Rhodium-catalysed hydroacylation or reductive aldol reactions: a ligand dependent switch of reactivity†

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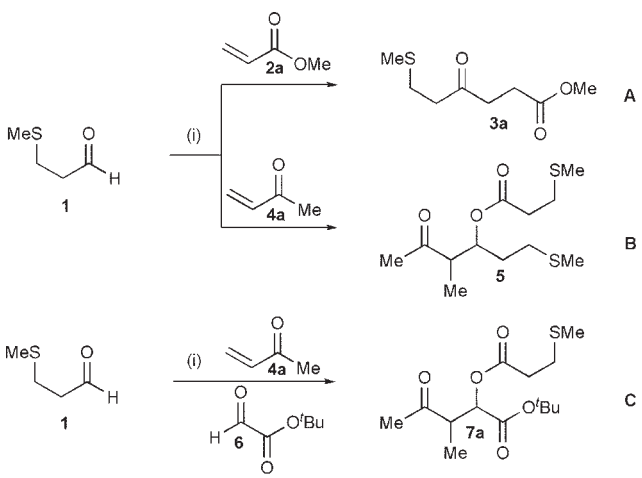
The pathway for the combination of enones and β-*S*-substituted aldehydes using Rh-catalysis can be switched between a hydroacylation reaction or a reductive aldol reaction by simple choice of the phosphine ligand; this catalyst controlled switch allows access to new ketone hydroacylation products; useful 1,4-diketone intermediates for the synthesis of N-, S- and O-heterocycles.

The use of 1,4-diketones in the Paal–Knorr synthesis of pyrroles, furans and thiophenes is a well established protocol.[1] Synthetic routes to the required γ-keto-ketone intermediates centre around the formation of acyl anion equivalents and their addition to α,β-unsaturated ketones. Umpolung reagents such as dithianes[2] and protected cyanohydrin derivatives[3] have proven useful reagents for such 1,4-addition reactions, however these systems lack step economy.[4] The catalytic Stetter reaction using thiozolium salts, or associated carbenes, generates acyl anion equivalents directly, however, these catalysts can suffer from low reactivity or competing benzoin side reactions.[5] Other methods for the synthesis of 1,4-diketones include oxidation of alcohols obtained from enolate mediated epoxide ring opening,[6] and the oxidative dimerisation of ketones,[7] which again lack in step economy and substrate diversity. To date 1,4-diketones remain a challenging synthetic moiety. Metal-catalysed hydroacylation has emerged as a useful method for the synthesis of a variety of ketone-containing compounds.[8] Recently we reported that β-*S*-substituted aldehydes, such as **1**, are suitable substrates for chelation assisted intermolecular hydroacylation of alkenes and alkynes (Scheme 1).[9] During our investigations we found that the combination of aldehyde **1** and methyl acrylate (**2a**), using the catalyst [Rh(dppe)ClO_4], furnished the desired γ-keto-ester hydroacylation product **3a** (Scheme 1, reaction A). However, reaction of aldehyde **1** with methyl vinyl ketone (MVK, **4a**) using the same catalyst furnished none of the desired 1,4-diketone, and instead underwent a reductive aldol coupling, providing ester **5** in a synthetically useful 73% yield (Scheme 1, reaction B). We further demonstrated that the reductive aldol system could be used in a three-component coupling incorporating *tert*-butyl glyoxylate (**6**), where the β-*S*-substituted aldehyde **1** acts as the reductant and delivers the acylated version of the reductive aldol product **7a** in good yield (Scheme 1, reaction C).[10,11] Although the reductive aldol reactions are useful in their own right, we still required an effective hydroacylation route to 1,4-diketones. In this communication we describe how this substrate controlled switch in reactivity can be converted to a *catalyst controlled* system, and in the process report the first intermolecular rhodium-catalysed hydroacylation of α,β-unsaturated ketones.

Our previously reported conditions for chelation assisted hydroacylation of alkenes and alkynes employed a [Rh(nbd)dppe]ClO_4 pre-catalyst, using either acetone or DCE as solvent;[9] we found that if DCE was used as solvent, acrylonitrile, MVK (**4a**), phenyl vinyl ketone (PVK, **4g**) and phenyl acrylate (**2b**) all gave good to excellent yields of the unexpected reductive aldol products. Attempts at using solvent effects to control the reactivity switch and deliver a hydroacylation process with ketone **4a** were unsuccessful. We next turned our attention to the use of alternative catalysts to control the reactivity. Our recently reported second-generation rhodium catalyst system, [Rh(nbd)DPEphos]ClO_4,[12] suppressed completely the formation of any reductive aldol product and gave exclusively the desired hydroacylation adduct.

The scope of the new hydroacylation system‡ was explored on a range of carbonyl containing compounds; **2a,b** and **4a–i** (Table 1). The [Rh(nbd)DPEphos]ClO_4 system tolerated the coupling of primary and secondary alkyl vinyl ketones in good



Scheme 1 Rh-catalysed hydroacylation and reductive aldol reactions: A *substrate* controlled reactivity switch.

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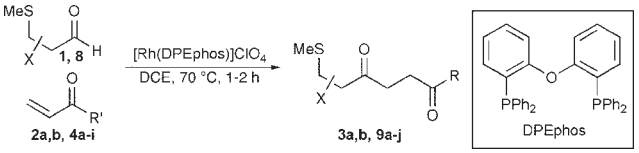
Table 1 Rh-catalysed hydroacylation reactions between α,β-unsaturated carbonyls and aldehydes **1** and **8**[a]



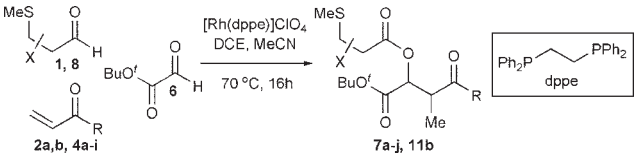
Entry	Aldehyde	Ketone	Product	Yield[b] (%)
1	**1**	(**4a**)	**9a**, R = Me	84
2	**1**	(**4b**)	**9b**, R = Et	79
3	**1**	(**4c**)	**9c**, R = Pent	68
4	**1**	(**4d**)	**9d**, R = ^{i}Pr	82
5	**1**	(**4e**)	**9e**, R = ^{t}Bu	53
6[c]	**1**	(**4f**)	**9f**, R = CHCHPh	69
7[c]	**1**	(**4g**)	**9g**, R = Ph	74
8[c]	**1**	(**4h**)	**9h**, R = 2-thienyl	75
9[c]	**1**	(**4i**)	**9i**, R = 2-furyl	68
10[c]	**1**	(**2a**)	**3a**, R = OMe	76
11	**1**	(**2b**)	**3b**, R = OPh	57
12[c]	**8**	(**4g**)	**9j**, R = Ph	95

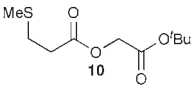
[a] *Reaction conditions*: aldehyde (1.0 equiv.), ketone (3.0 equiv.), [Rh(DPEphos)]ClO_4 (10 mol%). [b] Isolated yield. [c] Ketone (1.5 equiv.).

yields (up to 84%, entries 1–4). *tert*-Butyl-vinyl ketone also furnished the hydroacylation product but in a reduced yield of 53% (entry 5). The system tolerates both simple (entry 7) and heteroaromatic substrates (entries 8 and 9). The hydroacylation of cinnamyl vinyl ketone **4f** occurred exclusively at the terminal double bond in 69% yield (entry 6). Acrylates again gave the expected hydroacylation products (entries 10 and 11). Finally, the combination of PVK and the more conformationally constrained 2-(methylthio)benzaldehyde (**8**) proceeded in an excellent 95% yield (entry 12).

To demonstrate the generality of the reactivity switch we evaluated the same range of ketones in three-component reductive aldol reactions employing *tert*-butyl glyoxylate and the dppe-derived catalyst. The results are shown in Table 2. Whilst investigating the effect of solvents in the

Table 2 Rh-catalysed reductive aldol reactions between α,β-unsaturated carbonyls and aldehydes **1** and **8**[a]



Entry	Aldehyde	Ketone	Product	dr[b]	Yield[c] (%)
1	**1**	**4a**	**7a**, R = Me	3 : 1	92
2	**1**	**4b**	**7b**, R = Et	2.2 : 1	94
3	**1**	**4c**	**7c**, R = Pent	2.1 : 1	77
4	**1**	**4d**	**7d**, R = ^{i}Pr	2 : 1	96
5	**1**	**4e**		—	86
6[d]	**1**	**4f**	**7f**, R = CHCHPh	2.3 : 1	92
7[d]	**1**	**4g**	**7g**, R = Ph	2.1 : 1	83
8[d]	**1**	**4h**	**7h**, R = 2-thienyl	2.7 : 1	91
9[d]	**1**	**4i**	**7i**, R = 2-furyl	2.7 : 1	83
10[d]	**1**	**2b**	**11b**, R = OPh	2.3 : 1	54[e]
11	**1**	**2a**	**3a** (hydroacylation)	—	76
12[d]	**8**	**4g**	**7i**, R = Ph	2 : 1	82

[a] *Reaction conditions*: aldehyde (1.0 equiv.), ketone (3.0 equiv.), ^{t}Bu-glyoxylate (1.0 equiv.), [Rh(DPEphos)]ClO_4 (10 mol%). [b] Measured by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] Ketone (1.5 equiv.). [e] Compound **11b** isolated together with 42% of ester **10**.

[Rh(nbd)dppe]ClO_4 promoted reactions, we found that the addition of two equivalents of MeCN, a known hydroacylation additive,[13] to the reaction, increased the yield of the reductive aldol product from 73 to 92% and suppressed formation of any hydroacylation adduct. In general, all the ketones explored using these modified conditions gave the three-component coupled products in high yields with moderate diastereoselectivities (2:1 to 3:1). Primary and secondary aliphatic, aromatic and heteroaromatic vinyl ketones reacted to give the corresponding reductive aldol products in 77–96% yields (entries 1–4, 6–9). In the aliphatic systems a limiting factor appears to be the steric bulk of the ketone, with the hindered *tert*-butyl vinyl ketone (**4e**) furnishing only the Tischenko type product **10** and no hydroacylation product (entry 5). Again, cinnamyl vinyl ketone (**4f**) reacted to leave the internal double bond intact for possible further elaboration, in an excellent 92% yield (entry 6). Aromatic ester **2b** gave conversion to the reductive aldol compound **11b** in 54% yield in the absence of any hydroacylation product **3b**, however 42% of the Tischenko reduction product **10** was also produced (entry 10). In contrast, methyl acrylate **2a** gave exclusively the hydroacylation product **3a** in 76% yield (entry 11). The catalyst controlled switch was also demonstrated with 2-(methylthio)benzaldehyde (**8**) and PVK, where 82% of the reductive aldol product **7j** was isolated (entry 12).

Tables 1 and 2 demonstrate ten examples where we were able to successfully switch between the reductive aldol and hydroacylation pathways by tuning of the rhodium catalyst, based primarily on a change in the ligand. The origin of this catalyst control is not yet fully understood. However, in

collaboration with Weller and co-workers we have reported crystallographic and experimental data that demonstrates the DPEphos ligand functioning in a hemilabile manner, switching between bidentate and tridentate chelation, in a related hydroacylation reaction.[12,14] The dppe ligand is restricted to bidentate chelation. We believe the ability to adopt varied coordination modes plays an integral role in the catalytic cycle, as the tethered but structurally similar ligand Xantphos, and the carbon- and sulfur-linked analogues of DPEphos do not display activity in the studied rhodium-catalysed hydroacylation process.[12]

In conclusion, the [Rh(nbd)DPEphos]ClO_4 catalysed hydroacylation proved a versatile system; aliphatic, alkenyl, aromatic and heteroaromatic substrates were all successfully employed to form a variety of useful 1,4-diketone heterocycle precursors. In contrast, the use of the [Rh(nbd)dppe]ClO_4 catalyst, with MeCN as an additive, provided a parallel range of three-component reductive aldol products. Further investigation into the role of the phosphine ligands in these two important reactions is currently underway, along with the development of a one-pot synthesis of heterocycles *via* rhodium-catalysed hydroacylation/Paal–Knorr cyclisation cascade.

Notes and references

‡ *General procedure for the hydroacylation of α,β-unsaturated ketones*: DCE (2.0 mL) was added to pre-catalyst [Rh(DPEphos)(nbd)]ClO_4 (13 mg, 0.015 mmol) under argon. The catalyst was activated *in situ* by bubbling H_2 gas though the solution for 2 min or until a colour change from orange to red was observed. After this time the hydrogen atmosphere was purged by passing argon through the solution for 0.5 min. The aldehyde **1** or **8** (0.15 mmol) followed by the appropriate ketone (0.3 mmol) were then added to the reaction solution. The resulting mixture was stirred and heated at 70 °C for 1–2 h. After this time the solution was cooled to room temperature, filtered through a silica plug, reduced *in vacuo* and purified by flash chromatography.

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