ACS Catalysis

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Synthetic and Mechanistic Studies on the Rhodium-Catalyzed Redox Isomerization of Cyclohexa-2,5-dienols

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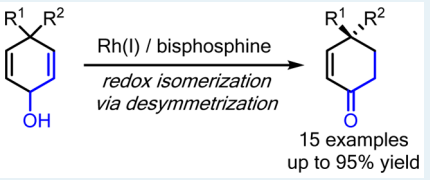
Supporting Information

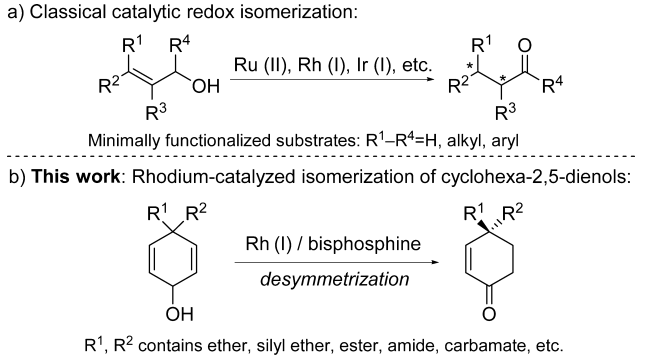
ABSTRACT: We report the application of cyclohexa-2,5-dienols in a catalytic redox isomerization: a rhodium-catalyzed desymmetrization for the synthesis of γ,γ-disubstituted cyclohexenones. The reaction generates products which are useful intermediates in organic synthesis, and its functional group tolerance compares favorably to that of classical redox isomerizations. Through deuteration, crossover, and competition experiments, the mechanism was found to involve an intramolecular 1,3-hydride shift. The enantioselective version of the reaction was also studied.



KEYWORDS: *homogeneous catalysis, rhodium, isomerization, redox reaction, allylic alcohols*

The catalytic isomerization of allylic alcohols into saturated carbonyl compounds stands as one of the earliest transition-metal-catalyzed reactions to have been studied (Scheme 1a).[1] Indeed, Pettit in 1962 made the seminal observation that an iron pentacarbonyl complex induced the transformation of but-3-en-2-ol to 2-butanone.[2] Other substrates such as allylic amines have also been exploited, as best exemplified by the venerable Takasago process for the industrial synthesis of L-menthol, the key step of which is an asymmetric rhodium-catalyzed isomerization.[3] Since these pioneering efforts, an active area of research has been the development of catalysts which show enhanced performance in terms of turnover numbers, high enantioselectivity, and mild conditions. Another challenge was the difficulty in isomerizing trisubstituted double bonds. While excellent catalysts for this transformation are now accessible (mostly Ru-,[4] Rh-,[5] or Ir-based[6]), the types of compounds that have been isomerized are remarkably limited. In fact, the vast majority of reported examples have been for the production of simple α and/or β-branched aldehydes and ketones with minimal to absent functionality (Scheme 1a).[1b,7] Even in the field of natural product synthesis, the few applications of this process have mostly been on unadorned scaffolds.[3b,8] Therefore, it appeared to us that the potential of this classical reaction had not yet been fully realized.

Scheme 1. Redox Isomerization of Allylic Alcohols[a,b]



[a]Classical catalytic isomerization of allylic alcohols has mostly been studied on non- or minimally functionalized substrates. [b]This work: rhodium-catalyzed desymmetrative isomerization of functionalized cyclohexa-2,5-dienols.

In this context, we envisioned that a redox isomerization could be designed to transform more complex molecules, namely, functionalized cyclohexa-2,5-dienols, into the corresponding substituted cyclohexenones (Scheme 1b). This process raises certain synthetic and mechanistic questions regarding the functional group tolerance of the reaction and the course of this desymmetrization process.[9]

To answer those questions, we began our studies using different standard rhodium catalysts and cyclohexadienol **1**, obtained as a 1:1 diastereomeric mixture from Luche reduction of the corresponding cyclohexadienone (Table 1).[10] While a neutral Rh complex was ineffective (Table 1, entry 1), cationic complexes with BINAP as the ligand performed well under various conditions (Table 1, entries 2−4)

Both DCE and THF can be used as solvents, and they were selected on the basis of the solubility of the respective catalysts. Notably, when the catalyst was activated by bubbling hydrogen through the solution containing the substrate for 1 min, the reaction could be run at 35 °C, following removal of H_2 by freeze−pump−thaw, and the product was obtained in 95% yield (Table 1, entry 4). This hydrogen treatment can be omitted if the reaction is run at higher temperature with $[Rh(cod)_2]BF_4$ as the precatalyst, providing the product in 85%

Received: October 23, 2015
Revised: December 15, 2015

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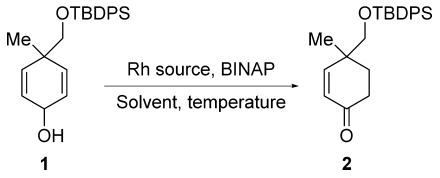
DOI: 10.1021/acscatal.5b02387
ACS Catal. 2016, 6, 747−750

Table 1. Catalyst Survey for the Isomerization of Cyclohexadienol 1[a]



1 2

entry	Rh source	solvent	T [°C]	yield [%][b]
1	$[Rh(cod)Cl]_2$	THF	65	<5%
2	$[Rh(cod)_2]OTf$	THF	65	65
3	$[Rh(cod)_2]BF_4$	DCE	75	85
4[c]	$[Rh(nbd)_2]BF_4$	DCE	35	95

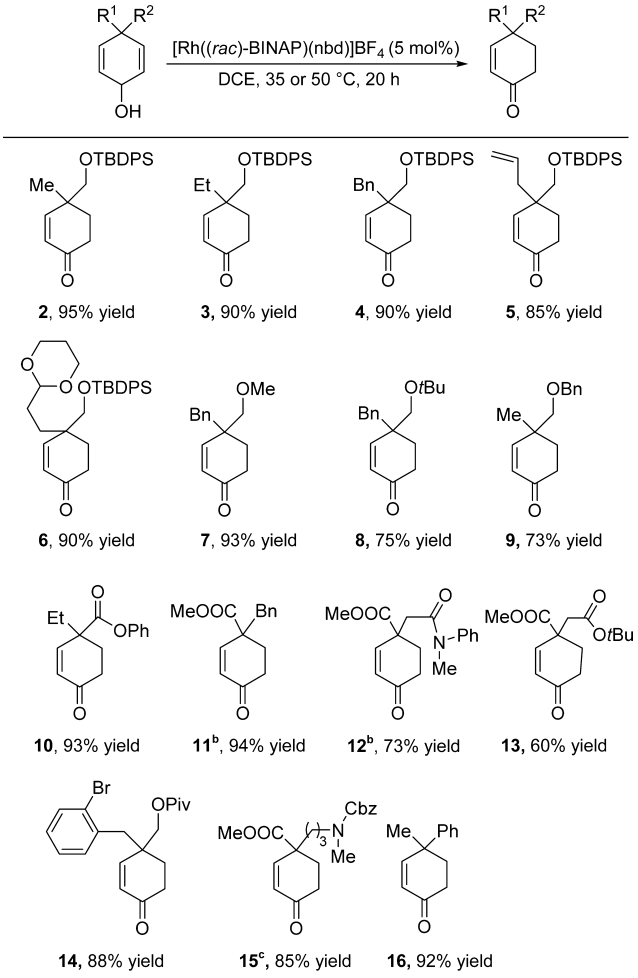
[a]Reactions run with **1** (dr =1:1, 0.1 mmol), Rh source (5 mol %), (*rac*)-BINAP (6 mol %) in solvent (1 mL) for 20 h. See Supporting Information for details. [b]Isolated yield after purification by flash chromatography (yields <5% determined by ^{1}H NMR). [c]Catalyst activated by bubbling H_2 through the reaction mixture for 1 min followed by freeze−pump−thaw. cod = 1,5-cyclooctadiene, nbd = norbornadiene, TBDPS = *tert*-butyldiphenylsilyl

yield (Table 1, entry 3). To study the scope of this reaction, we prepared a variety of cyclohexadienols, which we submitted to the optimized reaction (Table 2).

Products bearing different alkyl substituents and a $-CH_2OTBDPS$ group **2**−**6** were obtained in high yield under the standard conditions. In this series, the reaction is slower with increasing size of the alkyl substituent, going from Me (12 h) to Bn (18 h). In the same vein, for model substrate **1**, the diastereomer with the carbinol C−H on the same face as the alkyl group reacts faster than the opposite diastereomer (8 h for **1a** → **2**; 12 h for **1b** → **2**), most likely due to steric effects. Products having an ether (**7**−**9**) or ester (**10**−**11**) group in the backbone were also synthesized in good to high yields, and a tertiary amide was tolerated in the reaction leading to **12**. In the case of **11** and **12**, an alternate protocol using $[Rh(cod)_2OTf]$ and BINAP gave better results than the standard conditions (see also Table 1, entry 2). Two different ester groups were present in product **13**, which was obtained in moderate yield under the standard conditions. We also prepared a substrate containing a Cbz-protected amine, which reacted to give **14** in 88% yield. Cyclohexenone **15** could be obtained in 85% yield using a higher catalyst loading to ensure full conversion. Finally, product **16** with a phenyl group directly attached to the ring was prepared in 92% yield. In all these cases, a standard reaction time of 20 h was selected and allowed the reactions to proceed to completion. It should be noted that the synthesis of the starting materials is flexible, allowing for the introduction of various R^1 and R^2 groups from alkylation and functional group interconversion of methyl cyclohexa-2,5-diene-1-carboxylate,[11] and leading to a class of cyclohexenones that are versatile intermediates in total synthesis.[12] The tolerance of the reaction to coordinative and protic additives was also studied (Table S1).

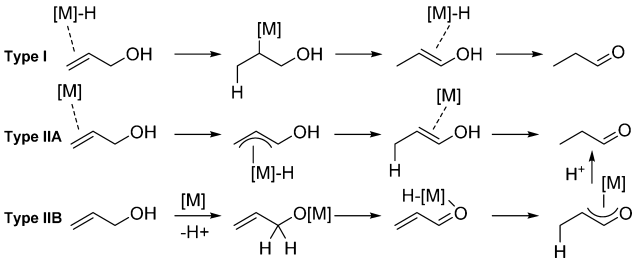
With the scope and limitations of the process well delineated, we performed experiments to understand the mechanistic features of this reaction. The mechanism of the classical redox isomerization of allylic alcohols (Scheme 1a) has been studied, and three limiting pathways have been established.[13] The first one involves a free metal-hydride species, which performs a migratory insertion−β-hydride elimination sequence in an intermolecular process (Type I in Scheme 2).[4a,6c,14] This

Table 2. Scope of the Isomerization Reaction[a]



[a]Reactions run with a diastereomeric mixture of cyclohexa-2,5-dienol (0.1−0.2 mmol), Rh source (5 mol %) in DCE (0.1 M), 35 or 50 °C, 20 h. Catalyst activated by bubbling H_2 through the reaction for 1 min, followed by freeze−pump−thaw. See Supporting Information for details. Isolated yields after purification by flash chromatography. [b]Reactions run with $[Rh(cod)_2OTf]$ (5 mol %), (*rac*)-BINAP (6 mol %) in THF (0.1 M) at 65 °C. [c]With 7.5 mol % Rh. Cbz = carboxybenzoyl, Piv = pivaloyl.

Scheme 2. Established Mechanisms for the Redox Isomerization of Allylic Alcohols



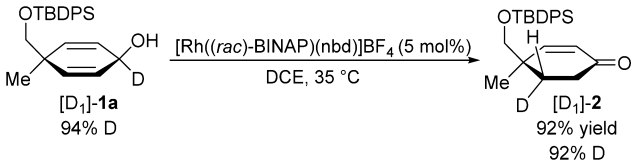
mechanism can operate starting from an isolated metal-hydride precatalyst or after generation of that species in situ. An alternate pathway operates without a free metal-hydride complex and consists in an intramolecular 1,3-hydride shift with the intermediacy of a π-allyl metal-hydride complex generated by oxidative addition to the allylic C−H bond (Type IIA in Scheme 2).[2,5a,b,15] Additionally, the reaction can also

DOI: 10.1021/acscatal.5b02387
ACS Catal. 2016, 6, 747−750

proceed via an intramolecular 1,3-hydride shift, but with the involvement of a metal alkoxide species (Type IIB in Scheme 2). This last pathway has been proposed with Ru (II)[5b−d,16] and with Rh (I) under basic or aqueous conditions,[5e,f] and is similar to the well-established mechanism of the rhodium-catalyzed isomerization of allylic amines.[3b]

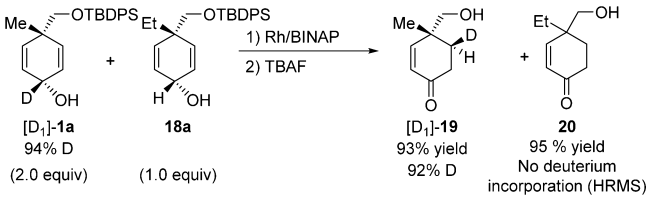
A unique aspect of the substrates under study is their diastereotopic faces (i.e., each face of the flat cyclohexadienol system) which each have two enantiotopic double bonds, a fact that warrants mechanistic investigation. To understand the stereo- and regiochemistry of hydride transfer, we prepared a deuterated analogue of starting material **1** and separated its two diastereomers ([D_1]−**1a** and [D_1]−**1b**). The structure of **1a** was confirmed by X-ray crystallography. When subjected to the standard conditions, [D_1]−**1a** led to the formation of a single deuterated species with deuterium transfer occurring in the 1,3-suprafacial mode, as determined by ^{2}H NMR and NOE experiments (Scheme 3). [D_1]−**1b** showed analogous behavior. These results prove the face selectivity of the reaction and suggest that it is intramolecular.

Scheme 3. Studying the Stereo- and Regiochemistry of Hydride (Deuteride) Transfer



To obtain additional confirmation for the intramolecularity of the process, we performed a crossover experiment between [D_1]−**1a** and **18a** at 35 °C and analyzed the product distribution by HRMS, after removal of the TBDPS group. Deuterium was transferred intramolecularly to [D_1]−**19** as no deuterated analogue of ethyl-containing product **20** was observed by HRMS (Scheme 4).

Scheme 4. Crossover Experiment[a]

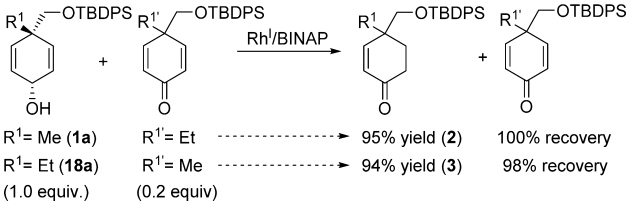


[a]Conditions: see footnote (a) in Table 2. Yields were determined by ^{1}H NMR analysis of the crude mixture using an internal standard.

A minor (<5%) side product in the isomerization process is the corresponding cyclohexadienone to the starting material, likely formed by *β*-hydride elimination (see Type IIB, Scheme 2). We wondered whether this free dienone was able to enter the catalytic cycle. When an external dienone (0.2 equiv) was added to the reaction, it was entirely recovered at the end, and no corresponding product (enone) was observed, indicating that the free cyclohexadienone does not enter the catalytic cycle as a productive intermediate (Scheme 5).

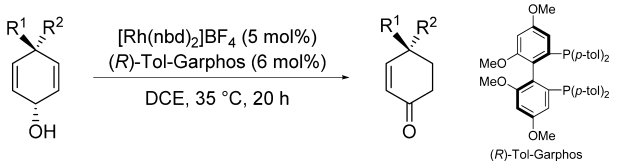
Motivated by the lack of general methods to access *γ*,*γ*-disubstituted cyclohexenones enantioselectively,[17] we investigated the asymmetric version of this isomerization. Among the chiral bisphosphines screened with model substrate **1a**, (*R*)-Tol-Garphos gave the highest enantioselectivity (Table 3, entry 1).

Scheme 5. External Cyclohexadienone Is Not Transformed When Added to the Reaction[a]



[a]Conditions: see footnote (a) in Table 2. Yield and recovery were determined by ^{1}H NMR analysis of the crude mixture using an internal standard.

Table 3. Enantioselective Redox Isomerization[a]



entry	R^1	R^2	yield[b]	ee[c]
1	Me	$CH_2OTBDPS$	92% (**2**)	60%
2	$CH_2OTBDPS$	Me	92% (**2**)	−34%
3	Et	$CH_2OTBDPS$	92% (**3**)	43%
4	$CH_2OTBDPS$	Et	92% (**3**)	−23%

[a]Reactions run with cyclohexa-2,5-dienols (0.1−0.2 mmol), [Rh(nbd)$_2$]BF_4 (5 mol %), (*R*)-Tol-Garphos (6 mol %) in DCE (0.1 M), 35 °C, 20 h. See Supporting Information for details. [b]Isolated yields after purification by flash chromatography. [c]Determined by HPLC using a chiral stationary phase.

Each diastereomer of a given substrate led to a different major enantiomer of the product (for example, Table 3, entries 1 vs 2), a situation consistent with the rest of our mechanistic observations. The level of enantioselectivity remains modest at this time.

The bulk of evidence indicates that the process under study is an intramolecular, suprafacial, 1,3-hydride shift and that less than 5% of cyclohexadienone (CHD) is produced in each reaction. We wondered if this side-product was proof of a dominant type IIB mechanism, or if type IIA was operating with CHD being produced by a catalytically irrelevant reaction. On one hand, the fact that CHD is not transformed when added to the reaction (Scheme 5) can be seen as evidence for mechanism IIA. On the other hand, mechanism IIB could still prevail if migratory insertion (1,4-addition) is fast so that external CHD cannot enter the cycle as a productive intermediate, as observed. The suprafacial nature of the process must also be considered. It favors mechanism IIA over IIB as the latter involves a proposed rhodium hydride−cyclohexadienone intermediate on which 1,4−hydride delivery would not necessarily be face selective.[18] In addition, we were able to isomerize the corresponding methyl ether to **1a**, a result compatible with the catalyst being able to react by mechanism IIA.[11]

In conclusion, we have studied the synthetic and mechanistic aspects of a new rhodium-catalyzed desymmetrative redox isomerization. This reaction provides diverse *γ*,*γ*-disubstituted

DOI: 10.1021/acscatal.5b02387
ACS Catal. 2016, 6, 747−750

cyclohexenones in good to excellent yield, and its functional group tolerance has been demonstrated and compares favorably to that of classical redox isomerizations. Mechanistic studies have shown that the reaction involves a stereospecific, intramolecular 1,3-hydride shift and that each diastereomer can take part in an enantioselective isomerization. These findings lay the basis for the development of a highly enantioselective version. Efforts are underway in our laboratory to discover additional applications of this reaction.

■ ASSOCIATED CONTENT

Supporting Information

Tables S1 and S2, detailed experimental protocols, compound characterization data and copies of ^{1}H and ^{13}C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b02387.

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Author Contributions

‡S.K. and T.J. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported financially by the Natural Sciences and Engineering Research Council of Canada (NSERC), the University of Toronto and Alphora Research Inc. S.K. acknowledges generous financial support from the Deutsche Forschungsgemeinschaft (DFG) for a postdoctoral research fellowship. T.J. thanks NSERC and the Fonds de recherche du Québec (FRQNT) for graduate scholarships. The authors thank Dr. Cédric Bürki (University of Toronto) for helpful discussions and experimental assistance.

■ REFERENCES

(1) For reviews on redox isomerizations, see: (a) Van der Drift, R. C.; Bouwman, E.; Drent, E. *J. Organomet. Chem.* **2002**, *650*, 1−24. (b) Uma, R.; Crévisy, C.; Grée, R. *Chem. Rev.* **2003**, *103*, 27−52. (c) Mantilli, L.; Mazet, C. *Chem. Lett.* **2011**, *40*, 341−344. (d) Ahlsten, N.; Bartoszewicz, A.; Martín-Matute, B. *Dalton Trans.* **2012**, *41*, 1660−1670.

(2) (a) Emerson, G. F.; Pettit, R. *J. Am. Chem. Soc.* **1962**, *84*, 4591−4592. For early work with Fe catalysts, see also: (b) Damico, R.; Logan, T. *J. Org. Chem.* **1967**, *32*, 2356−2358. (c) Cowherd, F. G.; von Rosenberg, J. L. *J. Am. Chem. Soc.* **1969**, *91*, 2157−2158. (d) Strauss, J. U.; Ford, P. W. *Tetrahedron Lett.* **1975**, *16*, 2917−2918.

(3) (a) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208−5217. (b) Tani, K. *Pure Appl. Chem.* **1985**, *57*, 1845−1854. (c) Otsuka, S.; Tani, K. *Synthesis* **1991**, *1991*, 665−680.

(4) (a) McGrath, D. V.; Grubbs, R. H. *Organometallics* **1994**, *13*, 224−235. (b) Bouziane, A.; Carboni, B.; Bruneau, C.; Carreaux, F.; Renaud, J.-L. *Tetrahedron* **2008**, *64*, 11745−11750. (c) Wu, R.; Beauchamps, M. G.; Laquidara, J. M.; Sowa, J. R., Jr. *Angew. Chem., Int. Ed.* **2012**, *51*, 2106−2110. (d) Arai, N.; Sato, K.; Azuma, K.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 7500−7504. (e) Kechaou-Perrot, M.; Vendier, L.; Bastin, S.; Sotiropoulos, J.-M.; Miqueu, K.; Menéndez-Rodríguez, L.; Crochet, P.; Cadierno, V.; Igau, A. *Organometallics* **2014**, *33*, 6294−62997.

(5) (a) Bergens, S. H.; Bosnich, B. *J. Am. Chem. Soc.* **1991**, *113*, 958−967. (b) Hiroya, K.; Kurihara, Y.; Ogasawara, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2287−2289. (c) Tanaka, K.; Qiao, S.; Tobisu, M.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 9870−9871. (d) Tanaka, K.; Fu, G. C. *J. Org. Chem.* **2001**, *66*, 8177−8186. (e) Ahlsten, N.; Martín-Matute, B. *Adv. Synth. Catal.* **2009**, *351*, 2657−2666. (f) Ahlsten, N.; Lundberg, H.; Martín-Matute, B. *Green Chem.* **2010**, *12*, 1628−1633 See also ref 1b for early studies.

(6) (a) Lin, Y.; Ma, D.; Lu, X. *Tetrahedron Lett.* **1987**, *28*, 3115−3118. (b) Mantilli, L.; Mazet, C. *Tetrahedron Lett.* **2009**, *50*, 4141−4144. (c) Mantilli, L.; Gérard, D.; Torche, S.; Besnard, C.; Mazet, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5143−5147. (d) Ahlsten, N.; Martín-Matute, B. *Chem. Commun.* **2011**, *47*, 8331−8333. (e) Li, H.; Mazet, C. *J. Am. Chem. Soc.* **2015**, *137*, 10720−10727 See also ref 1b for early studies.

(7) Notable exceptions are the industrial processes for the synthesis of hydrocodone and hydromorphone: (a) Gómez, A. B.; Holmberg, P.; Bäckvall, J.-E.; Martín-Matute, B. *RSC Adv.* **2014**, *4*, 39519−39522. (b) Diaz-Álvarez, A. E.; Cadierno, V. *Recent Pat. Catal.* **2012**, *1*, 43−50 and references cited therein.

(8) (a) Malanga, C.; Menicagli, R.; Dell'Innocenti, M.; Lardicci, L. *Tetrahedron Lett.* **1987**, *28*, 239−340. (b) Curran, D. P.; Jacobs, P. B.; Elliott, R. L.; Kim, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 5280−5282. (c) Kitamura, M.; Manabe, K.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1987**, *28*, 4719−4720.

(9) We are aware of one isolated example of the conversion of a cyclohexa-2,5-dienol to a cyclohexenone by redox isomerization, in ref 6a.

(10) An alternate sequence to obtain γ,γ-disubstituted cyclohexenones would involve a selective 1,4-reduction of cyclohexadienones. We obtained at best moderate selectivity in that process. See Table S2.

(11) See Supporting Information for details.

(12) Selected examples of their use in total synthesis: (a) Nicolaou, K. C.; Li, A.; Edmonds, D. J.; Tria, G. S.; Ellery, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 16905−16918. (b) Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293−295. (c) Liu, G.; Mei, G.; Chen, R.; Yuan, H.; Yang, Z.; Li, C. *Org. Lett.* **2014**, *16*, 4380−4383.

(13) For a relevant discussion of redox isomerization mechanisms, see ref 4a.

(14) Clark, H. C.; Kurosawa, H. *Inorg. Chem.* **1973**, *12*, 1566−1570.

(15) Batuecas, M.; Esteruelas, M. A.; García-Yerba, C.; Oñate, E. *Organometallics* **2010**, *29*, 2166−2175.

(16) Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 2027−2036.

(17) Racemic: (a) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775−1776. (b) Flaugh, M. E.; Crowell, T. A.; Farlow, D. S. *J. Org. Chem.* **1980**, *45*, 5399−5400. Enantioselective: (c) Inokoishi, Y.; Sasakura, N.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Org. Lett.* **2010**, *12*, 1616−1619. (d) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109−3112.

(18) Fu made similar mechanistic observations to ours, with cationic rhodium and linear allylic alcohols in THF, but did not come to any further conclusions on the nature of the mechanism. See ref 5d.

DOI: 10.1021/acscatal.5b02387
ACS Catal. 2016, 6, 747−750