Organic LETTERS

Letter

pubs.acs.org/OrgLett

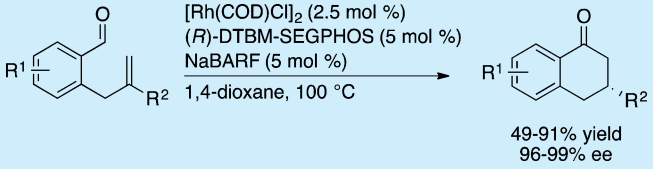
Rhodium-Catalyzed, Enantioselective Hydroacylation of *ortho*-Allylbenzaldehydes

Kirsten F. Johnson, Adam C. Schmidt, and Levi M. Stanley*

Department of Chemistry, Iowa State University, Ames, Iowa 50011, United States

Supporting Information

ABSTRACT: The development of a rhodium catalyst for *endo*- and enantioselective hydroacylation of *ortho*-allylbenzaldehydes is reported. A catalyst generated *in situ* from $[Rh(COD)Cl]_2$, (*R*)-DTBM-SEGPHOS, and NaBARF promotes the desired hydroacylation reactions and minimizes the formation of byproducts from competitive alkene isomerization and ene/dehydration pathways. These rhodium-catalyzed processes generate the 3,4-dihydronaphthalen-1(2*H*)-one products in moderate-to-high yields (49−91%) with excellent enantioselectivities (96−99% ee).

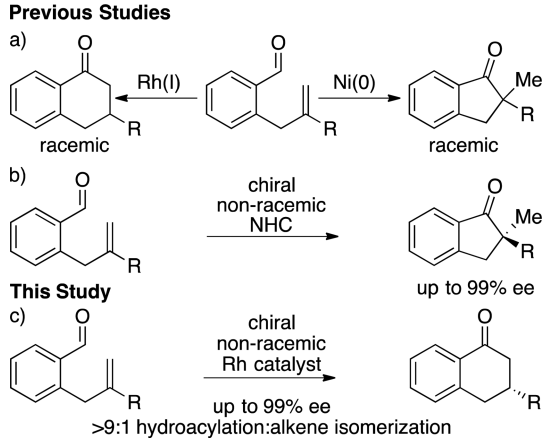


The development of new catalysts has rendered intramolecular alkene hydroacylation a valuable strategy to generate a wide variety of carbocyclic and heterocyclic ketones.[1−4] These transformations, which involve the formal insertion of an aldehyde C−H bond into an alkene, can be promoted by transition metal or *N*-heterocyclic carbene (NHC) catalysts. The selection of transition metal or NHC catalysts for enantioselective intramolecular hydroacylations is often dictated by the desired regiochemical outcome of the reaction. NHC-catalyzed intramolecular hydroacylations occur with *exo* selectivity (formal Markovnikov selectivity),[2] while transition-metal-catalyzed hydroacylations can occur with either *endo* selectivity (formal anti-Markovnikov selectivity)[3] or *exo* selectivity.[4] The potential for complementary regioselectivity makes the synthesis of two distinct ketone products from the same substrate possible.

ortho-Allylbenzaldehydes are a class of substrates that highlights the two potential regiochemical outcomes of alkene hydroacylation. *Endo*-selective hydroacylations of *ortho*-allylbenzaldehydes occur in the presence of an achiral rhodium catalyst to form racemic 3,4-dihydronaphthalene-1(2*H*)-ones,[5] while the complementary *exo*-selective processes occur in the presence of an achiral nickel catalyst to form racemic 2,3-dihydro-1*H*-inden-1-ones (Scheme 1a).[6] During our studies, Glorius et al. reported the first catalytic, *exo*- and enantioselective hydroacylations of *ortho*-allylbenzaldehydes to form 2,3-dihydro-1*H*-inden-1-ones containing an all-carbon quaternary stereogenic center (Scheme 1b).[7] However, an *endo*- and enantioselective variant of the hydroacylation of *ortho*-allylbenzaldehydes has not been reported.

In 2014, we reported enantioselective hydroacylation of *N*-allylindole-2-carboxaldehydes and *N*-allylpyrrole-2-carboxaldehydes to generate six-membered ketone products with exclusive *endo* selectivity.[8] These reactions occur in the presence of rhodium complexes containing a chiral bisphosphine ligand and a weakly coordinating counteranion. We envisioned that a related rhodium catalyst would promote the *endo*-selective hydroacylation of *ortho*-allylbenzaldehydes to form 3,4-dihydronaphthalen-1(2*H*)-ones with high enantioselectivities (Scheme 1c).

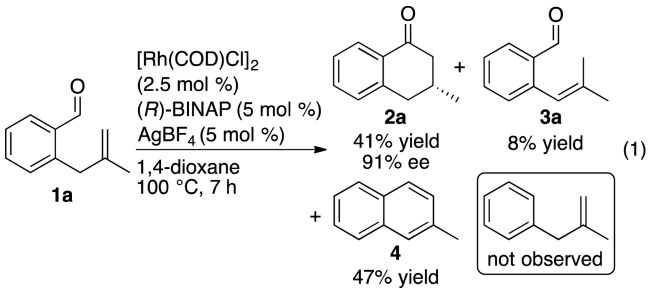
Scheme 1. Intramolecular Hydroacylation of *ortho*-Allylbenzaldehydes



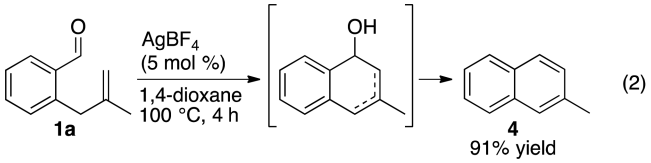
To assess the feasibility of *endo*- and enantioselective hydroacylation of *ortho*-allylbenzaldehydes, we evaluated the reaction of 2-(2-methylallyl)benzaldehyde **1a** in the presence of a catalyst generated from $[Rh(COD)Cl]_2$, (*R*)-BINAP, and $AgBF_4$ (eq 1). This reaction formed the desired hydroacylation product **2a** in 41% yield with 91% ee, the alkene isomerization product **3** in 8% yield, and 2-methylnaphthalene **4** in 47% yield. Although transition-metal-catalyzed hydroacylation reactions often require high catalyst loadings to overcome competitive decarbonylation,[3c−g,9] decarbonylation of **1a** was not observed under these conditions.

Received: May 29, 2015
Published: September 23, 2015

DOI: 10.1021/acs.orglett.5b02559
Org. Lett. 2015, 17, 4654−4657



The formation of 2-methylnaphthalene **4** from the reaction of **1a** was unexpected and has not been described in the context of alkene hydroacylation. However, the formation of substituted naphthalene derivatives from *ortho*-allylbenzaldehydes is known to occur by a sequence of Lewis acid catalyzed intramolecular ene reaction and dehydration.[10] To evaluate whether the silver salt used to generate the active catalyst promotes the formation of **4**, **1a** was exposed to 5 mol % $AgBF_4$ in the absence of $[Rh(COD)Cl]_2$ and the bisphosphine ligand (eq 2). This reaction generated **4** in 91% yield and demonstrates that $AgBF_4$ is a noninnocent additive under our catalytic reaction conditions.



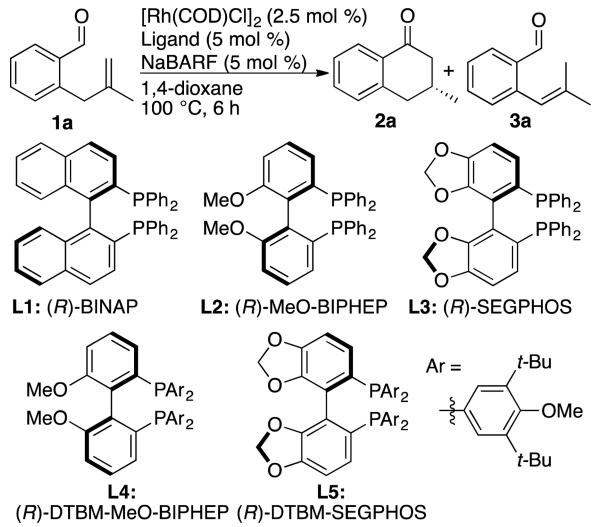
To effect counteranion exchange and enable the *in situ* generation of the active, cationic rhodium complex while mitigating the silver-catalyzed ene/dehydration pathway, we employed sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate (NaBARF) in place of $AgBF_4$.[11] We hypothesized the absence of Ag(I) would eliminate the formation of **4**. To test this hypothesis, we evaluated the hydroacylation of **1a** in the presence of a catalyst generated from $[Rh(COD)Cl]_2$, (*R*)-BINAP, and NaBARF (Table 1, entry 1). The reaction occurred to form the ketone product **2a** in 77% yield and the alkene isomerization product **3a** in 23% yield. The formation of 2-methylnaphthalene **4** was not observed.

Although the *in situ* generated catalyst eliminates the ene reaction/dehydration pathway to **4**, the enhanced cationic character of this rhodium complex increases the rate of alkene isomerization relative to the rate of alkene hydroacylation.[12,13] The ratio of hydroacylation to isomerization is 5.1:1 when the catalyst contains the tetrafluoroborate counteranion; the ratio decreases to 3.3:1 when the catalyst contains the tetraarylborate counteranion.

We hypothesized that the steric and electronic properties of the chiral bisphosphine ligand could be leveraged to improve the rate of alkene hydroacylation relative to the rate of alkene isomerization. Rhodium catalysts with less cationic character should attenuate the rates of both alkene isomerization and alkene hydroacylation.[3c,d,12] However, bisphosphine ligands with bulky aryl substituents on phosphorus should significantly increase the overall rate of alkene hydroacylation relative to the rate of alkene isomerization by increasing the rate of the turnover-limiting reductive elimination to form the ketone product.[14,15]

To evaluate the impact of steric and electronic properties of the ligand, we conducted hydroacylations of **1a** with catalysts

Table 1. Identification of Catalysts for Hydroacylation of 2-(2-Methylallyl)benzaldehyde 1a



entry	ligand	yield **2a** (%)[a,b]	ee **2a** (%)[c]	yield **3** (%)[a]	ratio **2a**:**3a**[d]
1	**L1**	77 (56)	87	23	3.3:1
2	**L2**	75 (75)	90	16	4.7:1
3	**L3**	80 (72)	88	16	5.0:1
4	**L4**	80 (80)	99	9	8.9:1
5	**L5**	85 (81)	98	8	10.7:1
6[e]	**L5**	65 (63)	99	10	6.5:1
7[f]	**L5**	50 (52)	99	5	10:1

[a]Yield determined by ^1H NMR spectroscopy with dibromomethane as the internal standard. [b]Isolated yield of **2a** is shown in parentheses. [c]Determined by chiral HPLC analysis. [d]Determined by ^1H NMR spectroscopy of the crude reaction mixture. [e]$[Rh(COD)_2]BF_4$ (5 mol %) used in place of $[Rh(COD)Cl]_2$ and NaBARF. [f]$[Rh(COD)_2]$-BARF (5 mol %) used in place of $[Rh(COD)Cl]_2$ and NaBARF.

derived from a series of bisphosphine ligands with axially chiral backbones (Table 1). The rhodium(I) complexes of (*R*)-MeO-BIPHEP **L2** and (*R*)-SEGPHOS **L3**, which are more electron-rich than the complex derived from (*R*)-BINAP **L1**, catalyze the reaction of **1a** with improved ratios of hydroacylation to isomerization (4.7:1 and 5.0:1) relative to the rhodium(I) complex of **L1** (compare entries 2 and 3 with entry 1). We then conducted hydroacylations of **1a** in the presence of rhodium catalysts prepared from ligands containing bulky, electron-rich 3,5-di-*tert*-butyl-4-methoxyphenyl substituents on phosphorus. The hydroacylation of **1a** occurs with an 8.9:1 ratio of hydroacylation to isomerization when the reaction is run in the presence of the rhodium(I) complex of (*R*)-DTBM-MeO-BIPHEP **L4**, and ketone product **2a** is isolated in 80% yield (entry 4). The ratio of hydroacylation to isomerization products can be further improved by conducting the reaction of **1a** with a rhodium(I) complex of the more electron-rich (*R*)-DTBM-SEGPHOS **L5** (entry 5).[16] In the presence of this rhodium(I) catalyst, the hydroacylation of **1a** occurs with a 10.7:1 ratio of hydroacylation to isomerization, and ketone **2a** is isolated in 85% yield. The absolute configuration of **2a** was determined to be (*R*) by comparison of optical rotation data with literature values.[17]

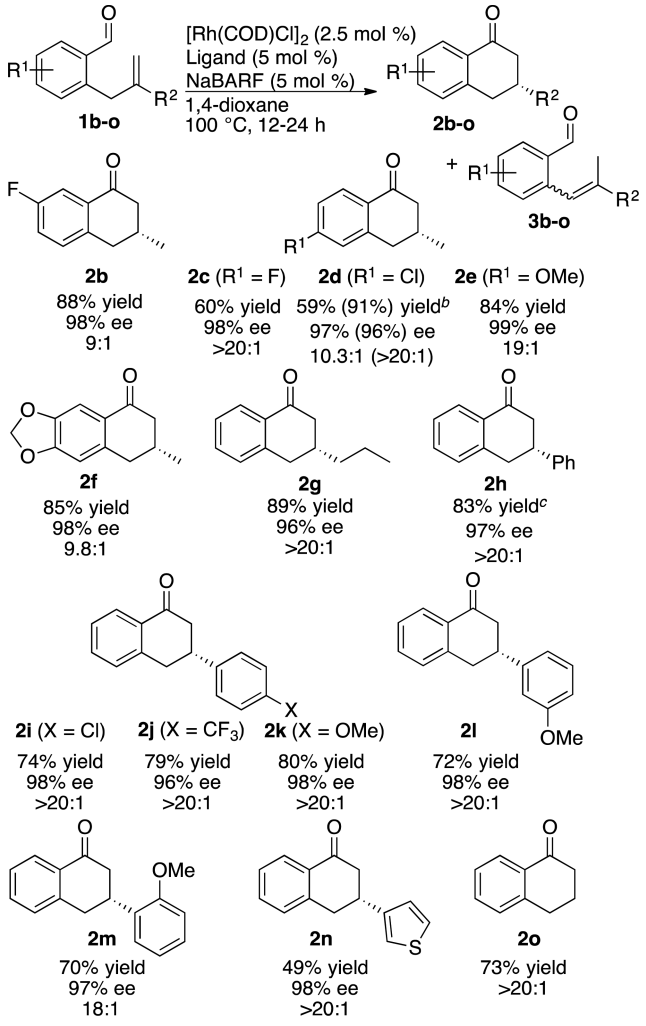
Additional rhodium(I) precursors were evaluated for the hydroacylation of **1a** using the electron-rich (*R*)-DTBM-SEGPHOS ligand **L5**. A significant decrease in the yield of **2a** and the ratio of hydroacylation to isomerization products is

DOI: 10.1021/acs.orglett.5b02559
Org. Lett. 2015, 17, 4654−4657

observed when $[Rh(COD)_2]BF_4$ is employed as the catalyst precursor for the hydroacylation of **1a** (63% yield, 6.5:1) (compare entries 5 and 6). Conducting the reaction of **1a** in the presence of a catalyst generated from $[Rh(COD)_2]BARF$ results in a 10:1 ratio of hydroacylation to isomerization products. However, the yield of **2a** was comparatively low (compare entries 5 and 7). Thus, we chose to evaluate the scope of hydroacylations of additional *ortho*-allylbenzaldehydes using the reaction conditions from entry 5.

With a practical catalyst system identified, we evaluated the hydroacylations of a variety of *ortho*-allylbenzaldehydes containing substitution around the aryl core and on the central carbon of the allyl moiety (Scheme 2). Hydroacylations of 5-fluoro-2-(2-methylallyl)benzaldehyde **1b** and 4-fluoro-2-(2-methylallyl)benzaldehyde **1c** form the corresponding 3,4-dihydronaphthalen-1(2*H*)-ones **2b** and **2c** in 88% and 60% yield with 98% ee. The hydroacylation of 4-chloro-2-(2-methylallyl)benzaldehyde **1d** generated **2d** in modest yield in the presence of 5 mol % rhodium catalyst. However, the reaction of **1d** in the presence of 10 mol % catalyst formed **2d** in 91% yield with 96% ee.

Scheme 2. Rh-Catalyzed Hydroacylation of *ortho*-Allylbenzaldehydes 1a–i[a]

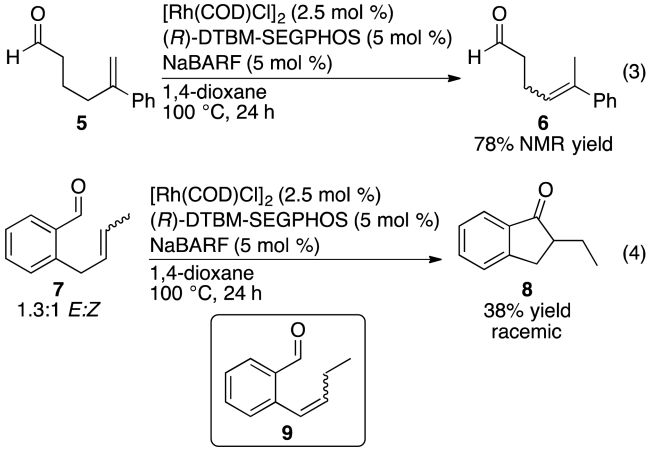


[a]Yields of **2** are isolated yields after column chromatography. Enantiomeric excesses were determined by chiral HPLC analysis. Ratios of hydroacylation to alkene isomerization products (**2b–o**:**3b–o**) were determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Values in parentheses are for the reaction of **1d** in the presence of 10 mol % rhodium catalyst. [c]Isolated as 96:4 mixture of **2h**:**3h**.

The hydroacylations of electron-rich *ortho*-allylbenzaldehydes also occur to form 3,4-dihydronaphthalen-1(2*H*)-ones in high yields with excellent enantioselectivities. The hydroacylations of 4-methoxy-2-(2-methylallyl)benzaldehyde **1e** and the piperonal-derived 2-(2-methylallyl)benzaldehyde) **1f** provide 3,4-dihydronaphthalen-1(2*H*)-ones **2e** and **2f** in 84% and 85% yields with 99% and 98% ee.

Alkyl and aryl substituents on the internal carbon of the allyl moiety are also well tolerated. The hydroacylations of *ortho*-allylbenzaldehydes **1g** and **1h** (R^2 = *n*-Pr and Ph) generate **2g** and **2h** in 89% and 87% yield with 96% and 97% ee. Hydroacylations of *ortho*-allylbenzaldehydes **1j–1m** containing substituted aryl groups at the central carbon of the allyl moiety generate the 3-aryl-3,4-dihydronaphthalen-1(2*H*)-one products **2j–2m** in good yields (70–80%) with excellent enantioselectivities (96–98% ee). In addition, the hydroacylation of 2-(2-(thiophen-3-yl)allyl)benzaldehyde **1n** forms 3,4-dihydronaphthalen-1(2*H*)-one **2n** in 49% yield with 98% ee. The hydroacylation of 2-allylbenzaldehyde **1o**, which lacks substitution at the central carbon of the allyl moiety, exclusively forms the 3,4-dihydronaphthalen-1(2*H*)-one **2o**; the formation of the five-membered ketone (2-methyl-2,3-dihydro-1*H*-inden-1-one) is not observed with the current catalyst system.

Although we have developed a practical catalyst for enantioselective hydroacylation of *ortho*-allylbenzaldehydes, the catalyst performs poorly for substrates in which the alkene and aldehyde units are not conformationally constrained. For example, the reaction of 5-phenylhex-5-enal **5** forms alkene isomerization product **6** in 78% yield, and the alkene hydroacylation product is not detected by ^{1}H NMR spectroscopy (eq 3). In addition, the hydroacylation of an *ortho*-allylbenzaldehyde with substitution at the terminal position of the allyl unit does not occur to form the expected 3,4-dihydronaphthalen-1(2*H*)-one product. The reaction of a 1.3:1 *E*/*Z* mixture of 2-(but-2-en-1-yl)benzaldehyde **7** forms 2-ethyl-2,3-dihydro-1*H*-inden-1-one **8** in 38% yield as a racemic mixture (eq 4). We hypothesize the formation of **7** results from *endo*-selective hydroacylation of alkene isomerization product **9**, but we cannot rule out *exo*-selective hydroacylation of **7** to form **8** at this time.



In summary, we have developed a rhodium catalyst that promotes the hydroacylation of *ortho*-allylbenzaldehydes to

DOI: 10.1021/acs.orglett.5b02559
Org. Lett. 2015, 17, 4654–4657

generate 3,4-dihydronaphthalene-1(2*H*)-ones with excellent enantioselectivities. These *endo*-selective processes are complementary to the recently reported *exo*- and enantioselective NHC-catalyzed hydroacylations of the same substrates.[7] Competitive alkene isomerization and ene/dehydration processes are mitigated by a rhodium catalyst containing a bulky, electron-rich bisphosphine ligand and a weakly coordinating counteranion. This catalyst is prepared from readily available precursors and promotes the desired hydroacylation reactions to form products in high yields. Studies to exploit the features of this catalyst system in additional classes of hydroacylation reactions are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02559.

Experimental procedures and characterization data for all new compound (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lstanley@iastate.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Iowa State University and the National Science Foundation (CHE-CAREER 1353819) for financial support of this work. We thank Professor Emeritus Richard Larock (Iowa State University) for instrumentation and chemicals.

■ REFERENCES

(1) For selected reviews, see: (a) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (b) Murphy, S. K.; Dong, V. M. *Chem. Commun.* **2014**, *50*, 13645.

(2) For selected examples, see: (a) Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190. (b) Biju, A. T.; Wurz, N. E.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 5970. (c) Padmanaban, M.; Biju, A. T.; Glorius, F. *Org. Lett.* **2011**, *13*, 5624. (d) Piel, I.; Steinmetz, M.; Hirano, K.; Fröhlich, R.; Grimme, S.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 4983. (e) Franz, J. F.; Fuchs, P. J. W.; Zeitler, K. *Tetrahedron Lett.* **2011**, *52*, 6952. (f) Wang, Z.; Yu, Z.; Wang, Y.; Shi, D. *Synthesis* **2012**, *44*, 1559. (g) Lu, H.; Lin, J.-B.; Liu, J.-Y.; Xu, P.-F. *Chem. - Eur. J.* **2014**, *20*, 11659. (h) Alcaide, B.; Almendros, P.; Fernàndez, I.; Martínez del Campo, T.; Naranjo, T. *Chem. - Eur. J.* **2015**, *21*, 1533.

(3) For selected examples, see: (a) Gulbis, J.; Everett, G. W., Jr.; Frank, C. W. *J. Am. Chem. Soc.* **1976**, *98*, 1280. (b) Larock, R. C.; Oertle, K.; Potter, G. F. *J. Am. Chem. Soc.* **1980**, *102*, 190. (c) Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 936. (d) Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 946. (e) Barnhart, R. W.; Wang, X. Q.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1994**, *116*, 1821. (f) Barnhart, R. W.; Bosnich, B. *Organometallics* **1995**, *14*, 4343. (g) Barnhart, R. W.; McMorran, D. A.; Bosnich, B. *Chem. Commun.* **1997**, 589. (h) Kundu, K.; McCullagh, J. V.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 16042. (i) Arnold, J. S.; Mwenda, E. T.; Nguyen, H. M. *Angew. Chem.* **2014**, *126*, 3762. (j) Ghosh, A.; Stanley, L. M. *Chem. Commun.* **2014**, *50*, 2765. (k) Hoffman, T. J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 10670.

(4) (a) Bendorf, H. D.; Colella, C. M.; Dixon, E. C.; Marchetti, M.; Matukonis, A. N.; Musselman, J. D.; Tiley, T. A. *Tetrahedron Lett.* **2002**, *43*, 7031. (b) Bendorf, H. D.; Ruhl, K. E.; Shurer, A. J.; Shaffer, J. B.; Duffin, T. O.; LaBarte, T. L.; Maddock, M. L.; Wheeler, O. W. *Tetrahedron Lett.* **2012**, *53*, 1275. (c) Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932. (d) Yang, F.; Jin, T.; Yamamoto, Y. *Tetrahedron* **2012**, *68*, 5223.

(5) Beletskiy, E. V.; Sudheer, C.; Douglas, C. J. *J. Org. Chem.* **2012**, *77*, 5884.

(6) Hoshimoto, Y.; Hayashi, Y.; Suzuki, H.; Ohashi, M.; Ogoshi, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 10812.

(7) Janssen-Müller, D.; Schedler, M.; Fleige, M.; Daniliuc, C. G.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *Ahead of Print* (doi: 10.1002/anie.201412302).

(8) Du, X.-W.; Ghosh, A.; Stanley, L. M. *Org. Lett.* **2014**, *16*, 4036.

(9) (a) Hyatt, I. F. D.; Anderson, H. K.; Morehead, A. T., Jr.; Sargent, A. L. *Organometallics* **2008**, *27*, 135. (b) Roy, A. H.; Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 2082.

(10) Jagdale, A. R.; Park, J. H.; Youn, S. W. *J. Org. Chem.* **2011**, *76*, 7204.

(11) (a) Nishida, H.; Takada, N.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600. (b) Brookhart, M.; Grant, B.; Volpe, A. F., Jr. *Organometallics* **1992**, *11*, 3920. (c) Yakelis, N. A.; Bergman, R. G. *Organometallics* **2005**, *24*, 3579.

(12) For examples of olefin isomerization in intramolecular hydroacylation and additional Rh-catalyzed processes, see: (a) Hassam, M.; Taher, A.; Arnott, G. E.; Green, I. R.; van Otterlo, W. A. L. *Chem. Rev.* **2015**, *115*, 5462. (b) Marder, T. B.; Roe, D. C.; Milstein, D. *Organometallics* **1988**, *7*, 1451. (c) Campbell, R. E., Jr.; Lochow, C. F.; Vora, K. P.; Miller, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5824. (d) Okamoto, R.; Tanaka, K. *Org. Lett.* **2013**, *15*, 2112. (e) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492. (f) Takeishi, K.; Sugishima, K.; Sasaki, K.; Tanaka, K. *Chem. - Eur. J.* **2004**, *10*, 5681. (g) Okamoto, R.; Okazaki, E.; Noguchi, K.; Tanaka, K. *Org. Lett.* **2011**, *13*, 4894. (h) Zhuo, L. G.; Yao, Z.-K.; Yu, Z.-X. *Org. Lett.* **2013**, *15*, 4634. (i) Vora, K. P.; Lochow, C. F.; Miller, R. G. *J. Organomet. Chem.* **1980**, *192*, 257.

(13) The isomerization of **1a** does not occur via endocyclic β-hydride elimination as recently reported for the rhodium-catalyzed isomerization of 4-pentenals to 3-pentenals (Yip, S. Y. Y.; Aissa, C. *Angew. Chem., Int. Ed.*, **2015**, *54*, 6870). See the Supporting Information for details on hydroacylation and isomerization of deuterated **1a**.

(14) For the influence of ligand sterics and electronics on reductive elimination, see: (a) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2010. (b) Brown, J. M.; Cooley, N. A. *Chem. Rev.* **1988**, *88*, 1031. (c) Jones, W. D.; Kuykendall, V. L. *Inorg. Chem.* **1991**, *30*, 2615. (d) Brown, J. M.; Guiry, P. J. *Inorg. Chim. Acta* **1994**, *220*, 249. (e) Freixa, Z.; van Leeuwen, P. W. N. M. *Dalton Trans.* **2003**, 1890.

(15) The kinetic isotope effect for the hydroacylation of **1a** and *d*-**1a** was determined to be 1.19. This value is consistent with reductive elimination as the turnover-limiting step of the reaction mechanism. See Supporting Information for experimental details.

(16) (a) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405. (b) Shen, Z.; Dornan, P. K.; Khan, H. A.; Woo, T. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 1077.

(17) (a) Muerling, A. *Chemica Scripta* **1987**, *27*, 349. (b) Barry, J.; Kagain, H.-B. *Tetrahedron* **1971**, *27*, 4737.

DOI: 10.1021/acs.orglett.5b02559
Org. Lett. 2015, 17, 4654−4657