SYNTHETIC COMMUNICATIONS, 23(9), 1251-1259 (1993)

ENANTIOSELECTIVE APPROACHES TO RHODIUM

CATALYSED ALDOL-TYPE REACTIONS

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ABSTRACT: Homochiral catalysts, [Rh(norbornadiene)-(homochiral diphosphine)]⁺ X^-/H_2 , were tested to assess possible enantiocontrol in the aldol-type coupling of activated vinyl components with aldehydes. A related approach, via *in situ* rhodium silyl enolates, was also investigated.

 α,β -Unsaturated carbonyl systems 1 have found wide use as electrophiles at the β - and carbonyl carbons. In stark contrast, the introduction of nucleophilic character at the α -carbon has proven much more difficult. Since the reaction of an electrophile (especially in aldol-type reactions) at the sp²hybridised position constitutes a valuable synthetic manipulation, much effort has been expended in the development of viable methods to achieve this trans-

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SCHEME 1



formation. Reported routes have largely been based on the stepwise procedure depicted in **SCHEME 1**.¹ The primary drawback of these solutions is the need for stoichiometric quantities of M-X, although direct catalytic conversion of **1** to **2** has been achieved via the Baylis-Hillman reaction.²

Catalytically controlled asymmetric synthesis of organic molecules remains a topic of major current interest. Despite significant success with chiral rhodium catalysts in reductive processes, asymmetric adaptations to rhodium catalysed C-C bond formation reactions have been largely restricted to carbene insertion systems.³ Various workers have pointed out the putative involvement of a rhodium enolate species in the coupling of silyl enol ethers with carbonyl electrophiles⁴ (EQU.1).



The silyl enol ethers used can be preformed^{4a,b,c,e,f} or generated *in*,*itu*.^{4d g} The recent contribution by Heathcock *et al*.^{4f} presents the first compelling experimental evidence for rhodium enolate involvement via independant metal exchange synthesis. In a related vein, Matsuda *et al*. have reported the rhodium hydride catalysed direct coupling of vinyl systems with aldehydes.⁵ This latter report suggests that the reaction proceeds via the catalytic cycle depicted in **SCHEME 2** and, unlike the silyl enol system, has no stoichiometric requirement for enolate generation. We here report our preliminary attempts to extend the generality of, and to develop asymmetric variants for, the above coupling reactions (**EQU.1** and **SCHEME 2**)



The silyl enol ether system has been subject to greater study and a single attempt at asymmetric induction reported.⁴^c This, the first example of enantioselective aldol addition with chiral rhodium catalysis, was



effected by formally prepared rhodium(I)-chiral diphosphine catalysts 3-5. The e.e. (5-12%) achieved with 5 mol% of catalyst were disappointing. $[Rh_4(CO)_{12}]$ has been shown to be the most efficient catalyst (< 0.5 mol%) for this three component coupling (vinyl, trialkylsilane, aldehyde) where the enolate is generated *in situ* (EQU.2).³⁸ The additional observation that phosphine additives enhanced the efficiency (yield and stereoselectivity) prompted us to investigate the

possible enantioselectivity that homochiral diphosphines could provide.



In order to assess this, the MVK, PhCHO, Et_2MeSiH combination was chosen as the standard reaction mixture. Treatment of this with $[Rh_4(CO)_{12}]$ - chiral diphosphine (7-9) catalyst mixtures unfortunately yielded optically inactive coupling product 6. As an alternative for this system, the neutral rhodium carboxylate $[Rh(RCO_2)_4]$ catalyst types were tested for activity. In the light of their ease of access⁶ and great efficiency in carbone insertions³, it was disappointing to observe no catalytic activity.

Attention was then focussed on the alternative hydride approach. The required catalyst species **11** were prepared according to **SCHEME 3** and tested with the MVK - EtCHO substrate combination. The results of these couplings are reported in the **TABLE**. Whilst the e.e. values are at best modest, they represent the first indications that this catalytic approach merits further

SCHEME 3



investigation. In addition, whilst we have found that acrylic esters are not reactive as coupling partners, acrylonitrile is and can serve as an indirect source of the analogous carboxyl containing coupling products. Further exploitation of these observations is currently underway.



7 (+)-BDPMC





9 (-)-DIOP



10 (-)-BINAP

TABLE

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	Catalyst(mol%)	Time(h)	[α] _D	E.e.(%)	12
	lla (1%)	5	+5.39	15.7	
	11a (1%)	7	+5.85	17.0	
	lla (3%)	5	+6.30	18.3	
	11b (1%)	5	+5.40	15.7	
	11c (1%)	5.5	-7.82	22.7	
	11d (1%)	5	0	0	
	11d (2%)	14	0	0	

EXPERIMENTAL:

MVK = methyl vinyl ketone and NBD = norbornadiene. N.m.r. analyses were performed on a Varian Gemini 200 MHz spectrometer. All procedures involving the catalyst species were performed under argon using standard Schlenk and vacuum line techniques.⁷

Rhodium-diphosphines 11 a-d : General preparation.8

A stirred solution of $[Rh_2(\mu-Cl)_2(NBD)_2]^9$ (0.10g, 1 equiv) in degassed acetone (10 ml) was treated dropwise with AgBF₄ (0.11 g, 2 equiv) in acetone (10 ml) at room temperature. After stirring for an additional 2 h., the AgCl precipitate was removed by filtration. The mixture was then cooled to -15°C and treated dropwise with the diphosphine (1.7 equiv) in acetone (20 ml) over 30 min. The orange mixture was allowed to warm to room temperature over 2 h. Hydrogen was bubbled through the mixture for 15 min. and the solvent removed under vacuum to afford the final catalytic species as an orange-brown powder. These were used directly in the coupling reactions.

General coupling procedure to afford 12.10

Freshly distilled MVK (0.35 g, 5 mmol) and propanal (0.58 g, 10 mmol) were sealed under argon in a glass reaction vial with the catalyst (1-3 mol%) and oven heated at 105°C for 5-14 h. After cooling, the reaction mixture was passed through a short silica gel column (eluant 20% ethyl acetate-hexane) to remove the catalyst. Solvent was removed *in vacuo* and the coupling product analysed by n.m.r. using Eu(hfc)₃ chiral shift reagent.

ACKNOWLEDGEMENT: The authors thank the FRD and the University of Natal for financial support.

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(Received in UK 16 November 1992)