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A Novel Nitroaldol Reaction Catalyzed by Rhodium Complex in the Presence of a Silyl Ketene Acetal

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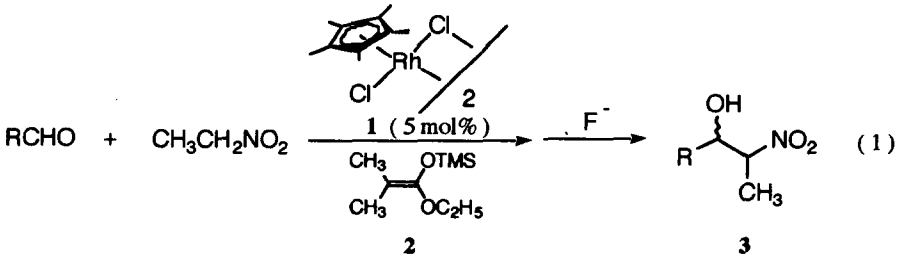
Abstract: A rhodium complex, $[\{Rh(C_5Me_5)Cl\}_2(\mu\text{-}Cl)_2]$ (**1**), catalyzed smoothly the nitroaldol reaction of nitroethane with aldehydes in the presence of a silyl ketene acetal (**2**). This reaction is the first example of transition metal complex-assisted nitroaldol reactions under mild and neutral conditions.

Nitroaldol (the Henry) reaction is one of the fundamental C-C bond-forming reaction to afford nitro alcohols which are known to have potential utility as useful synthetic intermediates for further transformations in synthesis and the classical nitroaldol reaction is routinely performed under basic conditions.[1] Recent improvements have been focused on diastereo-[2] and enantio-selectivity[3]. To our knowledge nitroaldol reactions using transition metal complexes are not yet found.[1] During the course of studies on the Mukaiyama aldol reaction using rhodium complexes[4], we found a novel and quite interesting reaction assisted by a rhodium complex, $[\{Rh(C_5Me_5)Cl\}_2(\mu\text{-}Cl)_2]$ (**1**).

Admixture of silyl ketene acetal **2** with benzaldehyde in CH_2Cl_2 in the presence of catalytic rhodium complex **1** at room temperature overnight resulted in low yield (~20%) of the corresponding aldol product. Replacing the solvent by nitroethane which is capable of enhancing the nucleophilicity of silyl nucleophiles[5], *to our great surprise,* altered the reaction course and resulted in the formation of only nitroaldol[6] (syn/anti=2:3) in good yield with virtually no products arising from normal aldol condensation (eq 1). This is apparently a result that the solvent itself works as a nucleophile by being activated through *unknown* mode in the reaction system.



2 3 (1)

Typical procedure is as follows ; To a solution of Rh-Cp* complex **1** (20.4 mg, 0.033 mmol) in nitroethane (3mL, 43 mmol) were added benzaldehyde (71.2 mg, 0.67 mmol) and silyl ketene acetal **2** (126.2 mg, 0.67 mmol). After stirring for 12 h, the excess nitroethane was removed with a rotary evaporator. The crude product, consisting of free nitro alcohol and the silylated one, was treated with TBAF and purified by flash column chromatography to give a mixture of nitroaldol isomers.

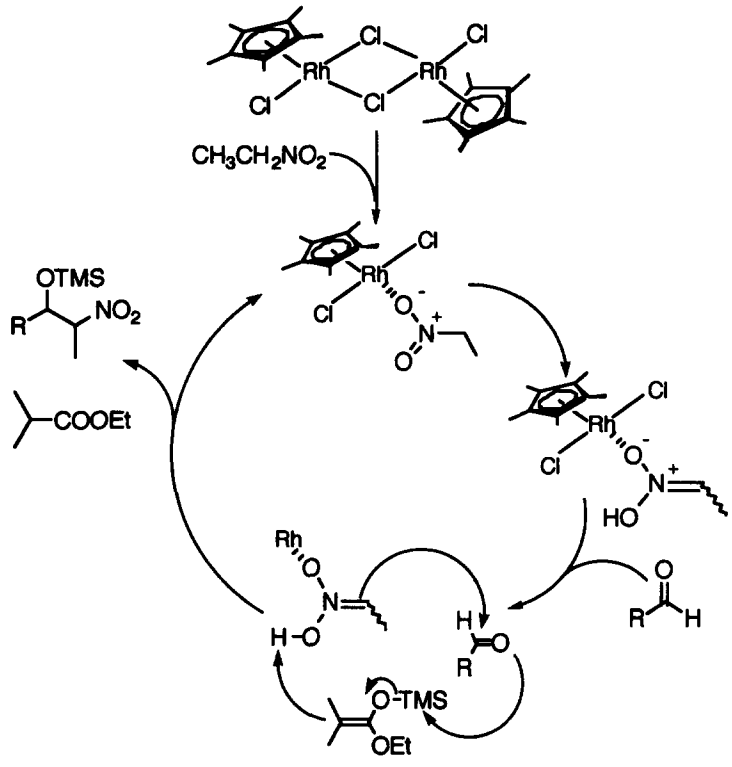
Table 1. Rhodium Catalyzed Nitroaldol Reaction (eq 1)[a]

Entry	RCHO	Mole Equiv. of Nitroethane[b]	%Yield of Nitroaldol **3**[c]
1	PhCHO	5 (CH_2Cl_2)[d]	no reaction
2	PhCHO	10 (THF)[d]	16 (**3a**)
3	PhCHO	43	82 (**3a**) (syn/anti=39/61)[e]
4	PhCHO	43	24[f] (**3a**)
5	$PhCH_2CHO$	43	62[g] (**3b**)
6	PhCH=CHCHO	43	48 (**3c**)
7	$PhCH_2CH_2CHO$	43	54[g] (**3d**)

[a] The reaction was carried out at rt for 12 h with a stoichiometric amount of silyl ketene acetal **2** in the presence of Rh complex **1** (5 mole%), see the text. [b] Large excess of nitroethane was used as solvent. [c] Isolated yield. [d] Used as co-solvents (CH_2Cl_2, THF). [e] See note 6. [f] One third mole equiv. of silyl ketene acetal **2** was used. [g] 2 days reaction.

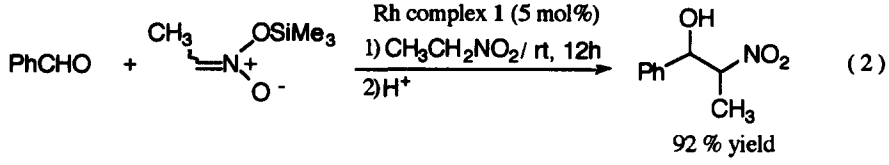
Some preliminary features of the rhodium-assisted nitroaldol reaction should be fairly confirmed from the results, shown in Table 1. The reaction was remarkably prevented by using the solvents (CH_2Cl_2 and THF), capable of competing with nitroethane for coordination to the rhodium, so that nitroethane in the reaction should be activated by the metal (entries 1,2). From the controlled experiment conducted in entry 4, where the yield of product was reduced in proportion by using one third molar ratio of silyl ketene acetal **2**, it was proved that the stoichiometric amount of **2** is responsible for the satisfactory yield. In view of the high nucleophilic reactivity of **2** in Lewis acid media[7], we assume that the silane **2** must be consumed before the suspected Mukaiyama aldol reaction in order to secure the nitroaldol reaction. It therefore seems logical that silyl ketene acetal **2** works cooperatively facilitating the nitroaldol reaction.[8] After prolonged reaction times, reaction with alkyl aldehydes proceeded in moderate yields.

Willkinson complex did not work whereas Cp*$RhCl_2$·DMSO, equivalent to a monomer of the rhodium complex **1**, catalyzed the reaction well. Considering the effectiveness of such a monomer complex, the reaction is supposed to be practically initiated by dissociation of the dimer complex **1** to a monomer species coordinated with nitroethane. In addition, the occurrence of trimethylsilyl nitroethane was not detected in the reaction of nitroethane with silyl ketene acetal **2** in the presence of catalytic rhodium complex **1** without aldehydes.



Scheme 1

Based on the above-mentioned consideration, we propose a catalytic cycle for the sequence depicted in Scheme 1. Nitroethane coordinated to the rhodium complex undergoes easily isomerization to the *aci*-nitro species, followed by deprotonation with silyl ketene acetal **2** to produce an active nucleophile which realizes the following condensation. In the case of nitromethane, that is prone not to take its *aci*-form, the nitroaldol reaction with benzaldehyde led to the corresponding nitro alcohol **4**[6] in low yield (~18%) under reaction conditions similar to those of entry 3.



(2)

Additional experiment was conducted in order to confirm an alternative and effective route to nitro alcohols in the presence of catalytic rhodium complex **1**. The reaction using the preformed trimethylsilyl nitroethane quite easily proceeded with a variety of aldehydes in nitroethane under similar conditions in good to excellent yields

(syn/anti=1:2.5) (eq 2) where the rhodium complex seems to presumably play a role of Lewis acid.[10] Studies on this Lewis acid assisted reaction will be reported elsewhere in due course.

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6. **3a** : ^{1}H-NMR ($CDCl_3$) : δ 1.30 (d, J=6.59, 1.8H, anti), 1.49 (d, J=6.81, 1.2H, syn), 2.74 (brs, 1H), 4.59-5.40 (m, 2H), 7.34 (s, 5H). **3b** : ^{1}H-NMR ($CDCl_3$) : δ 1.62 (d, J=6.81, 3H), 2.24 (brs,1H), 2.67-2.88 (m, 2H), 4.07-4.26 (m, 0.5H), 4.33-4.76 (m, 1.5H), 7.28 (s, 5H). ^{13}C-NMR ($CDCl_3$) : δ 12.73, 16.23, 39.59, 39.71, 72.88, 73.74, 85.45, 86.48, 127.09, 128.80, 129.14, 129.35, 136.15, 136.30 syn/anti=1:1 (from ^{13}C-NMR). **3c** : ^{1}H-NMR ($CDCl_3$) : δ 1.56 (d, J=6.59, 1H), 1.60 (d, J=6.81, 2H), 2.43 (brs, 1H), 4.50-4.75 (m, 1H), 4.76-4.96 (m, 1H), 6.11 (AB, J=15.83, 5.94, 1H), 6.77 (d, J=15.83, 1H), 7.34 (s, 5H). **3d** : ^{1}H-NMR ($CDCl_3$) : δ 1.52 (d, J=6.81, 1.5H), 1.54 (d, J=6.81, 1.5H), 1.64-1.96 (m, 2H), 2.38 (brs, 1H), 2.57-3.06 (m, 2H), 3.77-4.25 (m, 1H), 4.33-4.67 (m, 1H), 7.22 (s, 2.5H), 7.24 (s, 2.5H). **4** : ^{1}H-NMR ($CDCl_3$) : δ 2.86 (brs, 1H), 5.46 (dd, J=7.91, 4.61, 1H), 7.39 (s, 5H). ^{13}C-NMR ($CDCl_3$) : δ 70.96, 81.18, 125.84, 128.83, 129.08, 138.13. anti-Acetate from **3a** : ^{1}H-NMR ($CDCl_3$) : δ 1.34 (d, J=6.81, 3H), 2.01 (s, 3H), 4.92 (dq, J=9.88, 6.81, 3H), 6.05 (d, J=9.88, 1H), 7.38 (s, 5H). syn-Acetate from **3a** : ^{1}H-NMR ($CDCl_3$) : δ 1.56 (d, J=6.81, 3H), 2.14 (s, 3H), 4.81 (dq, J=5.06, 6.81, 1H), 6.33 (d, J=5.06, 1H), 7.34 (s, 5H).
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8. The reactions did not work with trimethylchlorosilane, *N*-(trimethylsilyl)imidazole, and the TBDMS isomer of silyl ketene acetal **2** instead of **2.**
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