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Communication

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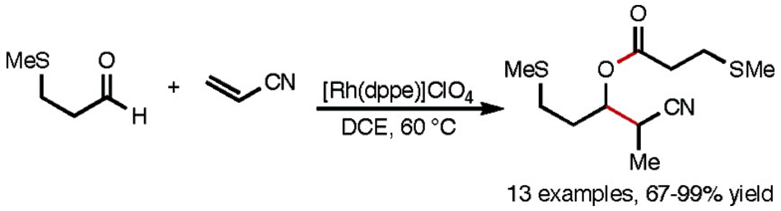

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Rhodium-Catalyzed Reductive Aldol Reactions Using Aldehydes as the Stoichiometric Reductants

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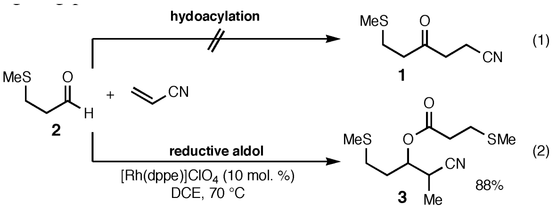
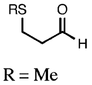
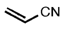
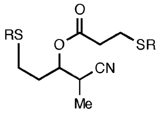
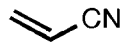
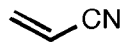
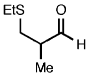
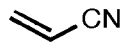
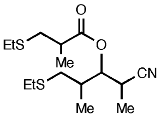
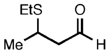
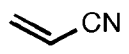
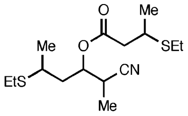
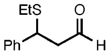
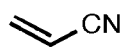
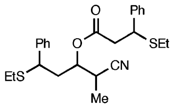
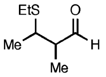
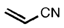
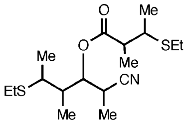
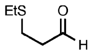
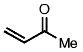
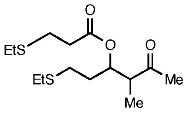
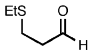
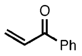
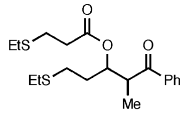
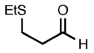
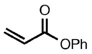
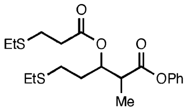
Transition metal catalyzed reductive aldol reactions are proving to be valuable synthetic tools. They allow the required enolates to be generated regioselectively in situ, can be catalyzed by a number of different metals,[1] and have recently been shown to deliver good levels of diastereo- and enantioselectivity.[2] Despite these attributes, there still remain limitations stemming from the use of stoichiometric reductants, such as silanes or molecular hydrogen. In particular, the formation of side products, such as enol silanes, or C−C or C−O double-bond reduction products, can be responsible for reduced efficiency.[3] In this Communication, we report the development of a versatile new reductive aldol process that employs aldehydes as the stoichiometric reductants.

During a recent investigation into chelation-controlled Rh(I)-catalyzed intermolecular hydroacylation reactions, we attempted to generate ketone **1** through the union of β-methyl sulfide-substituted propanal **2** and acrylonitrile (reaction 1).[4] While none of the desired ketone was generated, we isolated ester **3** in good yield (reaction 2). Despite the absence of a recognized reductant in the reagent system, ester **3** represents the acylated version of the reductive aldol product generated from aldehyde **2** and acrylonitrile.[5] The lack of precedent for this transformation prompted us to investigate the scope and mechanism of this intriguing process.[6]



Under the conditions developed for our hydroacylation chemistry ([Rh(dppe)]ClO$_4$ (10 mol %), DCE, 70 °C, 8 h), the reductive aldol process proved to be tolerant of a variety of aldehyde and alkene substrates (Table 1).[7,8] Variation of the size and/or electronic properties of the sulfide group proved to have little effect on the reaction, with Me-, Et-, and Ph-sulfide-substituted aldehydes all combining with acrylonitrile with comparable yields (entries 1−3). The introduction of α- or β-methyl or β-phenyl substituents on the aldehyde was also accepted well (entries 4−6). Similarly, the α,β-dimethylated aldehyde combined with acrylonitrile to deliver the acylated adduct in an excellent 93% yield (entry 7). We next explored variation in the nature of the electron-poor alkene.[9] Both methyl- and phenylvinyl ketone could be combined with the simple ethyl sulfide-substituted aldehyde to deliver the esterified aldol adducts in good yields (entries 8 and 9). Although we have previously shown that simple unsaturated alkyl esters undergo hydroacylation chemistry,[4] we were pleased to find that the use of the more electron-poor phenyl acrylate allowed the reductive aldol pathway to be followed (entry 10).

Table 1. Scope of the Rh-Catalyzed Reductive Aldol Reaction Using β-Sulfide-Substituted Aldehydes as Reductants and Electrophiles[a]

Entry	Aldehyde	Alkene	Product	Yield (%)[b,c]
1	 R = Me		 R = Me	88
2	R = Et		R = Et	79
3	R = Ph		R = Ph	78
4				88
5				73
6				71
7[d]				93
8				73
9				74
10[e]				67

[a] Conditions: aldehyde (1.0 equiv), alkene (5.0 equiv), [Rh(dppe)]ClO$_4$ (10 mol %), DCE, 70 °C. Catalyst generated in situ from [Rh(dppe)-(nbd)]ClO$_4$ and H$_2$. [b] Isolated yields. [c] See Supporting Information for diastereomeric ratios. [d] Starting aldehyde used as a 1:1 mixture of diastereomers. [e] With 3% of the hydroacylation adduct observed by ^{1}H NMR.

To provide convenient reaction times, we routinely employed 10 mol % of the catalyst; however, it was possible to lower the catalyst loading. For example, reaction between aldehyde **2** and acrylonitrile (reaction 2) can be achieved with only 1 mol % catalyst in 36 h at 70 °C to deliver ester **3** in 77% yield.

Having demonstrated the utility of the process to deliver a range of aldol adducts, we began to investigate potential mechanisms; two possibilities are outlined in Scheme 1. Both commence with

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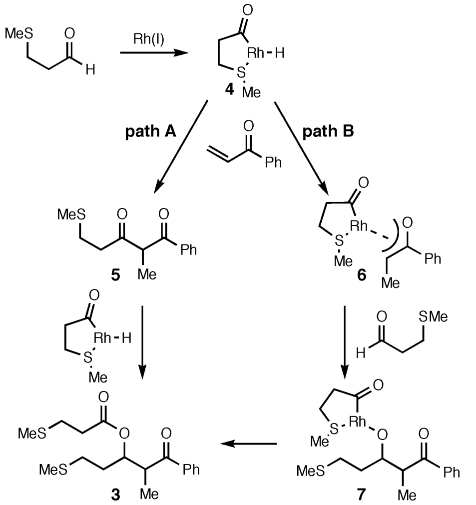
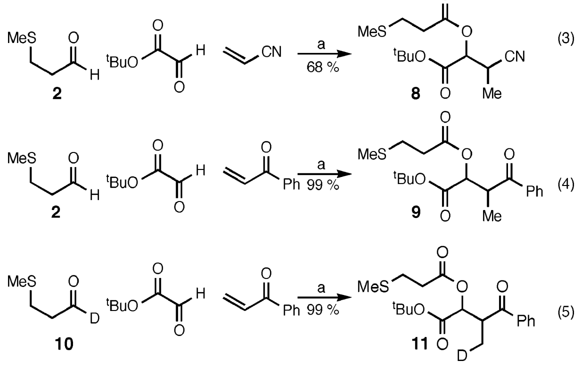
Scheme 1



the oxidative addition of Rh(I) into the aldehyde C−H bond to generate chelated acyl rhodium hydride **4**. Path A continues with addition of the rhodium acyl across acrylonitrile in the manner of a hydroacylation reaction, to generate ketone **5**.[10] Tischenko-like reduction of ketone **5**,[11] involving a second equivalent of rhodium acyl **4**, then affords ester **3**. Path B involves conjugate addition of the hydride present in intermediate **4** to acrylonitrile, generating rhodium enolate **6**.[12] Addition of the enolate to a further equivalent of the starting aldehyde delivers aldolate **7**, which can reductively eliminate Rh(I) to provide the final esterified aldol adduct.

Scheme 2 [a]



[a] [Rh(dppe)]ClO$_4$ (10 mol %), DCE, 70 °C, 16 h.

To test for the intermediacy of ketone **5**, we independently prepared this ketone and attempted to convert it to ester **3**; exposure of the ketone to the standard reaction conditions resulted in no reaction. To investigate the possibility of an enolate intermediate, we sought to trap the enolate with an alternative aldehyde; a three-component reaction involving sulfide-substituted aldehyde **2**, acrylonitrile, and *tert*-butyl glyoxylate provided acylated aldol adduct **8** in good yield (Scheme 2). Alternatively, acrylonitrile could be replaced with phenylvinyl ketone to provide adduct **9** in excellent yield. Finally, the use of deuterated aldehyde **10** delivered ester **11**, in which deuterium incorporation occurred exclusively β to the original ketone. Taken together, these preliminary investigations are consistent with path B (Scheme 1).

In conclusion, we have demonstrated that catalytically generated chelated acyl rhodium hydrides can function as the stoichiometric reductants in reductive aldol processes. Unsaturated nitriles, esters, and ketones can be used as enolate equivalents, and provided a β-sulfide substituent is present, a variety of simple α- and β-substituted aldehydes can be employed. The use of a second, more electrophilic, aldehyde allows three-component reactions to be performed. Although the diastereoselectivities observed were poor, no effort at optimization was attempted during this initial study, with the focus being to secure efficient bond construction. Chelated acyl rhodium hydrides, such as **4**, represent a new class of hydrides for use in synthesis; this opening investigation has demonstrated their reactivity and potential to act as alternatives to traditional reducing systems. Further investigations exploring their reactivity, alternative applications, and asymmetric variants are underway.

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Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) For the formation of a similar acylated adduct in a Rh-catalyzed silane-mediated reductive aldol, see ref 2b.

(6) For a related Rh(I)-catalyzed alkynal redox process, see; Tanaka, K.; Fu, G. C. *Angew. Chem., Int. Ed*. **2002**, *41*, 1607−1609.

(7) See Supporting Information for details.

(8) The diastereoselectivities obtained in all reductive aldol reactions were only modest, ranging from 1:1 to 3.3:1.

(9) Using the present reaction conditions, we have been unable to utilize substituted alkenes in the reductive aldol process.

(10) This requires the hydroacylation to provide the branched adduct. In reactions with aldehyde **2**, we have only observed this for a single electron-poor alkene, phenylvinyl sulfone.

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