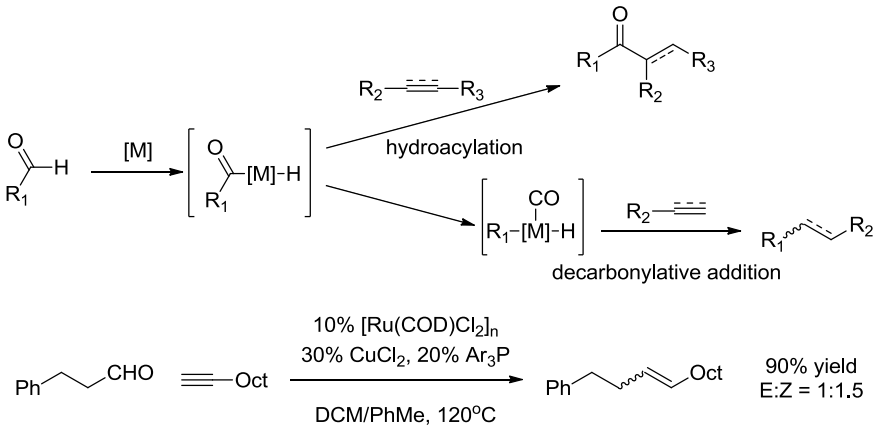
Aldehyde Functionality Reshuffle: Ru-Catalysed Synthesis of *α,β*-unsaturated Aldehydes from Aryl Aldehydes and β-Bromostyrenes

Aldehydes are well-known for their utility in synthesis due to the electrophilic nature of the carbonyl group and their use as carbon nucleophiles *via* generation of the enolate. Recently this utility has been extended to a variety of transition-metal catalysed functionalisations of the carbonyl C-H bond. These reactions generally proceed *via* oxidative addition to the aldehyde C-H bond, forming an acyl-metal hydride species which can further react with unsaturated compounds (alkenes, alkynes) with high regio- and stereoselectivity.[1] Recently, it has also been reported by Li *et al.* (McGill) that it is possible for aldehydes to undergo decarbonylative addition to unsaturated bonds *via* decarbonylation of the acyl-metal hydride species (**Scheme 1**).[2]



Scheme 1 Hydroacylation and decarbonylative addition of aldehydes to unsaturated bonds

It was postulated that the waste carbon monoxide from the decarbonylative addition reaction might be utilised as a one carbon building block rather than merely serving as a by-product. As such, the reaction of aryl aldehydes with *E-β*-bromostyrenes was investigated.[3] Screening of catalysts showed that a Ru(III) was capable of performing the desired transformation (**Table 1, Entry 1**). A range of products were observed, the desired (*E*)-2-(4-methoxyphenyl)cinnamaldehyde **3**, the (*Z*)-isomer **4**, along with debromination product **5**, and products **6** and **7**, corresponding to exchange of the bromide with chloride or iodide (depending on reaction conditions).

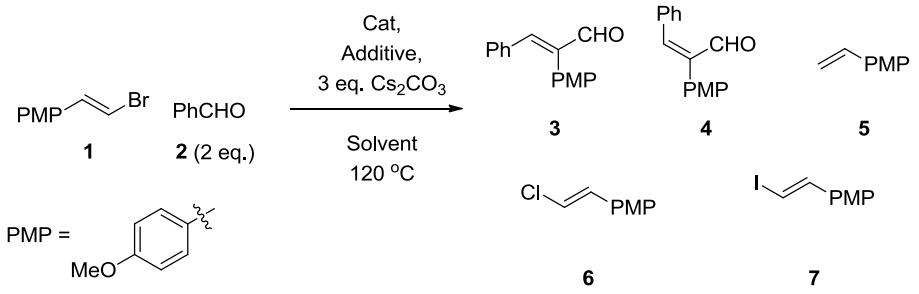


Table 1 Optimisation of reaction conditions

[1] Hydroacylation reviews: a) Willis, M., *Chem. Rev.*, **2010**, *110*, 725. b) Leung, J.C.; Krische, M. J., *Chem. Sci.*, **2012**, *3*, 2202.

[2] a) Guo, X.; Wang, J.; Li, C-J., *J. Am. Chem. Soc.,* **2009**, *131*, 15092. b) Guo, X.; Wang, J.; Li, C-J., *Org. Lett.*, **2010**, *12*, 3176.

[3] Wang, P.; Rao, H.; Zhou, F.; Hua, R.; Li, C-J., *J. Am. Chem. Soc.,* **2012**, *134*, 16468.

Entry	Catalyst	Additives	Solvent	% Yield (3/4/5/6/7)
1	10% $[RuCp^*Cl_2]_n$	-	DMF	<10/-/16/14/-
2	10% $[RuCp^*Cl_2]_n$, 10% CuI	-	DMF	46/t/16/16/t
3	10% $[RuCp^*Cl_2]_n$, 10% CuI	2 eq. KI	DMF	52/t/13/12/10
4[a]	10% $[RuCp^*Cl_2]_n$, 10% CuI	2 eq. KI	DMF	22/t/26/14/11
5	10% $[RuCp^*Cl_2]_n$, 10% CuI	2 eq. LiI	DMF	t/-/32/17/t
6	5% $[RuCp^*Cl_2]_n$, 5% CuI	2 eq. KI, 30% $Me_2NCH_2CO_2H$	DMF	66/t/14/t/13
7	5% $[RuCp^*Cl_2]_n$, 5% CuI	0.2 eq KI, 30% $Me_2NCH_2CO_2H$	DMF	75/t/<10/t/t

[a] 5 equivalents of **2**.

Addition of a Cu(I) co-catalyst gave a marked increase in yield (**Entry 2**), suggested to be a result of activation of the vinyl C-Br bond by CuI. Addition of 2 equivalents of KI (**Entry 3**) also resulted in an increase in yield, potentially due to the conversion of some of the vinyl bromide to the more reactive vinyl iodide *in situ*. However, other iodide salts did not give such positive results, including LiI (**Entry 5**), which essentially halted the reaction, yielding only a trace of product after 24 hours. Addition of *N,N*-dimethylglycine (**Entry 6**) resulted in a further increase in yield of the desired product, and allowed catalyst loading to be lowered to 5 mol%. The benefit of adding sub-stoichiometric amounts of *N,N*-dimethylglycine has also been observed in CuI catalysed Ullman-type couplings of vinyl bromides with amines. Lowering the loading of KI to 0.2 eq. (**Entry 7**) also resulted in an improved yield of the reaction, presumably due to lowering of the amount of observed side-product **7**. It is also worth noting that increasing the amount of aldehyde to 5 equivalents (**Entry 4**) resulted in a significantly lower yield of product **3**.

With optimal conditions in hand, the authors screened a number of different aldehydes and (*E*)-*β*-bromostyrenes (**Table 2**).

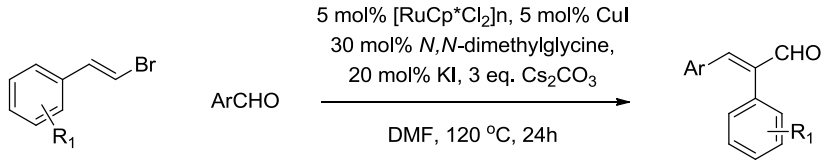
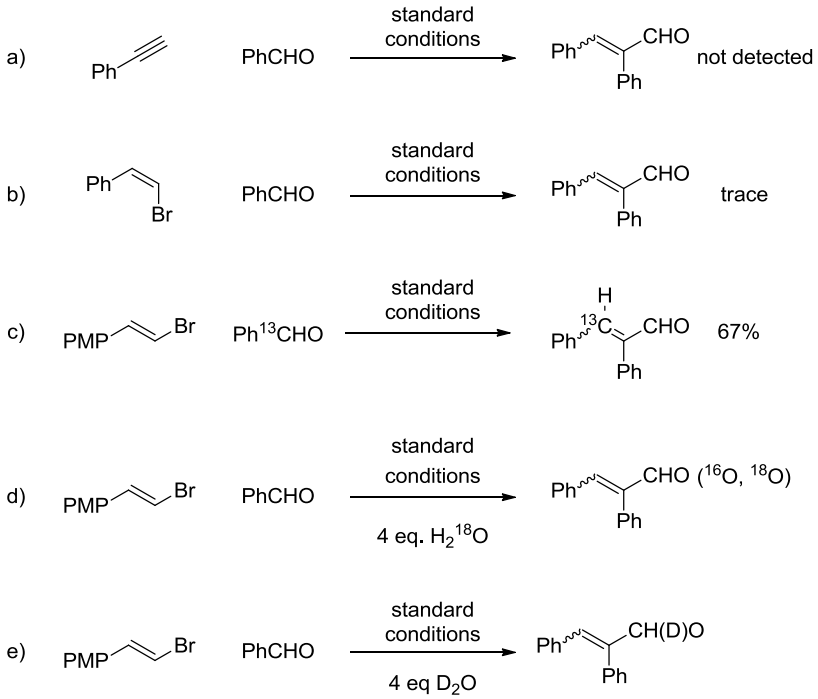


Table 2 Substrate scope

Entry	R_1	Ar	% Yield (*E*:*Z*)
1	*p*-MeO	Ph	72 (94:6)
2	*p*-MeO	*p*-$MeOC_6H_4$	65 (95:5)
3	*p*-MeO	*p*-MeC_6H_4	51 (94:6)
4	*p*-MeO	*p*-PhC_6H_4	58 (93:7)
5	*p*-MeO	*p*-$CF_3C_6H_4$	77 (95:5)
6	*p*-MeO	*p*-ClC_6H_4	68 (95:5)
7	*p*-MeO	*m*-ClC_6H_4	79 (95:5)
8	*p*-MeO	3,4-$Cl_2C_6H_3$	74 (95:5)
9	*p*-MeO	4-quinolyl	34 (50:50)
10	*p*-MeO	3-pyridyl	45 (83:17)
11	H	Ph	48 (96:4)
12	H	*p*-$MeOC_6H_4$	54 (95:5)
13	H	*p*-MeC_6H_4	39 (97:3)
14	H	*p*-PhC_6H_4	25 (97:3)
15	H	*p*-$CF_3C_6H_4$	63 (97:3)
16	H	*p*-ClC_6H_4	55 (97:3)
17	H	*m*-ClC_6H_4	66 (95:5)
18	H	3,4-$Cl_2C_6H_3$	60 (96:4)
19	*m*-F	Ph	44 (96:4)

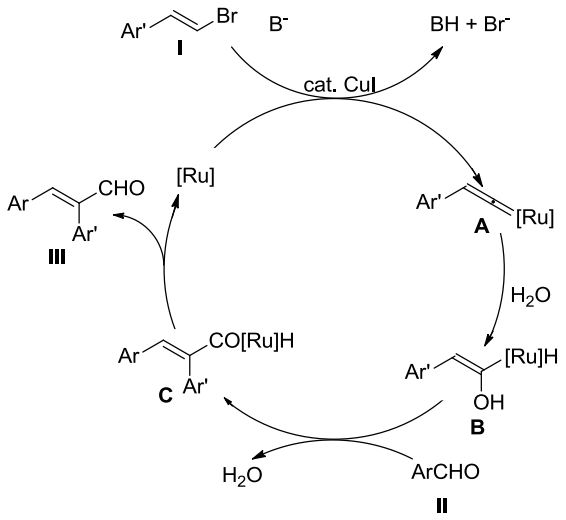
From **Table 2** it is evident that an electron-rich bromostyrene gave better yields (**Entries 1-10**), with electron-neutral (**Entries 11-18**) giving poorer yields of the corresponding 2-arylcinnamaldehydes, although better than in the case of the electron poor *m*-fluorobromostyrene (**Entry 19**). Interestingly, while the vinylic bromide is lost during the reaction, halogens were tolerated on the aromatic aldehyde (and bromostyrene), giving moderate to good yields of the corresponding product (**Entries 6-8, 16-19**). In most cases *E*:*Z* selectivites were greater than 95:5, and appear to be greater in the case of unsubstituted bromostyrenes (**Entries 11-18**) than in the *p*-methoxyseries (**Entries 1-8**). In the case of the heteroaryl aldehydes (**Entries 9 and 10**), both the yield of product and *E*:*Z* selectivity were lower. It is noted by the authors that aliphatic aldehydes are not able to participate in this reaction, although it is not postulated why this is the case.

A range of control experiments were then conducted to explore the possible mechanism of the reaction (**Scheme 2**).



Scheme 2 Investigation into the mechanism of arylformylation

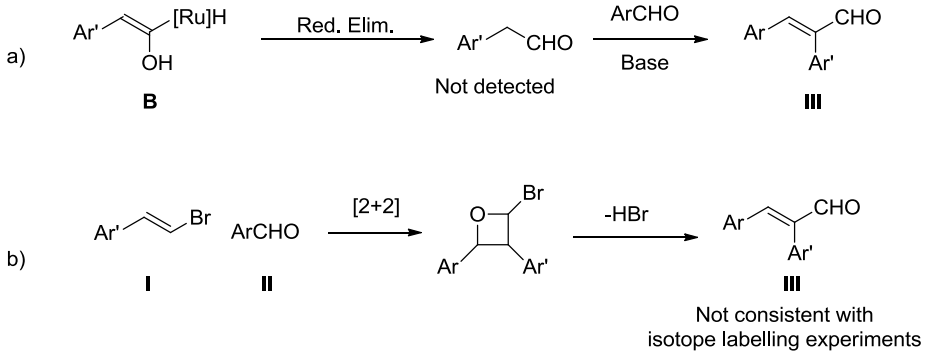
The reaction of phenylacetylene with benzaldehyde under the optimised reaction conditions yielded no 2-phenylcinnamaldehyde (**Scheme 2a**), suggesting that *in situ* elimination of HBr to form phenylacetylene was not involved in the reaction. The configuration of the bromostyrene was also shown to be important (**Scheme 2b**), with the (*Z*)-bromostyrene yielding only a trace amount of product. Surprisingly, use of ^{13}C-labelled benzaldehyde (**Scheme 2c**) showed incorporation of ^{13}C into the β-carbon of the double bond. Addition of 4 equivalents ^{18}O-labelled water in the reaction showed a 2:1 ratio of ^{16}O:^{18}O incorporated into the aldehyde carbonyl group by GC/MS (**Scheme 2d**). Addition of deuterium oxide to the reaction mixture also showed a mixture of deuterated carbonyl and regular aldehyde product (**Scheme 2e**). These results have led the authors to suggest the following mechanism for the reaction:



Scheme 3 Tentative mechanism for arylformylation

1) Reaction of vinyl bromide **I** with base, the active ruthenium catalyst and potentially CuI to give the vinylidene intermediate **A**.
2) Nucleophilic addition of water to give intermediate **B**.
3) Aldol-type reaction of intermediate **B** with aldehyde **II** to give acylruthenium hydride **C**, regenerating water.
4) Reductive elimination of **C** to yield product **III** and regenerate the active ruthenium catalyst.

The authors note that the mechanism may possibly proceed *via* reductive elimination of **B** followed by aldol condensation with the aldehyde (**Scheme 4a**). However, phenylacetaldehyde was not detected in a control experiment with only vinyl bromide **I**. Similarly, replacing vinyl bromide **I** with phenylacetaldehyde did not give the desired product under the reaction conditions. Another possibility is the Ru/Cu-catalysed formal [2+2]-cycloaddition of **I** and **II** to give an oxetane which can ring-open to the product directly. However, this is not consistent with the isotope labelling experiments conducted.



Scheme 4 Alternative mechanisms

In summary, the Li group has developed a novel “reshuffling” of aldehyde functionality *via* the reaction of aryl aldehydes with (*E*)-β-bromostyrenes in the presence of a Ru(III) catalyst with Cu(I) co-catalyst. The reaction is most efficient for electron-rich bromostyrenes, and gives high *E*:*Z* selectivity for a range of different aryl aldehydes. A number of control experiments have been conducted to investigate the mechanism of this reaction, suggesting that rather than going *via* Ru-catalysed hydrolysis of the vinyl bromide and subsequent aldol reaction, or *via* a formal [2+2]-cycloaddition of the two components followed by ring opening, that the reaction proceeds *via* a vinylidene intermediate, which undergoes an aldol-type reaction with the aryl aldehyde, followed by reductive elimination.