarbonyl catalysts in the enantioselective addition of diethyl zinc to benzaldehyde. See Uemura, M. ; Miyake, R. ; Hayashi, Y. ; *J. Chem. Soc. Chem. Commun.* , **1991**, 1696 and references therein. The enantioexcesses reported are lower than those obtained using **3, R=Bu** (the transition state assembly does not involve attractive interactions).
10. 1H NMR (300 MHz; $CDCl_3$) 0.85-0.90 (6H, m, $\mathbf{CH_3}CH_2CH_2\mathbf{CH_2}$), 1.03 (3H, d, J=6.8Hz, $\mathbf{CH_3}CH$), 1.17-1.40 (8H, m, $CH_3\mathbf{CH_2CH_2}CH_2$), 2.34 (4H, m, $CH_3CH_2CH_2\mathbf{CH_2}$), 2.87 (1H, q, J= 6.8 Hz, CHMe), 3.48 (1H,br s, **OH**), 4.19 (1H, t, J= 6.8 Hz, $CO_3CrPh\mathbf{CH}$), 5.18-5.58 (5H, m, $CO_3Cr\mathbf{Ph}$).

(Received in USA 31 December 1991)