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Catalytic, Nucleophilic Allylation of Aldehydes with Allyl Acetate

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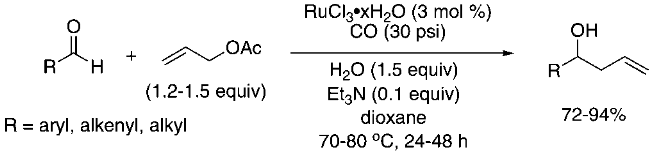
ABSTRACT



A new catalytic allylation of aldehydes has been developed that employs allyl acetate as the allylating reagent. Under catalysis by ruthenium trichloride (3 mol %) in the presence of carbon monoxide (30 psi), water (1.5 equiv), and triethylamine (0.1 equiv), a wide range of aromatic, olefinic, and aliphatic aldehydes are efficiently allylated under mild conditions (70 °C, 24−48 h). The stoichiometric byproducts of this reaction are carbon dioxide and acetic acid.

The allylation of carbonyl compounds is now universally recognized as one of the premier methods for carbon−carbon bond formation.[1] The most prominent reasons for the popularity of the method include: (1) the extreme diversity of reagent reactivity based on allylmetal reagent, (2) the high degree of both diastereo- and enantioselectivity observed in many cases,[2] and (3) the latent functionality in the homoallylic alcohol product which makes the reaction ideal for synthetic planning.[1d] Although many reagent variations are known, the reactions generally involve the use of discrete allylmetallic (or nonmetallic) reagents, either directly or in combination with Lewis acidic or basic catalysts. In some cases, the allylmetallic reagent is prepared in situ by the combination of an allyl source (halide, acetate, alcohol) with a stoichiometric amount of a metal salt.[3] In addition, a number of reports have described using one metal to catalyze the formation of the allylmetallic reagent and a stoichiometric amount of a second metal or metallic reagent to turn over the catalyst.[4] Although this approach avoids the preparation of the discrete allylmetal species, a large amount of inorganic waste is nevertheless generated which must be removed in the purification step and reduces the overall atom efficiency.

To address these issues, we sought to develop a new process for carbonyl allylation that is catalytic in metal,

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(4) For representative examples, see Pd(pincer)/diboron: (a) Selander, N.; Kipke, A.; Sebelius, S.; Szabo, K. *J. Am. Chem. Soc.* **2007**, *129*, 13723–13731. Co(acac)$_2$/SnCl$_2$: (b) Chaudhuri, M. K.; Dehury, S. K.; Hussain, S *Tetrahedron Lett.* **2005**, *46*, 6247–6251. PdCl$_2$/SnCl$_2$: (c) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577–2586. CdSO$_4$/Zn and SnCl$_2$/Zn: (d) Zhou, C.; Zhou, Y.; Jiang, J.; Zhen, X.; Zhiyong, W.; Zhang, J.; Wu, J.; Yin, H. *Tetrahedron Lett.* **2004**, *45*, 5537–5540. Pd(Ph$_3$P)$_4$/SmI$_2$: (e) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 1195–1196. InCl$_3$/Al or Zn: (f) Araki, S.; Jin, S-J.; Idou, Y.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1736–1738. [Ir(cod)Cl]$_2$/SnCl$_2$: (g) Roy, S.; Banerjee, M. *J. Mol. Catal. A* **2006**, *246*, 231–236. [RhCl(cod)]$_2$/SnCl$_2$: (h) Masuyama, Y.; Kaneko, Y.; Kurusu, Y. *Tetrahedron Lett.* **2004**, *45*, 8969–8971. Pd(OAc)$_2$/Et$_2$Zn: (i) Kimura, M.; Shimizu, M.; Shibata, K.; Tazoe, M.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3392–3395. Pd(OAc)$_2$/Et$_3$B: (j) Kimura, M.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 3627–3629.

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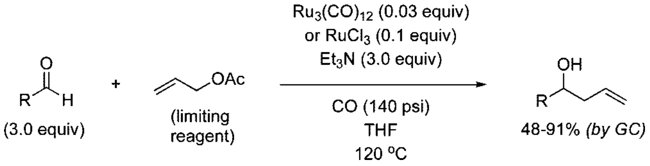
environmentally benign, and amenable to large-scale applications. At the time we initiated this work, only three such catalytic processes for carbonyl allylation were known: the carbonyl−ene process,[5] the hydrogenative coupling of dimethylallene,[6,7] and the ruthenium-catalyzed allylation of aldehydes using allyl acetate.[8] Whereas the first two processes had appeared to be suitable only for highly reactive aldehydes, the ruthenium-catalyzed process showed the potential for a wider substrate scope. Curiously, however, this method has not received much attention, most likely because of the harsh conditions required.[9] Herein, we disclose our development of a practical, ruthenium-catalyzed carbonyl allylation process using allyl acetate. Our studies revealed critical insights into the roles of triethylamine, halide anion, carbon monoxide, and water and enabled us to create a simple, economical, and efficient procedure for allylation of aliphatic, olefinic, and aromatic aldehydes.

In the original report from Wantanabe and co-workers, allyl acetate was the limiting reagent (Scheme 1).[8] For most synthetic applications, the aldehyde is the precious reagent; thus, it was necessary to reevaluate the roles of all reaction components and experimental variables.

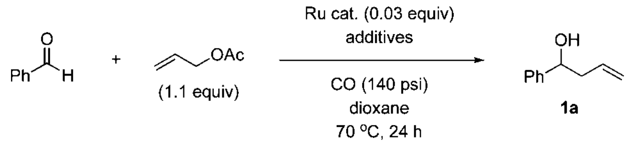
Scheme 1. Originally Reported Allylation Conditions



To orient our efforts, the preliminary reactions were run under the original conditions, employing benzaldehyde as a model substrate with 1.1 equiv of allyl acetate at 70 °C in a variety of solvents with $RuCl_3$ as the catalyst. Because of the high pressure of CO required, a six-well autoclave was employed to perform the optimization. Interestingly, we discovered that the reaction proceeded faster after the autoclave was cooled and opened in air for monitoring. To identify the origin of this effect, a battery of experiments was performed in which controlled amounts of oxygen gas and/or water were blended into the reaction mixtures. From these experiments we found that water accelerated the reaction but also caused significant consumption of allyl acetate via an unproductive pathway (oxygen had no beneficial effect). Next, the stoichiometries of Et_3N and water were systematically varied. Interestingly, when the amount of Et_3N was reduced to 0.1 equiv and water was adjusted to 1.5 equiv, the reaction proceeded to 95% conversion at 70 °C in 24 h. This result marked a critical departure from the original conditions in which Et_3N was believed to be the stoichiometric reducing reagent.[10]

The conclusion that Et_3N is not a hydride donor in this system is supported by two observations: (i) ^{1}H NMR analysis of the reaction mixtures indicated that triethylamine was not consumed;[11] (ii) when Et_3N was replaced by quinuclidine, an amine that cannot function as a hydride donor, the reaction still proceeded to comparable conversion in the same reaction period. In addition to Et_3N, other secondary and tertiary amines such as i-Pr_2EtN and i-Pr_2NH were also effective. However, in the absence of an amine, no reaction occurred (Table 1, entries 1 and 2).

Table 1. Catalytic Carbonyl Allylation: Effects of Triethylamine and Chloride



entry	Ru sources	Et_3N (equiv)	TBACl (equiv)	conversion[a] (%)
1	$RuCl_3{\cdot}xH_2O$	0	0	0
2	$RuCl_3{\cdot}xH_2O$	0.1	0	95
3	allylRu$(CO)_3$Br	0	0	12
4	allylRu$(CO)_3$Br	0.1	0	93
5	allylRu$(CO)_3$OAc	0	0	43
6	allylRu$(CO)_3$OAc	0.1	0	70
7	allylRu$(CO)_3$OAc	0	0.03	84
8	$Ru_3(CO)_{12}$[b]	0	0	15
9	$Ru_3(CO)_{12}$[b]	0	0.03	78

[a] Conversions were calculated from ^{1}H NMR integration values of the reaction mixtures using hexamethylbenzene as internal standard. [b] 0.01 equiv was used.

To elucidate whether the amine is needed only in the initial reduction of $RuCl_3$ to Ru(0) at the beginning of the process[12]

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(5) (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021–1050. (b) Mikami, K.; Terada, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Chapter 32. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335.

(6) (a) Skucas, E.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12678–12679. (b) Ngai, M.-Y.; Skucas, E.; Krische, M. J. *Org. Lett.* **2008**, *10*, 2705–2708.

(7) During the completion and submission of this manuscript, Krische and co-workers reported a hydrogenative allylation by using an *alcohol* as the hydrogen donor and reducing reagent for the allylation of aldehydes and alcohols: (a) Kim, I. S.; Ngai, M-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891–14899. (b) Kim, I. S.; Ngai, M-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340–6341. (c) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14120–14122. (d) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338–6339.

(8) (a) Tsuji, Y.; Mukai, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1989**, *369*, C51−C53. For dehydrogenative allylation to prepare enones, see: (b) Kondo, T.; Mukai, T.; Watanabe, Y. *J. Org. Chem.* **1991**, *56*, 487–489.

(9) For an intramolecular example, see: Yu, C-M.; Lee, S.; Hong, Y-T.; Yoon, S-K. *Tetrahedron Lett.* **2004**, *45*, 6557–6561.

(10) For an isotope labeling study and mechanistic discussion, see:(a) Kondo, T.; Ono, H.; Satake, N.; Mitsudo, T.; Watanabe, Y. *Organometallics* **1995**, *14*, 1945–1953. (b) Kondo, T.; Misudo, T. *Curr. Org. Chem.* **2002**, *6*, 1163–1179. (c) Sakaki, S.; Ohki, T.; Takayama, T.; Sugimoto, M.; Kondo, T.; Mitsudo, T. *Organometallics* **2001**, *20*, 3145. (d) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067–2096.

(11) ^{1}H NMR spectra of these reaction mixtures (without workup) only showed signals arising from benzaldehyde, allyl acetate, **1a**, triethylammonium acetate, and propene (in trace amounts).

(12) For the role of base in the reduction of $RuCl_3$ to $Ru_3(CO)_{12}$, see: Roveda, C.; Cariati, E.; Lucenti, E.; Roberto, D. *J. Organomet. Chem.* **1999**, *580*, 117–127.

or also needed throughout the catalytic cycle, allylRu$(CO)_3$Br[13] and allylRu$(CO)_3$OAc[8a] were prepared and used in the catalytic reactions (Table 1). Addition of Et_3N in both cases significantly improved the conversions, especially in the reaction that employed allylRu$(CO)_3$Br (Table 1, entries 3−6).

These results suggest that the amine is acting as a base perhaps to neutralize HCl generated during the reduction of $RuCl_3$ (or HBr when allylRu$(CO)_3$Br is used) and to partially buffer the medium from becoming too acidic from the acetic acid generated as a byproduct. An excess of Et_3N, on the other hand, causes the unproductive consumption of allyl acetate possibly because Et_3N competitively binds to the allyl−Ru complex and thus inhibits the carbonyl allylation process while favoring the undesired protonolysis of the π-allyl complex to produce propene.[14]

The observation that reactions with $RuCl_3$ and allylRu$(CO)_3$Br showed higher conversions than reactions with allylRu$(CO)_3$OAc (Table 1, entries 2, 4, and 6) indicated a possible halide affect.[15] Indeed, when tetrabutylammonium chloride (TBACl) was added to a reaction catalyzed by allylRu$(CO)_3$OAc, the conversion improved from 43 to 84% (Table 1, entries 5 and 7). More significantly, the conversion improved from 15 to 78% when $Ru_3(CO)_{12}$ was used as the precatalyst (Table 1, entries 8 and 9).[16]

The effect of halides on the structure and reactivity of ruthenium carbonyl complexes has been the subject of countless investigations since the early 1980s.[17] Geoffroy[18] has shown that halide anions (X) can displace one or more CO ligands in the $Ru_3(CO)_{12}$ complex to produce anionic species such as $[Ru_3(CO)_{11}X]^-$,[19] $[Ru_3(CO)_{10}X]^-$, and $[Ru_4(CO)_{13}X]^-$. Furthermore, neutral Ru(0) complexes such as $Ru_3(CO)_{12}$ and Ru(COD)(COT) do not react with allyl acetate even in refluxing toluene.[8a] Amatore and Jutand have established the role of chloride ion in palladium-catalyzed, cross-coupling reactions in which anionic chloropalladium(0) ate species participate in the oxidative addition step.[20]

By analogy, we postulate that the rate enhancement caused by chloride observed in this process is due to the chloride-ligated anionic complexes **(I)** formed by displacement of carbon monoxide ligand(s) from the neutral Ru(0) species by chloride (Figure 1). These anionic complexes should be more nucleophilic than the neutral Ru(0) complexes and thus can readily react with allyl acetate to form the requisite π-allyl-Ru complex **(II)** which ultimately delivers the allyl group to the aldehyde. It is possible that this process occurs via the coordination of the aldehyde carbonyl to the ruthenium center causing a shift of the π-allylruthenium from the η^3- to the η^1- binding mode and the (η^1-allyl)ruthenium undergoes the nucleophilic attack at the carbonyl.[21] A plausible mechanism for the catalyst turnover involves hydrolysis of the ruthenium alkoxide complex (**III**) to release the homoallylic alcohol and generate a ruthenium hydroxide species (**IV**). Insertion of CO into the Ru−OH bond of complex **IV**, followed by extrusion of CO_2 and subsequent reductive elimination of acetic acid, regenerates the Ru(0) catalyst. This mechanistic formulation allows a clearer insight into the roles of CO and water; i.e., the combination of CO and water must provide the stoichiometric reducing equivalents (water gas shift reaction).[22]

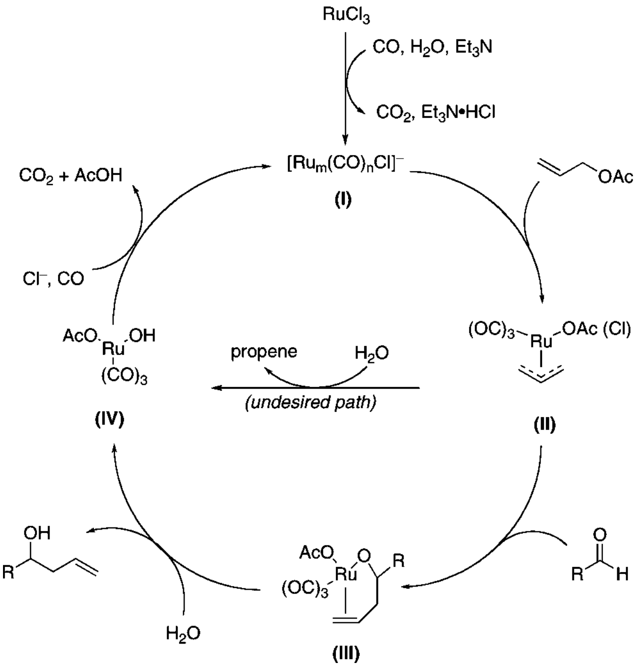

Figure 1. Proposed mechanism for the $RuCl_3$-catalyzed carbonyl allylation.

The final stages of the optimization concerned pressure, temperature, and solvent. We examined reactions at pressures from 15 to 200 psi of CO and found that the conversions did not change at pressures above 30 psi. The reactions proceeded even at 15 psi of CO but required longer time. Thus, for the survey of aldehyde scope, the CO pressure was kept at 30−35 psi. This was a significant improvement in

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(13) Sbrana, G.; Braca, G.; Piacenti, F.; Pino, P. *J. Organomet. Chem.* **1968**, *13*, 240–242.

(14) Approximately 0.10 equiv of propene was observed by NMR analysis in the crude reaction mixture when 3 equiv of triethylamine was used.

(15) Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26–47.

(16) Addition of TBAI also improved the conversions but to a lesser extent.

(17) For reviews, see: (a) Kaesz, H. D. *J. Organomet. Chem.* **1990**, *383*, 413–420. (b) Lavigne, G. *Eur. J. Inorg. Chem.* **1999**, 917–930. (c) Hill, A. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 130–133.

(18) Han, S.-H.; Geoffroy, G. L.; Dombek, B. D.; Rheingold, A. L. *Inorg. Chem.* **1988**, *27*, 4355–4361.

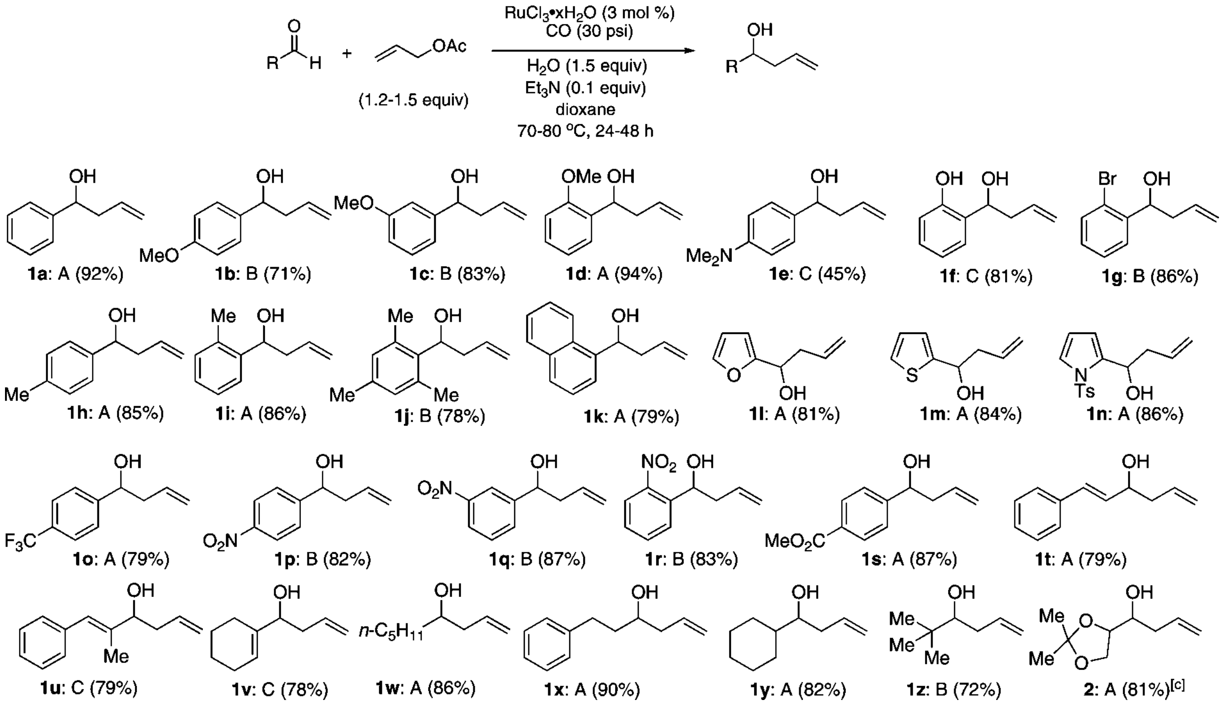
(19) For an X-ray crystallographic determination of this structure (X = Cl), see: Chin-Choy, T.; Harrison, W. T. A.; Stucky, G. D.; Keder, N.; Ford, P. C. *Inorg. Chem.* **1989**, *28*, 2028–2029.

(20) (a) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531–9541. (b) Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375–8384.

(21) For analogy in allylpaladium catalysts, see: (a) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641–6647. (b) Nakamura, H.; Aoyagi, K.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372–377. (c) Szabo, K. J. *Chem.—Eur. J.* **2000**, *6*, 4413–4421. (d) Solin, N.; Kjellgren, J.; Szabo, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 7026–7033.

(22) (a) Laine, R. M.; Wilson, R. B. In *Aspects of Homogeneous Catalysis*; Ugo, R., Ed.; Reidel (Kluwer): Dodrecht, 1984; Vol. 5. (b) Laine, R. M.; Rinker, R. G.; Ford, P. C. *J. Am. Chem. Soc.* **1977**, *99*, 252–253.

Table 2. Catalytic Carbonyl Allylation: Substrate Survey[a,b]



[a] Reaction conditions: (A): 1.2 equiv of allyl acetate, 70 °C, 24 h; (B): 1.2 equiv of allyl acetate, 80 °C, 24 h; (C): 1.5 equiv of allyl acetate, 80 °C, 48 h. [b] Yields of isolated products. [c] *dr* 1.6:1

the procedure because it can now be easily adapted to conventional reactors. We found that 70−80 °C was adequate for reaction to be complete within 24−48 h for most substrates. The reaction did proceed at temperatures as low as 40 °C but again required longer time. Comparable yields were also obtained when reactions were run in other solvents such as tetrahydrofuran, *tert*-butyl alcohol, ethyl acetate, and cyclohexanone; however, the reactions were slower in strongly coordinating solvents such as *N,N*-dimethylformamide and dimethyl sulfoxide.

Under the optimized conditions (A, Table 2), a wide range of aldehyde substrates were tested. The only changes that were needed to observe full conversion with slower acting aldehydes was a minor increase in temperature (B: 80 °C) and an increase in reaction time (C: 80 °C, 48 h). For the aromatic aldehydes examined, the reaction was remarkably insensitive to electronic effects and steric effects. Both electron-rich (**1b**, **1c**, **1d**, **1h**) and electron-poor substrates (**1o**, **1p**, **1q**, **1r**, **1s**) reacted in good yield with little influence of substituent location. Only the most electron-rich substrate with a 4-dimethylamino group (**1e**) did not react completely under conditions C. Functional group compatibility is quite good considering the reducing conditions. Thus, nitro, ester, and hydroxyl groups (**1f**) and a bromide (**1g**) are compatible. Sterically hindered aldehydes (**1i**, **1j**, **1k**, **1z**) reacted smoothly as well. Heterocyclic aldehydes (**1l**, **1m**, **1n**) reacted under the standard conditions to give good yields of the allylation products. We were very pleased to find that olefinic aldehydes (**1t**, **1u**, **1v**) reacted without problem. Perhaps most satisfying was the ability to allylate aliphatic aldehydes including linear (**1w**, **1x**), branched (**1y**), and even the hindered pivalaldehyde (**1z**) in good yields. Finally, glyceraldehyde acetonide (**2**) reacted under the standard conditions (dr, 1.6:1) illustrating the compatibility of heteroatom-substituted aldehydes. Interestingly, alkynyl aldehydes were unreactive under these conditions.

In conclusion, we have developed a new, operationally simple, and highly efficient ruthenium-catalyzed carbonyl allylation process using inexpensive and noncorrosive allyl acetate, water, and a low pressure of carbon monoxide. The role of each reaction component has been defined and optimized. The reaction is catalytic in ruthenium trichloride, and because the stoichiometric byproducts are carbon dioxide and acetic acid, it is environmentally benign and readily adaptable to large-scale operation. The method shows excellent substrate generality, functional group compatibility, and high tolerance to electronic and steric factors. Further studies to determine structures of the catalytically active species to introduce stereocontrolling ligands for the carbonyl addition are underway.

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Supporting Information Available: Experiment procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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