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Catalytic Hydroacylation as an Approach to Homoaldol Products

Stephen K. Murphy, David A. Petrone, Matthew M. Coulter, and Vy M. Dong*

Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada

vdong@chem.utoronto.ca

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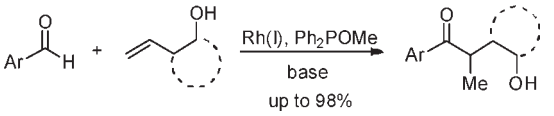
ABSTRACT



A method has been developed for the intermolecular hydroacylation of homoallyl alcohols with salicylaldehydes to furnish homoaldol products in 50−98% yields. The method also applies to the hydroacylation of 2-hydroxystyrenes. This work highlights the use of hydroacylation as a unified approach to both aldol and homoaldol products.

While significant progress has been made in aldol technology, these advances do not generally apply to the related homoaldol transformation. In contrast to enolates, homoenolates are difficult to prepare and readily undergo irreversible cyclization to oxyanionic cyclopropanes rather than desirable nucleophilic addition to electrophiles.[1] Given the importance of these "umpolung" or "reverse polarity" motifs in C−C bond construction,[2] much work has been devoted to generating homoenolate equivalents.[1,3] Nonetheless, no general catalytic strategy exists for targeting both the aldol structure and its homologue. Our laboratory is interested in studying hydroacylation as an atom economical and efficient strategy for organic synthesis.[4,5] In this context, we envisioned that hydroxyl-directed hydroacylation could provide a unified strategy for preparing both aldol and homoaldol products as shown in Scheme 1.

By using cooperative catalysis, we recently achieved the branched-selective hydroacylation[6] of allyl alcohols to form aldol products.[7] This transformation is promoted by a phosphinite catalyst that binds the alcohol and metal catalyst simultaneously to promote the olefin functionalization. With this strategy, Bedford developed a method for *ortho*-arylation of phenols, and Breit and Tan more recently achieved branched-selective hydroformylation of

(1) Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *155*, 1.
(2) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239.
(3) For reviews on the homoaldol reaction, see: (a) Hoppe, D. *Synthesis* **2009**, *1*, 43. (b) Crimmins, M. T.; Nantermet, P. G. *Org. Prep. Proc.* **1993**, *25*, 43. (c) Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M., Fleming, I., Eds.; Pergammon: Oxford, 1991; p 441. For a comprehensive full paper on the homoaldol reaction, see: (d) Lettan, R. B., II; Galliford, C. V.; Woodward, C. C.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 8805.
(4) Trost, B. M. *Science* **1991**, *254*, 1471.
(5) For reviews on hydroacylation, see: (a) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (b) Fu, G. C. In *Modern Rhodium-Catalyzed Reactions*; Evans, P. A., Ed.; Wiley-VCH: New York, 2005; p 79. For selected examples of activated or strained olefins in Rh-catalyzed intermolecular olefin hydroacylation, see: (c) Osborne, J. D.; Willis, M. C. *Chem. Commun.* **2008**, 5025. (d) Tanaka, K.; Shibata, Y.; Suda, T.; Hagiwara, Y.; Hirano, M. *Org. Lett.* **2007**, *9*, 1215. (e) Osborne, J. D.; Randell-Sly, H. E.; Currie, G. S.; Cowley, A. R.; Willis, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 17232. (f) Kokubu, K.; Matsumasa, K.; Nishinaka, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 303. (g) Stemmler, R. T.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 1185. (h) Phan, D. H. T.; Kou, K. G. M.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16354.
(6) For hydroacylation of simple olefins using a double chelation approach, see: (a) Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16330. (b) Imai, M.; Tanaka, M.; Tanaka, K.; Yamamoto, Y.; Imai-Ogata, N.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem.* **2004**, *69*, 1144.
(7) Murphy, S. K.; Coulter, M. M.; Dong, V. M. *Chem. Sci.* (DOI: 10.1039/c1sc00634g).
(8) For *ortho*-arylation of phenols using phosphinites, see: (a) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112. (b) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669. For branched-selective hydroformylation of alkenyl alcohols using phosphorus-based ligands that reversibly bind the alcohol, see: (c) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *120*, 7456. (d) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 967. (e) Usui, I.; Nomura, K.; Breit, B. *Org. Lett.* **2011**, *13*, 612. (f) Ueki, Y.; Ito, H.; Usui, I.; Breit, B. *Chem.—Eur. J.* **2011**, *17*, 8555. For a recent review, see: (g) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450. (h) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210. (i) Lightburn, T. E.; De Paolis, O. A.; Cheng, K. H.; Tan, K. L. *Org. Lett.* **2011**, *13*, 2686. (j) Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757. For a recent review, see: (k) Tan, K. L. *ACS Catal.* **2011**, *1*, 877.

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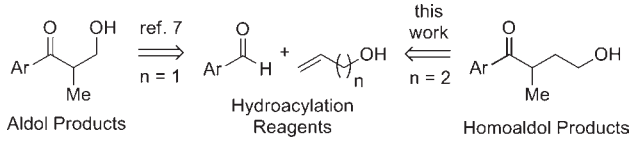
alkenyl alcohols.[8] On the basis of these results, we imagined that homoallyl alcohols could undergo hydroacylation by

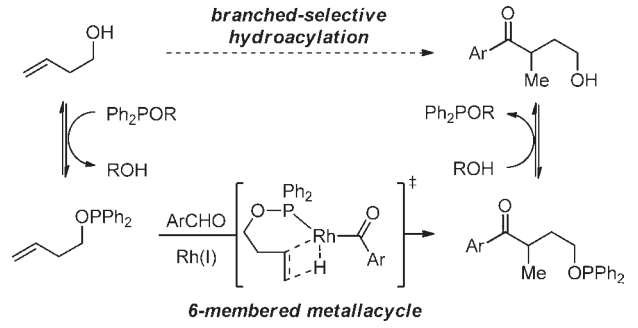
Scheme 1. Hydroacylation as a Unified Approach to both Aldol and Homoaldol Products



the analogous pathway shown in Scheme 2; however, two key challenges must be overcome. First, the homoallyl phosphinite intermediate, which is generated by the reversible exchange of homoallyl alcohol with methyl diphenylphosphinite (Ph_2POMe), would have to undergo hydroacylation via a six-membered metallacycle which would be the largest chelate size reported for intermolecular olefin hydroacylation.[9] Second, competitive decarbonylation and olefin migration may be expected to cause substantial catalyst deactivation and side product formation because reactivity diminishes with the increased chelate size.[10]

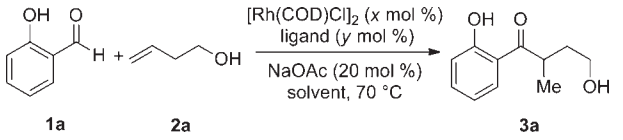
To explore these challenges, we studied the reaction of salicylaldehyde with homoallyl alcohol using $[Rh(COD)Cl]_2$ as the precatalyst in the presence of Ph_2POMe and catalytic NaOAc (Table 1). We chose salicylaldehyde because its phenolic group is known to coordinate to Rh and promote hydroacylation.[5f] By applying conditions similar to those

Scheme 2. Branched-Selective Hydroacylation of Homoallyl Alchols Promoted by Phosphinites (Ar = 2-hydroxyphenyl)



our group previously reported for hydroacylation of allyl alcohols (Table 1, entry 1),[7] the desired homoaldol product **3a** was observed in only 60% yield along with products of olefin migration. Because these two products diverge from a common acyl-Rh-alkyl intermediate via competing reductive elimination and β-hydride elimination, we predicted that a coordinating solvent might promote hydroacylation over olefin migration. Indeed, changing the solvent from $(CH_2Cl)_2$ to THF afforded the desired homoaldol product **3a** in 97% yield as a single regioisomer after 2.5 h (Table 1, entry 2). Reducing the catalyst loading further to 1 mol % $[Rh(COD)Cl]_2$ afforded the product in 70% yield after 9 h (Table 1, entry 3). No catalytic activity was observed when the phosphinite ligand was replaced with triphenylphosphine (Table 1, entry 4), which supports the role of Ph_2POMe as an exchangeable directing group.

Table 1. Optimization of Hydroacylation of Homoallyl Alcohol with Salicylaldehyde[a,b]



entry	x	y	ligand	solvent	yield (%)[c]	time (h)
1	5	50	Ph_2POMe	$(CH_2Cl)_2$	60	18
2	2.5	25	Ph_2POMe	THF	97	2.5
3	1	10	Ph_2POMe	THF	70[d]	9
4	5	20	PPh_3	THF	0[e]	48

[a] Stoichiometry: salicylaldehyde (0.25 mmol, 1.0 equiv), olefin (1.5 equiv). [b] The branched-to-linear selectivity was >20:1 by ^1H NMR analysis of the crude reaction mixtures for entries 1–3. [c] Isolated yield. [d] Salicylaldehyde (1 mmol, 1 equiv). [e] No product could be detected by GC-MS.

Nine sterically and electronically diverse salicylaldehydes were investigated as coupling partners for homoallyl alcohol under our optimized conditions (Table 1, entry 2). The corresponding α-branched ketones were obtained as single regioisomers in 75–98% yields (Table 2). Both fluoro and chloro substituents were well tolerated (Table 2, entries 2 and 3), and 5-iodosalicylaldehyde produced the desired hydroacylation product in good yield without any observable Mizoroki–Heck coupling or proto-deiodination (Table 2, entry 4).[11] Electron-rich methoxysalicylaldehydes (Table 2, entries 5–7) and substrates with increased steric bulk at the 3- or 6-positions (Table 2, entries 7 and 8) provided excellent reactivity. The Lewis basic pyridine ring in 5-(4-pyridyl)salicylaldehyde did not inhibit catalysis despite its potential to compete with the substrate for metal coordination sites, and the desired α-branched ketone was isolated in 75% yield (Table 2, entry 9).

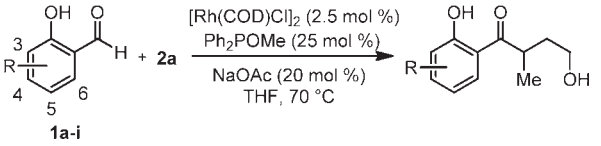
A series of γ-hydroxyketones were prepared by coupling salicylaldehyde with six homoallyl alcohols (Table 3). Disubstituted olefins are difficult substrates for intermolecular hydroacylation; however, *cis*- and *trans*-3-hexen-1-ol underwent coupling to the desired branched ketones in moderate yields under our optimized conditions (Table 3, entries 2 and 3). Substitution at the α and β positions of

(9) Bishomoallylic alcohols have been reported to undergo phosphinite-promoted hydroformylation via seven-membered metallacycles; see ref 8d.

(10) (a) Khan, H. A.; Kou, K. G. M.; Dong, V. M. *Chem. Sci.* **2011**, *2*, 407. (b) See ref 6b.

(11) For examples of Rh-catalyzed Heck reactions, see: (a) Sugihara, T.; Satoh, T.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4672. (b) Martinez, R.; Voica, F.; Genet, J-P.; Darses, S. *Org. Lett.* **2007**, *9*, 3213.

Table 2. Regioselective Hydroacylation of Homoallyl Alcohol with Salicylaldehydes[a,b]



1a-i

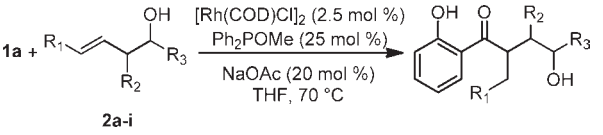
entry	1	R	yield (%)[c]	time (h)
1	**1a**	H	97	2.5
2	**1b**	5-F	88	3.5
3	**1c**	5-Cl	92	3.5
4	**1d**	5-I	75	3.5
5	**1e**	4-OMe	92	3
6	**1f**	5-OMe	86	2.5
7	**1g**	3-OMe	83	4
8	**1h**	6-Me	98	3
9	**1i**	5-(4-py)	75	4

[a] Stoichiometry: salicylaldehyde (0.25 mmol, 1.0 equiv), olefin (1.5 equiv). [b] The branched-to-linear selectivity was >20:1 by ^{1}H NMR analysis of the crude reaction mixtures in all cases. [c] Isolated yield.

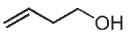
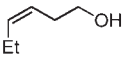
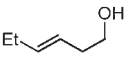
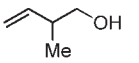
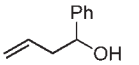
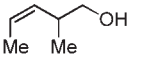
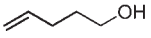
homoallyl alcohol (Table 3, entries 4 and 5) was tolerated, although the secondary alcohol **2e** required a longer reaction time. The diastereoselectivities were moderate in both cases and were not improved when **2f** was employed as the coupling partner despite the increased A(1,3) strain present in that molecule (Table 3, entry 6). Homoallylbenzylether did not furnish any hydroacylation products, likely because this substrate cannot undergo phosphinite exchange (Table 3, entry 7). Additionally, the further homologated alcohol **2h** provided only trace amounts of the desired hydroacylation product along with products of olefin isomerization as detected by ^{1}H NMR analysis of the crude reaction mixture. We attribute the lower reactivity of this substrate to the larger distance between the directing group and olefin compared to the homoallyl alcohol.

We next explored 2-hydroxystyrene substrates, which undergo hydroacylation via six-membered metallacylces similar to homoallyl alcohols, and found that they were highly reactive toward hydroacylation under our optimized conditions (Table 4). 2-Hydroxystyrene underwent coupling to yield the α-aryl ketone product as a single regioisomer in 88% yield after 4 h (Table 4, entry 1). We considered that the phenolic group of 2-hydroxystyrene could coordinate to Rh under basic reaction conditions and promote a background reaction. Because no products were observed when Ph_2POMe was replaced with PPh_3, the phosphinite likely undergoes exchange with the phenolic group and promotes the reaction. The effects of olefin electronics and substitution on reaction efficiency were investigated next. The electron-deficient olefin 5-fluoro-2-hydroxystyrene (Table 4, entry 2) underwent rapid hydroacylation, whereas the electron-rich olefin 4-methoxy-2-hydroxystyrene (Table 4, entry 3)

Table 3. Regioselective Hydroacylation of Homoallyl Alcohols with Salicylaldehyde[a,b]



2a-i

entry	2	olefin	yield (%)[c]	time (h)
1	**2a**		97 (70[d])	2.5
2	**2b**		50	24
3	**2c**		53	24
4	**2d**		92[e]	2.5
5	**2e**		98[f]	16
6	**2f**		53[g]	20
7	**2g**		0[h]	18
8	**2h**		trace	20

[a] Stoichiometry: salicylaldehyde (0.25 mmol, 1.0 equiv), olefin (1.5 equiv). [b] The branched-to-linear selectivity was >20:1 by ^{1}H NMR analysis of the crude reaction mixtures in all cases. [c] Isolated yield. [d] $[Rh(COD)Cl]_2$ (1 mol %), Ph_2POMe (10 mol %), salicylaldehyde (1 mmol), 9 h. [e] dr = 64:36. [f] dr = 71:29. [g] dr = 63:37. [h] No product could be identified by GC-MS after 24 h.

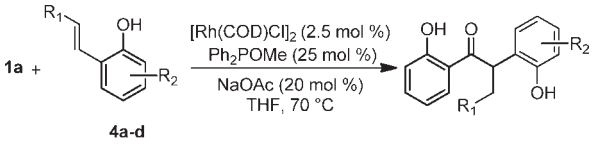
was slightly less efficient. The challenging disubstituted olefin 2-hydroxy-β-methylstyrene underwent efficient hydroacylation to yield the α-aryl ketone in 86% yield after 18 h (Table 4, entry 4).

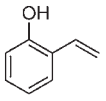
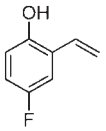
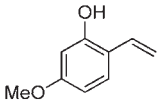
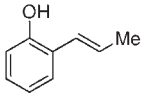
During our scope studies, we found that the products of homoallyl alcohol hydroacylation equilibrate to hemiketals upon storage. This cyclization prompted us to search for conditions to synthesize substituted heterocycles. We found that reduction of **3a** using sodium borohydride and subsequent treatment with aqueous HCl afforded tetrahydrofuran **5** in 78% yield with 33:1 diastereoselectivity in favor of the *trans* stereoisomer (Scheme 3).[12] Although the product of 2-hydroxystyrene hydroacylation **6** did not undergo appreciable equilibration to its hemiketal isomer compared to **3a**, we found that treatment of **6** with trifluoroacetic acid in dichloromethane resulted in near quantitative conversion to the 1,2-disubstituted benzofuran **7** (Scheme 3).

To conclude, we have reported a highly branched-selective method for hydroacylation of homoallyl alcohols

(12) The stereochemistry was assigned by comparison to *trans*-2-phenyl-3-methyltetrahydrofuran, see: Schmitt, A.; Reiβig, H.-U. *Eur. J. Org. Chem.* **2000**, 3893.

Table 4. Regioselective Hydroacylation of 2-Hydroxystyrene Derivatives with Salicylaldehyde[a,b]

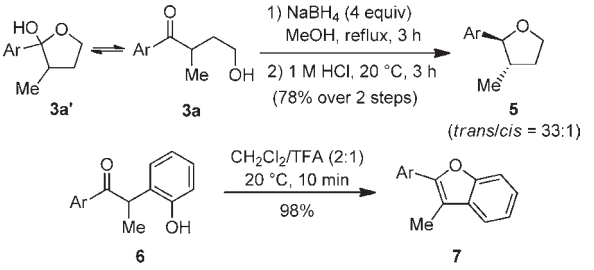


entry	4	olefin	yield (%)[c]	time (h)
1	**4a**		88 (0[d])	4
2	**4b**		98	4
3	**4c**		68	7
4	**4b**		86	18

[a] Stoichiometry: salicylaldehyde (0.25 mmol, 1.0 equiv), olefin (1.5 equiv). [b] The branched-to-linear selectivity was >20:1 by ^{1}H NMR analysis of the crude reaction mixtures in all cases. [c] Isolated yield. [d] No product was detected under the conditions in Table 1, entry 4.

and 2-hydroxystyrenes. In conjunction with our previous work on allyl alcohol hydroacylation, we have demonstrated the use of hydroacylation as an approach to both aldol and homoaldol products. Future work will focus on extending this strategy beyond salicylaldehyde substrates, mechanistic studies, and the development of enantioselective variants.

Scheme 3. Synthesis of Substituted Tetrahydrofuran and Benzofuran Derivatives (Ar = 2-hydroxyphenyl).



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Supporting Information Available. Experimental procedures, characterization data for new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.