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HIGH PRESSURE MEDIATED ASYMMETRIC HENRY REACTION OF NITROMETHANE WITH CARBONYL COMPOUNDS CATALYZED BY CINCHONA ALKALOIDS

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Abstract - Asymmetric nitroaldol reactions, catalyzed by cinchona alkaloid, of nitromethane have been investigated. High pressure played an interesting role in the overall reactions that form β-nitro alcohols. From the enantiomeric states of the products formed under different reaction conditions, we deduce that the nature of transition termolecular species formed by the carbonyl compounds with quinidine or quinine determines the stereoselective outcome of the reaction under high pressure.

The nitroaldol (Henry) reaction is one of the most important methods of carbon-carbon bond formation.[1] The reaction of nitromethane with carbonyl compounds proceeds under basic conditions to produce the corresponding β-nitro alkanols which are important and versatile intermediates in the synthesis of nitroalkenes, β-amino alcohols, and α-nitro ketones.[2] Amino alcohols are of particular significance in the synthesis of biologically important compounds such as epinephrine and anthra-

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Dedicated to Professor James P. Kutney with celebration of his 70th birthday.

cycline antibiotics, while nitro ketones are valuable intermediates in the synthesis of several natural products.

Shibasaki ***et al.*** employed successfully rare earth metal oxides in asymmetric catalytic reaction of nitromethane with various aldehydes,[3, 4] whereas others used as catalysts enantiomeric pure guanidines with and without C_2 symmetry in similar reactions.[5,6] However, successful asymmetric nitroaldol reactions of nitroalkanes with ketones appear to have remained unreported in the literature.

In earlier studies,[7] under high pressure conditions in the presence of catalyzing ***n***Bu_4NF, we conducted the nitroaldol reaction of nitroalkanes with ketones to produce the corresponding nitro alcohols in moderate to high yields (60-90%). In general, the nitroaldol reaction of ketones is sensitive to steric factors with quite low yields of β-nitro alcohols. Such differences between these two members of the carbonyl family indicate a significant chemoselectivity of the reaction. There are only a few reports in the field of high pressure asymmetric induction.[8]

In this account, we examine the asymmetric nitroaldol synthesis, under high pressure and in the catalytic presence of either quinidine or quinine, of β-nitro alcohols from nitromethane and benzaldehyde (**1**) (Table 1). In addition, we suggest a reaction sequence that accounts for the pressure effect and its contribution to the asymmetric nitroaldol reaction of nitromethane with ketones.

At ambient pressure, a 4% yield of the (***S***)-nitro alcohol (**2**) of 18% ***ee*** was obtained (Entry 1). On the other hand, elevating the pressure from 1 to 2000 bar increased ***ee*** to 35% together with a slight change in yield (Entry 2). Further, increases in pressure produced increases in the chemical yield, up to 38-80%, but the ***ee*** decreased to 6-3% (Entries 3-5). Reducing the reaction time from 12 h to 2 h increased slightly the ***ee*** to 11% (Entry 6). No reaction took place in the absence of quinidine at 7000 bar (Entry 7). Thus, we confirmed that the reaction proceeds through a transition state in which the three molecules, i.e. **1**, nitromethane, and quinidine, interact. When quinidine was replaced by quinine the resulting nitro alcohol (**2**) possessed the opposite configuration (Entry 8). These results suggest that pressure and reaction time has a significant effect on the increase on the yield of ***ee*** of the nitro alcohol (**2**).

As shown in Scheme 1, a steric requirement is the most important stereodifferentiating factor that produces a free energy difference between the two possible orientations of **1**

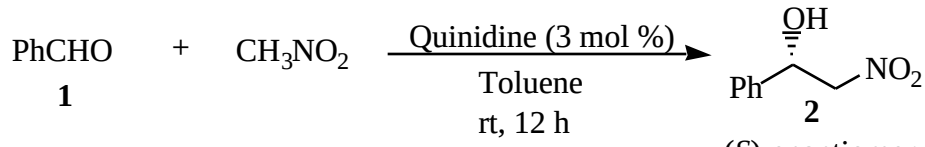


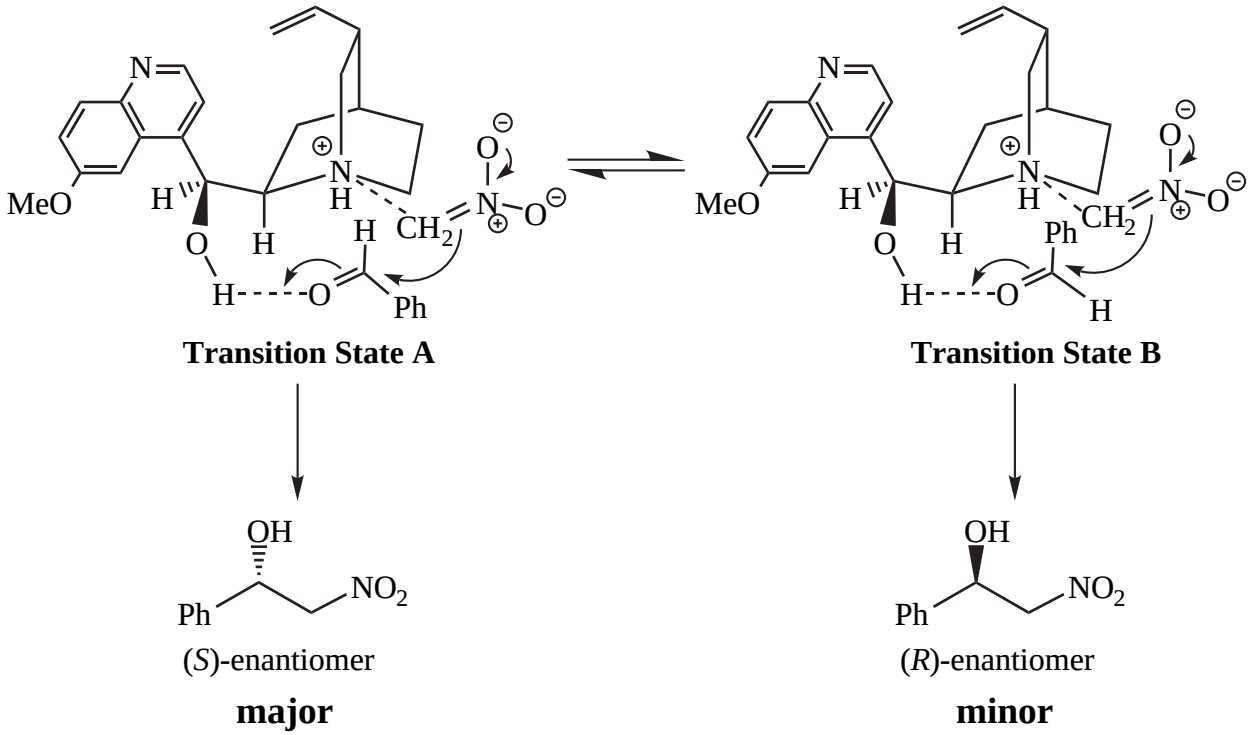
Table 1. The effect of pressure (addition of nitromethane to benzaldehyde)

Entry	Pressure (bar)	Time (h)	Yield of **2**[a] (%)	ee (%)[b]	config.
1	1	12	4	18	*S*
2	2000	12	9	35	*S*
3	3000	12	38	6	*S*
4	5000	12	66	4	*S*
5	7000	12	80	3	*S*
6	7000	2	37	11	*S*
7[c]	7000	12	-	-	-
8[d]	2000	12	8	28	*R*

a) Isolated yield based on **1**.
b) *Ee* was determined by HPLC analysis.
c) In the absence of catalyst. d) Quinine was used as the catalyst.

in the transition states that lead to the ***R*** or ***S*** products. Three features of the basic reaction can be deduced. Firstly, the alkaloid catalyst abstracts a proton from nitromethane to give an ion pair, whereas the hydroxy group of quinidine holds **1** by a hydrogen bond to give a termolecular complex. Secondly, the rate controlling addition of a carbanion, such as $^{-}CH_2NO_2$, to the carbonyl group of **1** occurs in two ways according to the two possible orientations of **1** in the termolecular complex. Thus, an addition to the ***re*** face of **1** produces the (***S***)-nitro alcohol (**2**) (**S**cheme 1 in the case of the transition state (**A**)) or an addition to the ***si*** face of **1** to give the (***R***)-nitro alcohol (**2**) (Scheme 1 in the case of the transition state (**B**)). Thirdly, in the case of Scheme 1 a steric interaction between the C_2 methylene group of the catalyst and the phenyl group of **1** makes the carbanion addition to the ***re*** face of **1** predominant, so that the ***S*** enantiomer is produced in excess.

Thus the termolecular complex **(B)** is the sterically more congested and unfavored transition state. In other word, the transition state **(B)** is weaker than transition

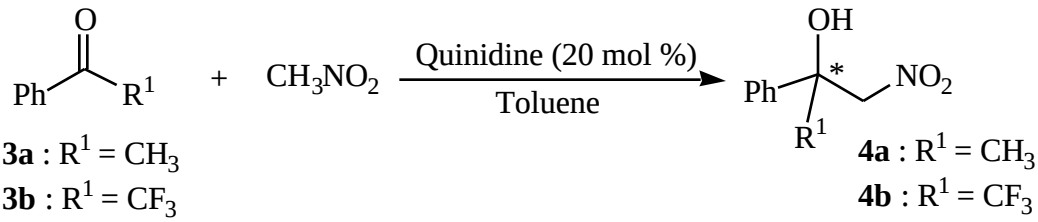


Scheme 1

state **(A)**. The free energy difference between the complexes **(A)** and **(B)** is responsible for the observed ***ee*** through the pressure changes from 1 bar up to 2000 bar. Increased pressure is anticipated to favor the formation of an enantiomer which is produced through a sterically more congested transition state. That is, pressure is expected to reduce the ***ee*** of the present asymmetric reaction. The observed decrease in the amount of ***ee*** with pressure is explained by this difference in the pressure effect on the two transition states. Presumably, a similar explanation also rationalize the quinine catalyzed additions, taking into account of conformations of similar termolecular transition state complexes.[9] The decrease of the ***ee*** with pressure can be explained by a lesser degree of selection between the transition states (**A**) and (**B**) at high pressure where the subtle interactions will be over ridden when the very high pressures exceed 3000 bar. Analogous results have been observed in high pressure mediated asymmetric Michael[9] and Baylis-Hillman reactions.[10]

Further studies explored the asymmetric nitroaldol reaction of nitromethane with acetophenone (**3a**) under high pressure (Table 2). At first, asymmetric nitroaldol reaction of nitromethane with **3a** was carried out in the presence of 20 mol% quinidine at ambient pressure, although the reaction did not proceed at all (Entry 1). By increasing

the pressure to 7000 bar a 2% yield of **4a** was obtained over 72 h but below 1 % ***ee*** (Entry 2). Elevation of the pressure from 7000 to 10000 bar increased the yield to 31% yield but unfortunately, did not improve the ***ee*** (Entry 3). In these cases, we recognized that the asymmetric nitroaldol reaction of a ketone, such as **3a**, needed high pressure. Therefore, we thought that replacement of CH_3 by CF_3 would likely be observed by higher reactivity. Indeed, as shown by Entry 4 of Table 2, the reaction of nitromethane with 2,2,2-trifluoroacetophenone (**3b**) took place in 84% yield without employing pressure, but the ***ee*** of the product was below 1%. Thus, there was a significant substituent effect. In order to increase the percentage of ***ee***, the reaction of nitromethane with **3b** was performed at -78 ^{o}C (Entry 5) to give the corresponding nitro alcohol (**4b**) in 81% yield. Unfortunately, the enantioselectivity was merely enhanced to 21% ***ee***.



3a : $R^1 = CH_3$
3b : $R^1 = CF_3$

4a : $R^1 = CH_3$
4b : $R^1 = CF_3$

Table 2 Nitroaldol reactions of ketones with nitromethane

Entry	R^1	Pressure (bar)	Temp. (^{o}C)	Time (h)	Yield of **4**[a)] (%)	*ee* (%)[b)]
1	CH_3	1	25	120	-	-
2	CH_3	7000	25	72	2	<1
3	CH_3	10000	25	1	31	<1
4	CF_3	1	25	12	84	<1
5	CF_3	1	-78	8	81	21

a) Isolated yield based on **3**.
b) *Ee* was determined by HPLC analysis.

In summary, we have investigated asymmetric nitroaldol reaction of nitromethane with carbonyl compounds. Although the enantiomeric excesses are moderate at

present, several important parameters have been delineated and the results of these investigations have provided useful insights into the understanding of this type of reaction under high pressure.

EXPERIMENTAL

(***S***)-2-Nitro-1-phenylethanol (**2**) : High pressure reactions were carried out in a Teflon tube plugged with Teflon stopper. To a solution of benzaldehyde (**1**) (106 mg, 1.00 mmol) and nitromethane (0.08 mL, 1.48 mmol) in toluene (3 mL) was added quinidine (12 mg, 0.037 mmol). The reaction mixture was stirred at rt under atmospheric pressure until most of quinidine was dissolved (10-15 min). The tube was placed in a high-pressure reactor and pressurized (0.7 GPa) at ambient temperature. After 12 h, the pressure was released and the reaction mixture was poured into ice-cold aqueous 5% HCl and extracted with ethyl acetate. The extracts were washed successively with 5% HCl, water and brine. The solution was dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The crude products were purified by column chromatography (SiO_2, Hexane/AcOEt : 5/1) to give the adduct (**2**) of 3 % ***ee*** in 80 % yield. The enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALCEL OJ: ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.65 (d, ***J*** = 3.1 Hz, 1H, OH); 4.46-4.64 (m, 1H, CH_2); 5.48 (dt, ***J*** = 9.2, 3.1 Hz, 1H, CH); 7.30-7.45 (m, 5H, C_6H_5). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 71.0, 81.2, 125.8, 128.8, 128.9, 138.0. IR (neat, cm^{-1}) 3449, 3034, 2922, 1556, 1379, 1066. MS (***m/z***) 167, 120, 105, 91, 77.

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