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Intermolecular Markovnikov-Selective Hydroacylation of Olefins Catalyzed by a Cationic Ruthenium−Hydride Complex

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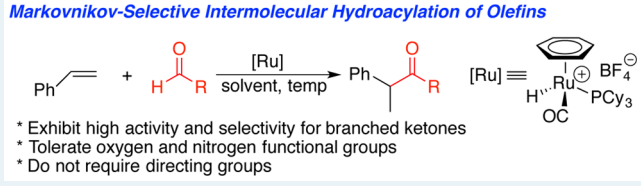
Supporting Information

ABSTRACT: The cationic Ru−H complex was found to be an effective catalyst for the intermolecular hydroacylation of aryl-substituted olefins with aldehydes to form branched ketone products. The preliminary kinetic and spectroscopic studies elucidated a ruthenium-acyl complex as the key intermediate species. The catalytic method directly afforded branched ketone products in a highly regioselective manner while tolerating a number of heteroatom functional groups.

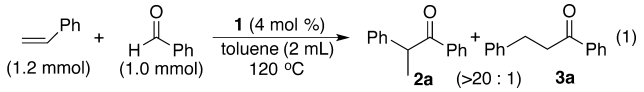


KEYWORDS: *hydroacylation, alkene, aldehyde, ruthenium catalyst, branched ketone*

The transition-metal-catalyzed hydroacylation reaction constitutes a highly expedient protocol for introducing acyl group to unsaturated organic substrates.[1] For the hydroacylation of olefins, the intramolecular version of the reaction has been effectively used to form cyclic ketone products.[2] Since the pioneering reports on the intermolecular hydroacylation of olefins,[3] a number of late-transition-metal catalysts have been found to mediate *anti*-Markovnikov hydroacylation of alkenes to form the linear ketones.[4−6] One of the most debilitating problems on the olefin hydroacylation reaction resides in competing decarbonylation of aldehyde substrates, which often leads to the deactivation of metal catalysts. A number of clever strategies have been implemented to circumvent the decarbonylation problem. One successful approach has been to employ aldehyde substrates with a heteroatom chelate group to promote the hydroacylation reaction.[4] Employing aldimines as a synthetic equivalent to aldehydes[5] and using activated olefin substrates[1c,6] have also been shown to be effective strategies for promoting regioselective hydroacylation reaction while limiting the decarbonylation side reaction. Because most of these catalytic methods generally exhibit *anti*-Markovnikov selectivity in forming linear ketone products, much research effort has been directed to develop Markovnikov-selective hydroacylation reaction to form the branched ketone products.[7,8] Even though the Markovnikov-selective asymmetric hydroacylation reaction has been achieved under intramolecular conditions,[8] relatively few examples of intermolecular Markovnikov-selective hydroacylation methods have been reported. Moreover, the substrate scope for the Markovnikov-selective hydroacylation reaction has been generally limited to either aldehydes with heteroatom chelate group or activated olefin substrates. Very recently, Zhou and co-workers reported the first example of Ni-catalyzed Markovnikov-selective hydroacylation of styrene derivatives.[9] Designing highly effective and generally applicable Markovnikov-selective hydroacylation technology remains a largely unsolved problem in the homogeneous catalysis field.

We recently devised a number of dehydrative C−H coupling reactions of olefins with alcohols by using a well-defined cationic ruthenium−hydride complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ (**1**) as the precatalyst.[10] In an effort to extend the scope of C−H acylation of phenol and related arenes,[11] we have been exploring the coupling reaction of aldehydes with olefin substrates. Herein, we disclose a highly Markovnikov-selective intermolecular hydroacylation of aryl-substituted olefins to yield branched ketone products. The catalytic method provides an atom-economical acylation protocol for styrene derivatives without employing any reactive reagents or directing groups.

We initially surveyed the coupling reaction of α-olefins with aldehydes to probe the feasibility of the hydroacylation reaction. The treatment of styrene (1.2 mmol) with benzaldehyde (1.0 mmol) in the presence of the catalyst **1** (4 mol %) was heated at 120 °C for 8 h, after which the product mixture was analyzed by both GC and NMR methods (eq 1).



The crude mixture showed high selectivity for the branched product **2a** over the linear product **3a** (82% GC yield based on the aldehyde, **2a**:**3a** > 20:1), along with a trace amount of the styrene dimer PhCH(Me)CH=CHPh (<5%). The preliminary screening of Ru catalysts confirmed uniquely high activity of the complex **1** for the coupling reaction (Table S1, Supporting Information (SI)).

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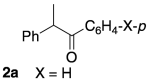
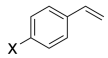
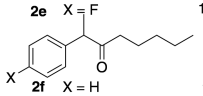
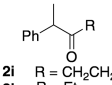
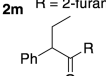
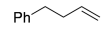
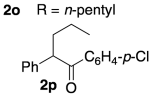
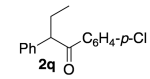
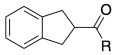
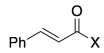
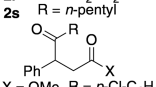
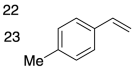
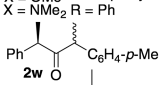
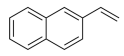
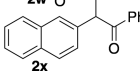
The catalyst **1** was used to explore the substrate scope of the hydroacylation reaction (Table 1). Both aliphatic and aryl-substituted aldehydes readily reacted with styrene derivatives to form the branched acylation products **2** (entries 1−13). For terminal olefins such as allylbenzene and 4-phenyl-1-butene, apparently facile olefin isomerization had taken place prior to the acylation to form the phenyl-substituted acylation products **2n−2p** (entry 14−16). We previously showed that the Ru catalyst promotes a very high olefin isomerization rate under the comparable conditions.[12] The coupling of indene with aldehydes predictively afforded the 2-acylated products **2r** and **2s** (entries 18,19), whereas the acylation of cinnamic acid derivatives proceeded smoothly to give the 1,4-diketone products **2t−2v** (entries 20−22). The hydroacylation of 4-methylstyrene with a chiral aldehyde substrate (*R*)−CH_3CHPhCHO led to a 1:1 diasteromeric mixture of the products **2w**, resulted from the epimerization of the olefinic carbon (entry 23). In most cases, the catalytic method achieves very high regioselectivity toward the branched acylated products over the linear ketone products without using any chelate-directing group (**2**:**3** > 20:1). It should be emphasized that the hydroacylation of styrene with simple aliphatic aldehydes has been rarely achieved.[9]

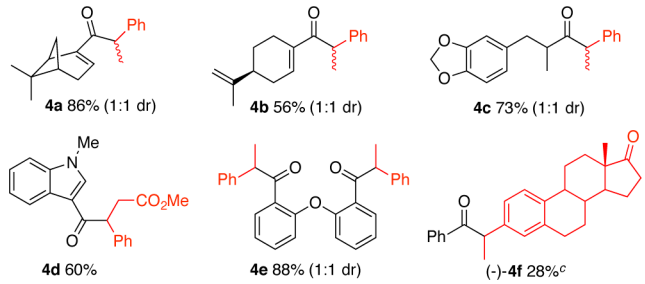
Table 1. Markovnikov-Selective Hydroacylation of Olefins[a]

entry	alkene	aldehyde	product (b:l)	temp (°C)	time (h)	yield (%)
		*p*-X-C_6H_4CHO				
1			**2a** X = H	125	8	91
2			**2b** X = OMe (10:1)	125	12	71
3			**2c** X = Me	125	8	86
4			**2d** X = Cl	125	6	91
5			**2e** X = F	125	6	95
		1-hexanal				
6			**2f** X = H	130	12	74
7			**2g** X = Me (10:1)	130	12	82
8			**2h** X = Cl	130	12	56
		R-CHO				
9			**2i** R = CH_2CH_2Ph	125	12	86
10			**2j** R = Et	125	12	71
11			**2k** R = CH=CHPh	100	12	73
12			**2l** R = 2-naphthyl	130	8	96
13			**2m** R = 2-furanyl (10:1)	125	12	64
		R-CHO				
14			**2n** R = Ph	110	16	66
15			**2o** R = *n*-pentyl	110	16	48
16		*p*-Cl-C_6H_4CHO		110	16	61
			2p			
17		*p*-Cl-C_6H_4CHO		110	16	76
			2q			
		R-CHO				
18			**2r** R = CH_2CH_2Ph	125	12	65
19			**2s** R = *n*-pentyl	125	16	62
		R-CHO				
20			**2t** X = OMe R = *p*-Cl-C_6H_4	110	36	58
21			**2u** X = OMe R = n-pentyl	90	12	68
22			**2v** X = NMe_2 R = Ph	110	36	46
23				125	12	84
			2w			
24		PhCHO		130	16	34
			2x			

[a]Reaction conditions: alkene (1.2 mmol), aldehyde (1.0 mmol), **1** (4−6 mol %), toluene (2 mL).

To further demonstrate synthetic utility, we next explored the hydroacylation of styrene with a number of biologically active aldehyde substrates. The treatment of (1*R*)-(−)-myrtenal and (*S*)-(−)-perillaldehyde with styrene formed a 1:1 diastereomeric mixture of the products **4a** and **4b** (Table 2).

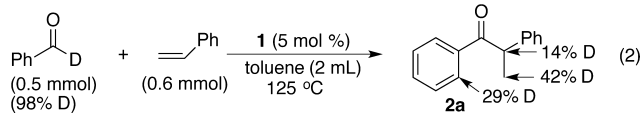
Table 2. Hydroacylation of Styrene Derivatives with Bioactive Aldehydes[a,b]



[a]Reaction conditions: alkene (1.2 mmol), aldehyde (1.0 mol), **1** (8−10 mol %), toluene (2 mL), 120 °C, 12−14 h. [b]Product yield is calculated on the basis of aldehyde substrate. Ratio of branched vs linear product is >20:1. [c]Reaction time = 36 h. The absolute stereochemistry of (−)-**4f** was not determined.

The reaction of biologically active helional with styrene and *N*-methyl-3-indolecarboxaldehyde with methyl cinnamate also yielded the products **4c** and **4d**, respectively. *Bis*-(2-formylphenyl)ether with 3 equiv of styrene selectively formed 2:1 coupling product **4e**, whereas vinylestrone with benzaldehyde formed a single diastereomer of (−)-**4f**. Both oxygen and nitrogen groups are tolerated in forming these hydroacylation products.

The following set of preliminary kinetic experiments was performed to gain mechanistic insights on the acylation reaction. First, we examined the H/D exchange pattern of the hydroacylation reaction (eq 2). The product **2a** was isolated



from the reaction mixture of benzaldehyde-d_1 (98% D, 0.5 mmol), styrene (0.6 mmol), and **1** (5 mol %) in toluene (2 mL) at 125 °C after 8 h. Deuterium content from the benzaldehyde was redistributed to CH_3 (42%) and CH (14%) as well as the *ortho*-arene (29%) of the isolated product **2a**, as determined by ^{1}H and ^{2}H NMR (Figure S1, SI). Nearly 10% of deuterium was also incorporated to the styrene dimer byproduct. A substantially higher amount of deuterium incorporation to CH_3 position compared to the CH group of **2a** suggests that the addition of aldehydic hydrogen to the terminal olefinic carbon is favored over the internal one. Nearly 30% of deuterium was also incorpoated to the *ortho*-arene postions, and such facile arene H/D exchange of arylketones has been commonly observed in chelate-assisted arene C−H insertion reactions.[13]

Next, we measured the kinetic isotope effect for the hydroacylation reaction. The reaction rate was measured for the hydroacylation reaction of styrene with PhCHO and PhCDO separately. The first-order plots on the formation of **2a**

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translated into a normal deuterium isotope effect of k_H/k_D = 2.6 ± 0.1 (Figure 1). The results suggest that the aldehyde C−H cleavage is the most likely turnover-limiting step for the coupling reaction.[14]

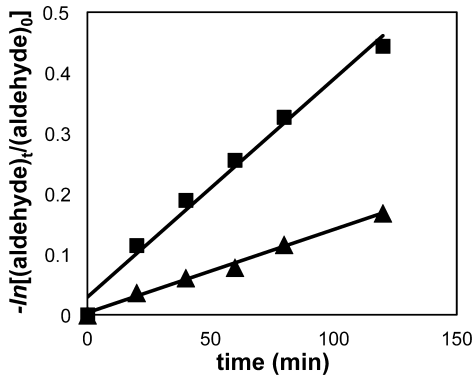


Figure 1. First-order rate plots from the hydroacylation of styrene with benzaldehyde (■) and benzaldehyde-*d* (▲).

To probe electronic influence on the aldehyde substrate, we constructed a Hammett plot from the rate of a series of *para*-substituted benzaldehydes *p*-X-C_6H_4CHO (X = OMe, Me, H, F, Cl). A linear correlation from the relative rate vs Hammett σ_p led to a positive ρ value of +0.8 ± 0.1 (Figure 2). The

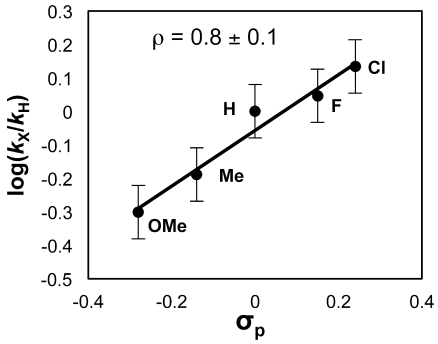
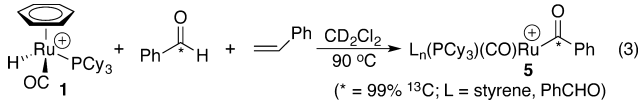


Figure 2. Hammett plot from the hydroacylation reaction of *p*-X-C_6H_4CHO (X = OCH_3, CH_3, H, F, Cl) with styrene.

promotional effect from electron-withdrawing group suggests that electrophilic nature of carbonyl group facilitates the aldehyde C−H activation. Dong and co-workers recently reported a similar Hammett ρ value in the catalytic hydroacylation of 4-nitro-2-vinylphenol with *para*-substituted benzaldehydes.[7g]

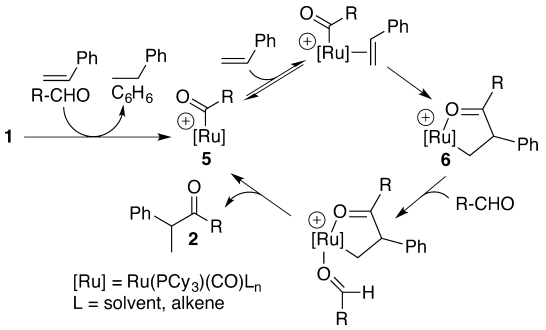
In an effort to elucidate the structure of catalytically relevant intermediate species, we monitored the reaction of **1** with styrene and aldehyde substrates. In a NMR tube, **1** (0.1 mmol), styrene (0.1 mmol), and ^{13}C-enriched benzaldehyde (0.1 mmol, 99% ^{13}C) were dissolved in CD_2Cl_2 (0.5 mL), and the tube was heated at 90 °C for 3 h, during which time, the formation of a new Ru complex was observed at the expense of the starting complex **1** as monitored by NMR (eq 3).



The $^{13}C\{^1H\}$ NMR spectrum of the reaction mixture at −40 °C showed a distinctively upfield-shifted carbonyl peak at δ 196.5 (d, J_{PC} = 18.4 Hz), which does not have any neighboring protons as analyzed by 2D NMR techniques (Figure S3, SI). We also detected a small amount of ethylbenzene (10%) and free benzene (90%) in the reaction mixture. We tentatively assigned the structure as a cationic Ru-acyl complex **5** on the basis of these NMR spectroscopic data.[15]

On the basis of these results, we present a possible mechanism of the hydroacylation reaction (Scheme 1). We

Scheme 1. Possible Mechanism for the Hydroacylation of Styrene



propose that the cationic Ru-acyl species **5** is initially generated from the coordination of aldehyde and the dehydrogenation steps. The spectroscopic detection of a Ru-acyl complex **5** from the stoichiometric reaction of **1** with benzaldehyde and styrene provides a strong argument for the acyl complex as catalytically active species. Ruthenium-acyl complexes have been considered as a key intermediate in hydroacylation and carbonylation of olefins.[1b,16] The regioselective migratory insertion of styrene would form the five-membered metallacyclic species **6**. Both Hammett and deuterium isotope effect data suggest that the aldehyde C−H bond cleavage is the turnover-limiting step, in which the C−H cleavage step would be facilitated by an electrophilic Ru center. The preferential deuterium incorporation to the methyl group of the product **2a**, as described in eq 2, is also consistent with a reductive elimination step via the metallacyclic species **6**.[17] A minor deuterium incorporation to the methyne position of **2a** can be explained via an alkene insertion/β-H elimination from the intermediate **6** and its concurrent H/D exchange with a Ru-D species.[18]

In conclusion, we successfully developed a highly Markovnikov-selective intermolecular hydroacylation protocol for the aryl-substituted alkenes to form branched ketone products. The catalytic method mediates high degree of Markovnikov selectivity without using any chelate directing groups, and it tolerates a number of oxygen and nitrogen functional groups in forming the acylation products. Efforts to design Ru chiral catalysts for the asymmetric version of the hydroacylation reaction are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b00856.

Experimental procedures and full characterization data of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Recent reviews: (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (b) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (c) Leung, J. C.; Krische, M. J. *Chem. Sci.* **2012**, *3*, 2202.

(2) (a) Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667. (b) Kundu, K.; McCullagh, J. V.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 16042. (c) Murphy, S. K.; Bruch, A.; Dong, V. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 2455. (d) Chen, Q.-A.; Kim, D. K.; Dong, V. M. *J. Am. Chem. Soc.* **2014**, *136*, 3772.

(3) (a) Marder, T. B.; Roe, D. C.; Milstein, D. *Organometallics* **1988**, *7*, 1451. (b) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286. (c) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 3165. (d) Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965.

(4) (a) Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J.-B. *Angew. Chem., Int. Ed.* **2000**, *39*, 3070. (b) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem. - Eur. J.* **2002**, *8*, 2422. (c) Willis, M. C.; McNally, S. J.; Beswick, P. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 340. (d) von Delius, M.; Le, C. M.; Dong, V. M. *J. Am. Chem. Soc.* **2012**, *134*, 15022.

(5) (a) Suggs, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 489. (b) Jun, C.-H.; Lee, H.; Hong, J.-B. *J. Org. Chem.* **1997**, *62*, 1200. (c) Jun, C.-H.; Huh, C.-W.; Na, S.-J. *Angew. Chem., Int. Ed.* **1998**, *37*, 145. (d) Yang, J.; Seto, Y. W.; Yoshikai, N. *ACS Catal.* **2015**, *5*, 3054.

(6) Anti-Markovnikov selective hydroacylation with with nonchelate-assisted aldehydes: (a) Tanaka, K.; Shibata, Y.; Suda, T.; Hagiwara, Y.; Hirano, M. *Org. Lett.* **2007**, *9*, 1215. (b) Shibata, Y.; Tanaka, K. *J. Am. Chem. Soc.* **2009**, *131*, 12552.

(7) (a) Tanaka, M.; Imai, M.; Yamamoto, Y.; Tanaka, K.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *Org. Lett.* **2003**, *5*, 1365. (b) Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. *J. Am. Chem. Soc.* **2008**, *130*, 14094. (c) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14120. (d) Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190. (e) Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16330. (f) Murphy, S. K.; Petrone, D. A.; Coulter, M. M.; Dong, V. M. *Org. Lett.* **2011**, *13*, 6216. (g) Murphy, S. K.; Bruch, A.; Dong, V. M. *Chem. Sci.* **2015**, *6*, 174.

(8) (a) Barnhart, R. W.; Wang, X.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1994**, *116*, 1821. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340. (c) Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932. (d) Piel, I.; Steinmetz, M.; Hirano, K.; Fröhlich, R.; Grimme, S.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 4983. (e) Hoffman, T. J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 10670. (f) Yang, J.; Yoshikai, N. *J. Am. Chem. Soc.* **2014**, *136*, 16748.

(9) Xiao, L.-J.; Fu, X.-N.; Zhou, M.-J.; Xie, J.-H.; Wang, L.-X.; Xu, X.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2016**, *138*, 2957.

(10) (a) Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *Science* **2011**, *333*, 1613. (b) Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *J. Am. Chem. Soc.* **2012**, *134*, 7325. (c) Kim, J.; Lee, D.-H.; Kalutharage, N.; Yi, C. S. *ACS Catal.* **2014**, *4*, 3881.

(11) Lee, H.; Yi, C. S. *Eur. J. Org. Chem.* **2015**, 1899.

(12) Lee, D. W.; Yi, C. S. *Organometallics* **2010**, *29*, 3413.

(13) (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (b) Albrecht, M. *Chem. Rev.* **2010**, *110*, 576.

(14) (a) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (b) Garralda, M. A. *Dalton Trans.* **2009**, 3635. (c) Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009**, *11*, 3120. (d) Chan, C.-W.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 3926. (e) Santhoshkumar, R.; Mannathan, S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2015**, *137*, 16116.

(15) The complete structural assignment of **5** was very difficult because the peaks due to styrene and unreacted benzaldehyde overlapped with the peaks for **5**. The complex **5** also slowly decomposes at room temperature within 12 h.

(16) (a) Kakiuchi, F.; Chatani, N. In *Topics in Organometallic Chemistry: Ruthenium Catalysts and Fine Chemistry*; Bruneau, C., Dixneuf, P. H., Eds; Springer-Verlag: Berlin, 2004, Vol. *11*, pp 45−79. (b) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879.

(17) As indicated earlier, we have previously found that the complex **1** is an exceptionally effective catalyst for the olefin isomerization reaction (ref 12). The observed deuterium scrambling pattern can be readily explained by an olefin isomerization mechanism, as illustated in SI (Figure S2).

(18) Ryu and co-workers proposed an alternate mechanism via a π-allyl-ruthenium species to explain Markovnikov selectivity for the hydroacylation of dienes.[7b] We cannot rigorously eliminate this mechanistic possibility, although it cannot readily explain the detection of the Ru-acyl species.

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