Rh^{I}-catalyzed aldol-type reaction of organonitriles under mild conditions†

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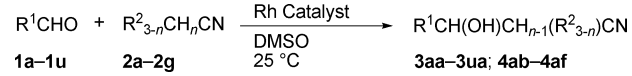
An aldol-type reaction of organonitriles with aldehydes was catalyzed by a Rh^{I}(OR) species under ambient conditions, and the reaction displayed a broad substrate scope with respect to both organonitrile and aldehyde components.

The nitrile functionality is synthetically versatile for many functional group conversions.[1] Incorporation of a nitrile fragment into a carbon framework provides rapid access to a number of useful chemicals such as α-amino and α-hydroxy carboxylic acid derivatives as well as nitrile-branching polymers. Concerned with this goal, cyanation strategies[2] have been most widely employed so far. In contrast, aldol-type reactions of alkylnitriles are those in which nitriles serve as enolate equivalents incorporating aldehyde directly. This alternative strategy for introducing the nitrile functionality is an attractive process, providing β-hydroxynitriles, which are potential precursors for pharmaceutically important substances.[2] Although pioneering achievements related to this end have been reported recently by Murahashi,[3] Verkade,[4] Knochel,[5] Shibasaki and Kanai[6] and others,[7] some drawbacks resulting from concomitant dehydration,[3] high catalyst loading (~0.05 molar equiv.) and alkylnitrile loading (*ca.* 20 molar equiv.)[4–6] need improvement in order to increase catalytic efficiency and atom economy. We report here on the first example of the Rh^{I}-catalyzed aldol-type reaction of unactivated alkylnitriles under mild conditions, employing lower catalyst and substrate loading, thereby expanding substrate scope with respect to both aldehyde and organonitrile components (Scheme 1).

The Rh catalyst was prepared by treatment of [Rh(OH)(cod)]$_2$ (0.01 molar equiv.) with Cy_3P (0.04 molar equiv.) in toluene at 25 °C for 0.5 h under argon (Cy = *c*-hexyl). After the solvent and cod were removed by evaporation in vacuum, MeCN (**2a**: 19 molar equiv.) and benzaldehyde (**1a**: 1 molar equiv.) were added sequentially to the resulting yellowish viscous oil containing the Rh complex at 25 °C. The resulting suspension was kept at 50 °C with stirring for 24 h, during which time the mixture became a clear solution, giving the β-hydroxynitrile **3aa** in an isolated yield of 61% after column chromatography on silica gel. The use of Cy_3P alone (0.04 molar equiv.) resulted in complete recovery of **1a**. In addition, when [RhCl(cod)]$_2$ was used in place of [Rh(OH)(cod)]$_2$, no reaction was observed, suggesting that the hydroxyl group of Rh worked as a base. In contrast, a slightly better yield of **3aa** was obtained with [Rh(OMe)(cod)]$_2$ (70%). Two molar equivalents of Cy_3P per Rh ([Rh(OMe)(cod)]$_2$: Cy_3P = 1 : 4) was most appropriate, as equal amounts decreased the yield considerably (40%) and a three-fold excess gave a comparable result (66%). For reference, less basic phosphines (Ph_3P, (o-Tol)$_3$P and n-Bu_3P) and a phosphite ((PhO)$_3$P) were tested but shown to be far less effective than Cy_3P under otherwise identical conditions (**3aa**: <16% with n-Bu_3P, and ~1% with the others). The use of bidentate phosphines such as dppe, dppp, dppb, and (*R*)-BINAP resulted consistently in lower conversions (<23%). The solvent screening with [Rh(OMe)(cod)]$_2$–4Cy_3P (Rh: 0.01 M; 50 °C, 24 h) suggested that aprotic polar solvents including DMSO, DMF, DMA, NMP and DMI were more promising (**3aa**: 77–84%). In *t*-BuOH the reaction proceeded more sluggishly (61%), but better than in MeOH (31%).

Finally, [Rh(OMe)(cod)]$_2$ was tested further, and after an additional set of experiments this was proven to be the best surrogate for [Rh(OH)(cod)]$_2$, affording the highest productivity (99% of **3aa** with [Rh(OMe)(cod)]$_2$ (0.01 molar equiv.) and Cy_3P (0.04 molar equiv.); Rh: 0.01 M in DMSO, 25 °C, 6 h). We chose DMSO as a representative solvent and further screened additional phosphine ligands (Fig. 1). Among the ones tested we found that R_3P ligands or the 2-(1,1′-biphenyl)PR_2 ligands **5a** (R = Cy) and **5b** (R = *i*-Pr) were the most potent, affording the highest conversion of **2a** (>95%). Surprisingly, t-Bu_3P or other $ArCy_2P$- and Ar(t-Bu)$_2$P-based phosphines **5c–e** were totally unsatisfactory (**3aa**: <5%), suggesting that the reaction is strongly structure-demanding and sensitive to the steric bulk around the outer sphere of Rh.

Given the above optimal conditions,‡ the substrate scope was then investigated (Tables 1 and 2). Aromatic, heteroaromatic, α,β-unsaturated and aliphatic aldehydes **1a–u** were all suitable substrates (Table 1), although a somewhat lower yield



Scheme 1 General scheme of the Rh-catalyzed nitrile aldol reaction.

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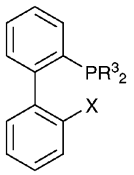
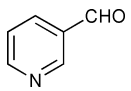
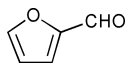
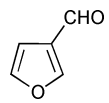
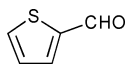
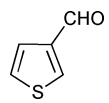


5a : R^3 = Cy; X = H
5b : R^3 = *i*-Pr; X = H
5c : R^3 = Cy; X = Me
5d : R^3 = Cy; X = NMe_2
5e : R^3 = *t*-Bu; X = H

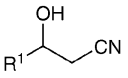
Fig. 1 Biphenyl-based phosphines tested in the nitrile aldol reaction.

was obtained with linear aldehyde **1p** due to accompanying self-condensation (entry 16). 1,2-Addition predominated with the α,β-unsaturated aldehyde **1n** (entry 14). The 0.005 and 0.02 molar equivalents of $[Rh(OMe)(cod)]_2$ and Cy_3P used (respectively) were enough to achieve a reasonable yield (**3aa**: 90%) (entry 1). *t*-BuOH was a better solvent in several cases (entries 16, 18, 19 and 21) in terms of isolated yields of **3**. An attempt to reduce the molar equivalents of MeCN from 19 to 2–3 was also successful (Table 2). Even under these nitrile-saving conditions, near-maximum product yields were obtained in several cases (entries 1–4 and 6), albeit with a prolonged reaction time (24 h). Although low diastereoselectivities were obtained from **2b–2e** (entries 2–5), this modification reduced the amount of time spent separating and processing the reaction mixture to remove excess alkylnitriles, especially those of a higher molecular weight, from the products (Fig. 2).

Table 1 Rh-catalyzed aldol-type reaction of CH_3CN (**2a**) with aldehydes (19 : 1 molar ratio)[a]

Entry	Aldehyde	Product	Yield (%)[b]
1	C_6H_5CHO (**1a**)	**3aa**	99 (90)[c,d]
2	*o*-$CH_3(C_6H_4)CHO$ (**1b**)	**3ba**	97
3	*m*-$CH_3(C_6H_4)CHO$ (**1c**)	**3ca**	98
4	*p*-$CH_3(C_6H_4)CHO$ (**1d**)	**3da**	88
5	*o*-$Cl(C_6H_4)CHO$ (**1e**)	**3ea**	98
6	*m*-$Cl(C_6H_4)CHO$ (**1f**)	**3fa**	99
7	*p*-$Cl(C_6H_4)CHO$ (**1g**)	**3ga**	99
8	*p*-$F(C_6H_4)CHO$ (**1h**)	**3ha**	99
9	*p*-$Br(C_6H_4)CHO$ (**1i**)	**3ia**	99
10	*p*-$Ph(C_6H_4)CHO$ (**1j**)	**3ja**	95
11	*o*-$CH_3O(C_6H_4)CHO$ (**1k**)	**3ka**	93
12	(α-naphthyl)CHO (**1l**)	**3la**	98
13	(β-naphthyl)CHO (**1m**)	**3ma**	95
14	(*E*)-PhCH=CHCHO (**1n**)	**3na**	89
15	CyCHO (**1o**)	**3oa**	99[d]
16	$CH_3(CH_2)_3CHO$ (**1p**)	**3pa**	76[d] (83)[e]
17	 (**1q**)	**3qa**	99
18	 (**1r**)	**3ra**	99[f]
19	 (**1s**)	**3sa**	73[g]
20	 (**1t**)	**3ta**	56
21	 (**1u**)	**3ua**	68[e]

[a] *Reagents and conditions*: $[Rh(OMe)(cod)]_2$: Cy_3P : **2a** : aldehyde = 0.01 : 0.04 : 19 : 1; 25 °C, 6 h in anhydrous DMSO (Rh: 0.01 M). [b] Yield of isolated, purified products **3aa**–**3ua** (Fig. 2). [c] 0.005 molar equiv. of $[Rh(OMe)(cod)]_2$ and 0.02 molar equiv. of Cy_3P were used. [d] Reaction time: 18–24 h. [e] $[Rh(OMe)(cod)]_2$: Cy_3P : **2a** = 0.02 : 0.08 : 38; 24 h; Rh: 0.01 M in *t*-BuOH. [f] $[Rh(OMe)(cod)]_2$: Cy_3P : **2a** = 0.02 : 0.08 :77 ; 24 h; Rh: 0.0066 M in *t*-BuOH. [g] $[Rh(OMe)(cod)]_2$: Cy_3P : **2a** = 0.02 : 0.08 : 77; 48 h; Rh: 0.005 M in *t*-BuOH.



3aa: R^1 = Ph; **3ba**: R^1 = *o*-$Me(C_6H_4)$; **3ca**: R^1 = *m*-$Me(C_6H_4)$;
3da: R^1 = *p*-$Me(C_6H_4)$; **3ea**: R^1 = *o*-$Cl(C_6H_4)$; **3fa**: R^1 = *m*-$Cl(C_6H_4)$;
3ga: R^1 = *p*-$Cl(C_6H_4)$; **3ha**: R^1 = *p*-$F(C_6H_4)$; **3ia**: *p*-$Br(C_6H_4)$;
3ja: R^1 = *p*-$Ph(C_6H_4)$; **3ka**: R^1 =*o*-$MeO(C_6H_4)$; **3la**: R^1 = α-naphthyl;
3ma: R^1 = β-naphthyl; **3na**: R^1 = (*E*)-PhCH=CH; **3oa**: R^1 = Cy;
3pa: R^1 = $Me(CH_2)_3$; **3qa**: R^1 = 3-pyridyl; **3ra**: R^1 = 2-furfuryl;
3sa: R^1 = 3-furfuryl; **3ta**: R^1 = 2-thiophenyl; **3ua**: R^1 = 3-thiophenyl

Fig. 2 Aldol products **3aa**–**3ua**.

In summary, we have demonstrated that the Rh(OMe)-catalyzed aldol-type reaction of organonitriles with aldehydes is a useful method for obtaining high yields of the corresponding β-hydroxynitriles. The reaction is chemoselective and promising, with catalyst precursor loading (as low as 0.005 molar equiv.) and nitrile loading (as low as 2 molar equiv.) lower than those reported previously.[3–6] Investigations into the mechanistic aspects, including *ab initio* calculations,§ are now underway in our laboratories.

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Table 2 Rh-catalyzed aldol-type reaction between organonitriles and PhCHO (**1a**) (3 : 1 or 2 : 1 molar ratio)[a]

Entry	Nitrile	Product	Yield %[b]
1	CH_3CN (**2a**)	$PhCH(OH)CH_2CN$ (**3aa**)	98 (88)[c]
2	CH_3CH_2CN (**2b**)	$PhCH(OH)CH(CH_3)CN$ (**4ab**)	98[d]
3	$CH_3(CH_2)_4CN$ (**2c**)	$PhCH(OH)CH[(CH_2)_3CH_3]CN$ (**4ac**)	81[d,e]
4	$(C_6H_5)CH_2CN$ (**2d**)	$PhCH(OH)CH(C_6H_5)CN$ (**4ad**)	99[d]
5	CH_3OCH_2CN (**2e**)	$PhCH(OH)CH(OCH_3)CN$ (**4ae**)	56[d,e]
6	$(CH_3)_2CHCN$ (**2f**)	$PhCH(OH)C(CH_3)_2CN$ (**4af**)	95

[a] *Reagents and conditions*: $[Rh(OMe)(cod)]_2$: Cy_3P : nitrile : aldehyde = 0.01 : 0.04 : 3 : 1; 25 °C, 24 h in anhydrous DMSO (Rh: 0.03–0.04 M). [b] Yield of isolated, purified products. [c] 2 molar equiv. of **2a** were used. [d] Diastereomeric ratio = *ca.* 1 : 1.2. [e] $[Rh(OMe)(cod)]_2$: Cy_3P = 0.02 : 0.08; 24 h; Rh: 0.04 M in DMSO.

Notes and references

‡ *General procedure*: To a degassed and argon-saturated solution of $[Rh(OMe)(cod)]_2$ (4.8 mg, 0.01 mmol) in anhydrous toluene (0.5 mL) was quickly added a 1.0 M toluene solution of Cy_3P (40 μL, 0.04 mmol; commercially available from Aldrich) at 25 °C and the mixture was stirred at this temperature for 0.5 h. After evaporation of any volatile compounds *in vacuo* (1–3 Torr), degassed and argon-saturated DMSO (1.0 mL) was added to the resulting slurry, followed by sequential addition of CH_3CN (**2a**) (1.0 mL, 19.1 mmol) and PhCHO (**1a**) (103 μL, 1 mmol). The reaction mixture was stirred at 25 °C for 6 h and was diluted with Et_2O to dissolve all the precipitate. The entire mixture was filtered through a short pad of silica gel, transferred into a 100 mL round-bottomed flask with Et_2O, evaporated and concentrated. The residue was purified by column chromatography on silica gel (EtOAc–*n*-hexane = 2 : 1) to give β-hydroxynitrile **3aa**[8] (146 mg, 99% yield).

§ Preliminary calculations (B3LYP/LANL2DZ level) revealed that the $Rh^{I}(OH)$, complexed with one or two Cy_3P, changed their oxidation state upon MeCN addition, giving cationic $(Cy_3P)_n$-$Rh^{III}(OH)(N{\equiv}CMe)$ species in both cases. Full accounts on this and further theoretical investigations will appear elsewhere.

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