Hydroacylation of Alkenes

Chelation-Controlled Intermolecular Hydroacylation: Direct Addition of Alkyl Aldehydes to Functionalized Alkenes[**]

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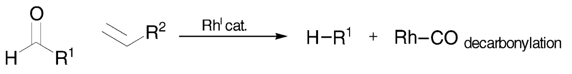
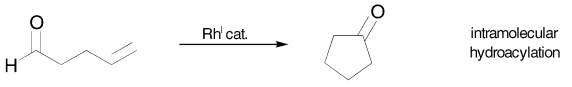
The hydroacylation of alkenes is an example of a growing number of transformations based on C–H bond activation.[1] The transformation has the potential to be a powerful synthetic tool; it is promoted by a number of transition-metal catalysts and is inherently atom-economic.[2] The utility of the reaction is limited by the propensity of the key acyl–metal intermediates to undergo decarbonylation, which results in reduced substrates and inactive catalysts [Eq. (1)].



(1)

Hydroacylation can become competitive with decarbonylation in intramoleculer variants of the process, although the ring size of the product is crucial in determining the success of the reaction [Eq. (2)].[3–6] Intermolecular alkene hydroacylation is a far more demanding transformation and remains a significant synthetic challenge.[7,8] Aside from the cobalt-based method of Brookhart and co-workers,[9] the majority of systems reported require high temperatures (typically 110–200 °C) and/or pressures of CO or ethene and are limited to aromatic aldehydes and simple unfunctionalized alkenes.[10] Of these systems, the method developed by Jun et al., employing the in situ formation of pyridyl imines, is the most synthetically useful, although only unfunctionalized alkenes have been used.[11] Herein we detail a new approach to intermolecular hydroacylation, utilizing chelation-stabi-



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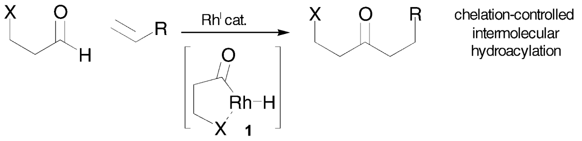
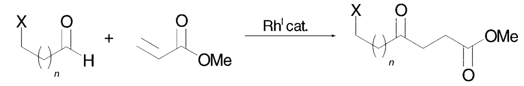
lized acyl–rhodium intermediates, that allows the direct addition of alkyl aldehydes to a range of functionalized alkenes under mild conditions with low catalyst loadings [Eq. (3)].

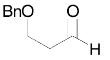
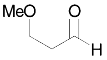
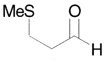
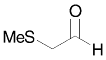
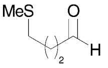


(3)

We speculated that the use of aldehydes that bear a pendant heteroatom would produce chelated acyl–metal intermediates (such as **1**) that are resistant to decarbonylation but disposed to hydroacylation.[12] The starting point of our investigation was to define appropriate chelating functionality and to identify a suitable catalyst. We recently showed that acrylate esters are excellent substrates in the related hydroiminoacylation reaction and accordingly selected methyl acrylate as a test alkene to evaluate potential aldehydes (Table 1).[13] Reaction of β-benzyloxypropanal with the Wilkinson complex led to decarbonylation (Table 1, entry 1), whereas the use of the cationic catalyst [Rh(dppe)]ClO$_4$ (**2**), which has been used extensively in intramolecular systems, resulted in deactivation of the catalyst (Table 1, entry 2). The analogous β-methoxypropanal produced small amounts of the desired adduct but the major pathway remained decarbonylation (Table 1, entry 3).[14] To obtain a stronger chelating interaction, we next examined sulfide-substituted aldehydes;[15] the reaction of β-methylsulfanyl aldehyde **3** with methyl acrylate at 40 °C produced the hydroacylation adduct in 36 % yield along with side product (27 %) that originates from a Tischenko-type process (Table 1, entry 4).[16] When dichloroethane was used as solvent and the reaction temperature was raised to 60 °C, the amount of side product decreased to < 3 % and the conversion into the desired adduct increased to 96 % (Table 1, entry 5). Altering the catalyst counterion from perchlorate to triflate had a negligible effect on the efficiency (Table 1, entry 6).[17] Finally, it appears that a five-membered S–Rh chelate is optimal, as both the α- and γ-methylsulfanyl-substituted aldehydes resulted in decarbonylation (Table 1, entries 7 and 8).

Table 1: Evaluation of aldehydes and catalysts in hydroacylation reactions.[a]



Entry	Aldehyde	Catalyst[b]	Solvent	*T* [°C]	Conversion [%][c]
1		[RhCl(PPh$_3$)$_3$]	PhMe	80	0
2		[Rh(dppe)]ClO$_4$	CH$_2$Cl$_2$	40	0
3		[Rh(dppe)]ClO$_4$	CH$_2$Cl$_2$	40	9
4		[Rh(dppe)]ClO$_4$	CH$_2$Cl$_2$	40	36[d]
5		[Rh(dppe)]ClO$_4$	ClCH$_2$CH$_2$Cl	60	96
6	**3**	[Rh(dppe)]OTf	ClCH$_2$CH$_2$Cl	60	91
7		[Rh(dppe)]ClO$_4$	ClCH$_2$CH$_2$Cl	60	0
8		[Rh(dppe)]ClO$_4$	ClCH$_2$CH$_2$Cl	60	0

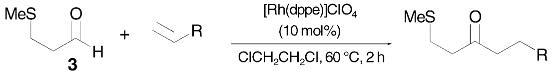
[a] Conditions: catalyst (10 mol %), aldehyde (1.0 equiv), alkene (2.5 equiv), 2 h. [b] Catalysts [Rh(dppe)]ClO$_4$ and [Rh(dppe)]OTf were prepared in situ (see Supporting Information for details). [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Together with Tischenko-type adduct (27 %; see Supporting Information). Tf = trifluoromethanesulfonyl, dppe = 1,2-bis-(diphenylphosphanyl)ethane.

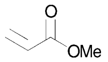
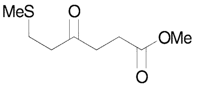
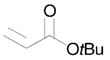
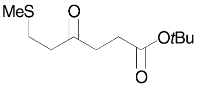
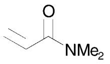
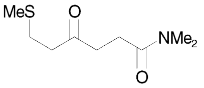
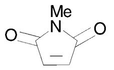
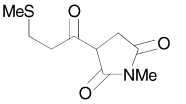
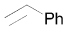
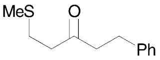
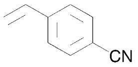
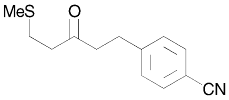
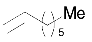
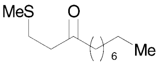
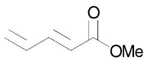
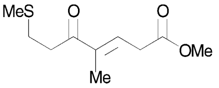
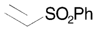
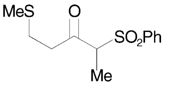
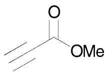
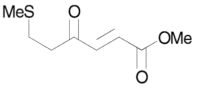
We next explored the scope of the reaction with respect to alkenes (Table 2). A range of functional groups, including esters, amides, and imides, are tolerated well, and the desired hydroacylation adducts are obtained in good yields (Table 2, entries 1–4). The reaction of styrene is slow, presumably due to deactivation of the catalyst. However, the performance of the more-electron-poor 4-cyanostyrene was superior (Table 2, entries 5 and 6). Simple alkyl-substituted alkenes are relatively poor substrates, and decarbonylation becomes competitive (Table 2, entry 7). Dienyl substrates are tolerated, for example, methyl penta-2,4-dienoate delivers the isomerized enone product in moderate yield (Table 2, entry 8). Sulfone functionality is also compatible; hydroacylation of phenyl vinyl sulfone provides the adduct in excellent yield (Table 2, entry 9). Interestingly, the sulfone adduct is obtained exclusively as the more valuable branched regioisomer. Finally, electron-poor alkynes can also be employed: methyl propiolate delivers the enone product in good yield (Table 2, entry 10).

To provide convenient reaction times, all reactions detailed in Table 2 were conducted with 10 mol % of catalyst **2** at 60 °C for 2 h. Modification of these conditions allows lower catalyst loadings to be employed; for example, the reaction between aldehyde **3** and methyl acrylate proceeds with 100 % conversion after only 45 min in the presence of 5 mol % of catalyst at 70 °C.[18] The methylsulfanyl substituent was necessary to allow the desired hydroacylation reactions to proceed, but from a synthetic perspective it is important that it can be removed to provide functionality suitable for further manipulation. Towards this end, adduct **4** was treated with MeOTf and KHCO$_3$ to effect elimination of the sulfide and furnish enone **5** in 76 % yield (Scheme 1).

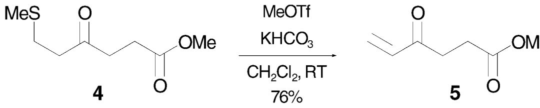
In summary, we have described a new method for intermolecular hydroacylation based on the proposed formation of chelation-stabilized acyl–rhodium intermediates. This new approach allows a commercially available methylsulfanyl-substituted aldehyde[19] to be combined directly with a range of commercial, variously functionalized alkenes to produce hydroacylation adducts in good to excellent yields. The reaction uses low catalyst loadings under mild conditions and is tolerant of a variety of functional groups. Studies to explore alternative chelating units, to investigate the regioselectivity further, and to develop asymmetric versions

Table 2: Hydroacylation of aldehyde **3** with representative alkenes.[a]



Entry	Alkene	Product	Regioselectivity[b]	Conversion [%][b]	Yield [%][c]
1			4:1	96	71
2			5:1	95	81
3			> 20:1	90	82
4			–	91	73
5			> 20:1	64	41
6			> 20:1	77	66
7			> 20:1	50	33
8			10:1	65	45
9			> 20:1	100	84
10			10:1[d]	98	82

[a] Conditions: catalyst (10 mol%), aldehyde (1.0 equiv), alkene (2.5 equiv). [b] Determined by ^{1}H NMR spectroscopic analysis. [c] Yield of isolated pure regioisomer. [d] Geometric isomers.



Scheme 1. Elaboration of sulfide **4**.

of the process are underway and will be reported in due course.

Experimental Section

General procedure: (Bicyclo[2.2.1]hepta-2,5-diene)(1,2-bis(diphenylphosphanyl)ethane) rhodium(I) perchlorate[20] (20 mg, 0.029 mmol) was dissolved in 1,2-dichloroethane (4 mL), and hydrogen gas was bubbled through for 15 min to generate the catalytically active species **2**. The solution was degassed and purged with argon, and the appropriate alkene (0.7 mmol) was then added, followed by aldehyde **3** (30 mg, 0.29 mmol). The reaction mixture was stirred at 60 °C for 2 h then evaporated under reduced pressure. ^{1}H NMR spectroscopic analysis of the crude residue was used to measure the approximate conversion of aldehyde into product (2,5-dimethylfuran was used as a quantitative internal standard).[21] Purification by flash chromatography (silica gel, Et$_2$O/petroleum ether) provided the pure hydroacylation adducts.

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Keywords: aldehydes · alkenes · homogeneous catalysis · hydroacylation · rhodium

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[10] The Co system reported by Brookhart and co-workers[9] employs alkyl aldehydes at moderate temperatures for the hydroacylation of terminal vinyl silanes.

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[17] For a counterion effect in intramolecular hydroacylation, see reference [6a].

[18] Longer reaction times could also be employed. For example, in the presence of 1.5 mol% of catalyst, 94% conversion was reached at 60 °C after 48 h.

[19] 3-(Methylsulfanyl)propanal is available from Sigma-Aldrich Co. Ltd.

[20] R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1971**, *93*, 2397–2407.

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